fetoprotein; amino acid profiles (arginine (Krebs cycle), histidine/urocanic acid, homocysteine, phenylalanine/tyrosine, tryptophan); andrenostenedione; antipyrine; arabinitol enantiomers; arginase; benzoylecgonine (cocaine); biotinidase; biopterin; c-reactive protein; carnitine; carnosinase; CD4; ceruloplasmin; chenodeoxycholic acid; chloroquine; cholesterol; cholinesterase; conjugated 1-ß hydroxy-cholic acid; cortisol; creatine kinase; creatine kinase MM isoenzyme; cyclosporin A; d-penicillamine; de-ethylchloroquine; dehydroepiandrosterone sulfate; DNA (acetylator polymorphism, alcohol dehydrogenase, alpha 1-antitrypsin, cystic fibrosis, Duchenne/Becker muscular dystrophy, analyte-6-phosphate dehydrogenase, hemoglobinopathies, A,S,C,E, D-Punjab, beta-thalassemia, hepatitis B virus, HCMV, HIV-1, HTLV-1, Leber hereditary optic neuropathy, MCAD, RNA, PKU, Plasmodium vivax, sexual differentiation, 21-deoxycortisol); desbutylhalofantrine; dihydropteridine reductase; diptheria/tetanus antitoxin; erythrocyte arginase; erythrocyte protoporphyrin; esterase D; fatty acids/acylglycines; free ß-human chorionic gonadotropin; free erythrocyte porphyrin; free thyroxine (FT4); free tri-iodothyronine (FT3); fumarylacetoacetase; galactose/gal-1-phosphate; galactose-1-phosphate uridyltransferase; gentamicin; analyte-6-phosphate dehydrogenase; glutathione; glutathione perioxidase; glycocholic acid; glycosylated hemoglobin; halofantrine; hemoglobin variants; hexosaminidase A; human erythrocyte carbonic anhydrase I ; 17 alpha-hydroxyprogesterone; hypoxanthine phosphoribosyl transferase; immunoreactive trypsin; lactate; lead; lipoproteins ((a), B/A-1, ß); lysozyme; mefloquine; netilmicin; phenobarbitone; phenytoin; phytanic/pristanic acid; progesterone; prolactin; prolidase; purine nucleoside phosphorylase; quinine; reverse tri-iodothyronine (rT3); selenium; serum pancreatic lipase; sissomicin; somatomedin C; specific antibodies (adenovirus, anti-nuclear antibody, anti-zeta antibody, arbovirus, Aujeszky's disease virus, dengue virus, Dracunculus medinensis, Echinococcus granulosus, Entamoeba histolytica, enterovirus, Giardia duodenalisa, Helicobacter pylori, hepatitis B virus, herpes virus, HIV-1, IgE (atopic disease), influenza virus, Leishmania donovani, leptospira, measles/mumps/rubella, Mycobacterium leprae, Mycoplasma pneumoniae, Myoglobin, Onchocerca volvulus, parainfluenza virus, Plasmodium falciparum, poliovirus, Pseudomonas aeruginosa, respiratory syncytial virus, rickettsia (scrub typhus), Schistosoma mansoni, Toxoplasma gondii, Trepenoma pallidium, Trypanosoma cruzi/rangeli, vesicular stomatis virus, Wuchereria bancrofti, yellow fever virus); specific antigens (hepatitis B virus,

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HIV-1); succinylacetone; sulfadoxine; theophylline; thyrotropin (TSH); thyroxine (T4); thyroxine-binding globulin; trace elements; transferrin; UDP-galactose-4-epimerase; urea; uroporphyrinogen I synthase; vitamin A; white blood cells; and zinc protoporphyrin. Salts, sugar, protein, fat, vitamins, and hormones naturally occurring in blood or interstitial fluids may also constitute analytes in certain embodiments. The analyte may be naturally present in the biological fluid, for example, a metabolic product, a hormone, an antigen, an antibody, and the like. Alternatively, the analyte may be introduced into the body, for example, a contrast agent for imaging, a radioisotope, a chemical agent, a fluorocarbon-based synthetic blood, or a drug or pharmaceutical composition, including but not limited to insulin; ethanol; cannabis (marijuana, tetrahydrocannabinol, hashish); inhalants (nitrous oxide, amyl nitrite, butyl nitrite, chlorohydrocarbons, hydrocarbons); cocaine (crack cocaine); stimulants (amphetamines, methamphetamines, Ritalin, Cylert, Preludin, Didrex, PreState, Voranil, Sandrex, Plegine); depressants (barbituates, methaqualone, tranquilizers such as Valium, Librium, Miltown, Serax, Equanil, Tranxene); hallucinogens (phencyclidine, lysergic acid, mescaline, peyote, psilocybin); narcotics (heroin, codeine, morphine, opium, meperidine, Percocet, Percodan, Tussionex, Fentanyl, Darvon, Talwin, Lomotil); designer drugs (analogs of fentanyl, meperidine, amphetamines, methamphetamines, and phencyclidine, for example, Ecstasy); anabolic steroids; and nicotine. The metabolic products of drugs and pharmaceutical compositions are also contemplated analytes. Analytes such as neurochemicals and other chemicals generated within the body may also be analyzed, such as, for example, ascorbic acid, uric acid, dopamine, noradrenaline, 3-methoxytyramine (3MT), 3,4-Dihydroxyphenylacetic acid (DOPAC), Homovanillic acid (HVA), 5-Hydroxytryptamine (5HT), and 5-Hydroxyindoleacetic acid (FHIAA).

[0143] The term "continuous glucose sensor" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a device that continuously or continually measures glucose concentration, for example, at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes, or longer. It should be understood that continuous glucose sensors can continually measure glucose concentration

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without requiring user initiation and/or interaction for each measurement, such as described with reference to U.S. Patent 6,001,067, for example.

[0144] The phrase "continuous glucose sensing" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the period in which monitoring of plasma glucose concentration is continuously or continually performed, for example, at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes, or longer.

[0145] The term "biological sample" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a sample of a host body, for example, blood, interstitial fluid, spinal fluid, saliva, urine, tears, sweat, tissue, and the like.

[0146] The term "host" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to plants or animals, for example humans.

[0147] The term "biointerface membrane" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a permeable or semi-permeable membrane that can include one or more domains and is typically constructed of materials of a few microns thickness or more, which can be placed over the sensing region to keep host cells (for example, macrophages) from gaining proximity to, and thereby damaging the membrane system or forming a barrier cell layer and interfering with the transport of glucose across the tissue-device interface.

[0148] The term "membrane system" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a permeable or semi-permeable membrane that can be comprised of one or more domains and is typically constructed of materials of a few microns thickness or more, which may be permeable to oxygen

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and are optionally permeable to glucose. In one example, the membrane system comprises an immobilized glucose oxidase enzyme, which enables an electrochemical reaction to occur to measure a concentration of glucose.

[0149] The term "domain" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to regions of a membrane that can be layers, uniform or non-uniform gradients (for example, anisotropic), functional aspects of a material, or provided as portions of the membrane.

[0150] The term "copolymer" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to polymers having two or more different repeat units and includes copolymers, terpolymers, tetrapolymers, and the like.

[0151] The term "sensing region" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the region of a monitoring device responsible for the detection of a particular analyte. In one embodiment, the sensing region generally comprises a non-conductive body, at least one electrode, a reference electrode and a optionally a counter electrode passing through and secured within the body forming an electrochemically reactive surface at one location on the body and an electronic connection at another location on the body, and a membrane system affixed to the body and covering the electrochemically reactive surface. In another embodiment, the sensing region generally comprises a non-conductive body, a working electrode (anode), a reference electrode (optionally can be remote from the sensing region), an insulator disposed therebetween, and a multi-domain membrane affixed to the body and covering the electrochemically reactive surfaces of the working and optionally reference electrodes.

[0152] The term "electrochemically reactive surface" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the surface of an electrode where an electrochemical reaction takes place. In one embodiment, a working electrode measures hydrogen peroxide creating a measurable electronic current.

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[0153] The term "electrochemical cell" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a device in which chemical energy is converted to electrical energy. Such a cell typically consists of two or more electrodes held apart from each other and in contact with an electrolyte solution. Connection of the electrodes to a source of direct electric current renders one of them negatively charged and the other positively charged. Positive ions in the electrolyte migrate to the negative electrode (cathode) and there combine with one or more electrons, losing part or all of their charge and becoming new ions having lower charge or neutral atoms or molecules; at the same time, negative ions migrate to the positive electrode (anode) and transfer one or more electrons to it, also becoming new ions or neutral particles. The overall effect of the two processes is the transfer of electrons from the negative ions to the positive ions, a chemical reaction.

[0154] The term "electrode" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a conductor through which electricity enters or leaves something such as a battery or a piece of electrical equipment. In one embodiment, the electrodes are the metallic portions of a sensor (e.g., electrochemically reactive surfaces) that are exposed to the extracellular milieu, for detecting the analyte. In some embodiments, the term electrode includes the conductive wires or traces that electrically connect the electrochemically reactive surface to connectors (for connecting the sensor to electronics) or to the electronics.

[0155] The term "enzyme" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a protein or protein-based molecule that speeds up a chemical reaction occurring in a living thing. Enzymes may act as catalysts for a single reaction, converting a reactant (also called an analyte herein) into a specific product. In one exemplary embodiment of a glucose oxidase-based glucose sensor, an enzyme, glucose oxidase (GOX) is provided to react with glucose (the analyte) and oxygen to form hydrogen peroxide.

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[0156] The term "co-analyte" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a molecule required in an enzymatic reaction to react with the analyte and the enzyme to form the specific product being measured. In one exemplary embodiment of a glucose sensor, an enzyme, glucose oxidase (GOX) is provided to react with glucose and oxygen (the co-analyte) to form hydrogen peroxide.

[0157] The term "constant analyte" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to an analyte that remains relatively constant over a time period, for example over an hour to a day as compared to other variable analytes. For example, in a person with diabetes, oxygen and urea may be relatively constant analytes in particular tissue compartments relative to glucose, which is known to oscillate between about 40 and 400 mg/dL during a 24-hour cycle. Although analytes such as oxygen and urea are known to oscillate to a lesser degree, for example due to physiological processes in a host, they are substantially constant, relative to glucose, and can be digitally filtered, for example low pass filtered, to minimize or eliminate any relatively low amplitude oscillations. Constant analytes other than oxygen and urea are also contemplated.

[0158] The term "proximal" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to near to a point of reference such as an origin or a point of attachment. For example, in some embodiments of a membrane system that covers an electrochemically reactive surface, the electrolyte domain is located more proximal to the electrochemically reactive surface than the resistance domain.

[0159] The term "distal" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to spaced relatively far from a point of reference, such as an origin or a point of attachment. For example, in some embodiments of a membrane system that covers an electrochemically reactive surface, a resistance domain is located more distal to the electrochemically reactive surfaces than the electrolyte domain.

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[0160] The term "substantially" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a sufficient amount that provides a desired function. For example, the interference domain of the preferred embodiments is configured to resist a sufficient amount of interfering species such that tracking of glucose levels can be achieved, which may include an amount greater than 50 percent, an amount greater than 60 percent, an amount greater than 70 percent, an amount greater than 80 percent, or an amount greater than 90 percent of interfering species.

[0161] The term "computer" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to machine that can be programmed to manipulate data.

[0162] The term "modem" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to an electronic device for converting between serial data from a computer and an audio signal suitable for transmission over a telecommunications connection to another modem.

[0163] The terms "processor module" and "microprocessor" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to a computer system, state machine, processor, or the like designed to perform arithmetic and logic operations using logic circuitry that responds to and processes the basic instructions that drive a computer.

[0164] The term "ROM" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to read-only memory, which is a type of data storage device manufactured with fixed contents. ROM is broad enough to include EEPROM, for example, which is electrically erasable programmable read-only memory (ROM).

[0165] The term "RAM" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a

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special or customized meaning), and refers without limitation to a data storage device for which the order of access to different locations does not affect the speed of access. RAM is broad enough to include SRAM, for example, which is static random access memory that retains data bits in its memory as long as power is being supplied.

[0166] The term "A/D Converter" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to hardware and/or software that converts analog electrical signals into corresponding digital signals.

[0167] The term "RF transceiver" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a radio frequency transmitter and/or receiver for transmitting and/or receiving signals.

[0168] The terms "raw data stream" and "data stream" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to an analog or digital signal directly related to the analyte concentration measured by the analyte sensor. In one example, the raw data stream is digital data in "counts" converted by an A/D converter from an analog signal (for example, voltage or amps) representative of an analyte concentration. The terms broadly encompass a plurality of time spaced data points from a substantially continuous analyte sensor, which comprises individual measurements taken at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes or longer. In some embodiments, raw data includes one or more values (e.g., digital value) representative of the current flow integrated over time (e.g., integrated value), for example, using a charge counting device, or the like.

[0169] The term "counts" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a unit of measurement of a digital signal. In one example, a raw data stream measured in counts is directly related to a voltage (for example, converted by an A/D converter), which is directly related to current from a working electrode.

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[0170] The term "electronic circuitry" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the components (for example, hardware and/or software) of a device configured to process data. In the case of an analyte sensor, the data includes biological information obtained by a sensor regarding the concentration of the analyte in a biological fluid. U.S. Patent Nos. 4,757,022, 5,497,772 and 4,787,398, which are hereby incorporated by reference in their entirety, describe suitable electronic circuits that can be utilized with devices of certain embodiments.

[0171] The term "potentiostat" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to an electrical system that applies a potential between the working and reference electrodes of a two- or three-electrode cell at a preset value and measures the current flow through the working electrode. Typically, the potentiostat forces whatever current is necessary to flow between the working and reference or counter electrodes to keep the desired potential, as long as the needed cell voltage and current do not exceed the compliance limits of the potentiostat.

[0172] The terms "operably connected" and "operably linked" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to one or more components being linked to another component(s) in a manner that allows transmission of signals between the components. For example, one or more electrodes can be used to detect the amount of glucose in a sample and convert that information into a signal; the signal can then be transmitted to an electronic circuit. In this case, the electrode is "operably linked" to the electronic circuit. These terms are broad enough to include wired and wireless connectivity.

[0173] The term "smoothing" and "filtering" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to modification of a set of data to make it smoother and more continuous and remove or diminish outlying points, for example, by performing a moving average of the raw data stream.

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[0174] The term "algorithm" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the computational processes (for example, programs) involved in transforming information from one state to another, for example using computer processing.

[0175] The term "regression" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to finding a line in which a set of data has a minimal measurement (for example, deviation) from that line. Regression can be linear, non-linear, first order, second order, and so forth. One example of regression is least squares regression.

[0176] The term "pulsed amperometric detection" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to an electrochemical flow cell and a controller, which applies the potentials and monitors current generated by the electrochemical reactions. The cell can include one or multiple working electrodes at different applied potentials. Multiple electrodes can be arranged so that they face the chromatographic flow independently (parallel configuration), or sequentially (series configuration).

[0177] The term "calibration" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the relationship and/or the process of determining the relationship between the sensor data and corresponding reference data, which may be used to convert sensor data into meaningful values substantially equivalent to the reference. In some embodiments, namely in continuous analyte sensors, calibration may be updated or recalibrated over time if changes in the relationship between the sensor and reference data occur, for example due to changes in sensitivity, baseline, transport, metabolism, or the like.

[0178] The term "sensor analyte values" and "sensor data" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without

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limitation to data received from a continuous analyte sensor, including one or more time-spaced sensor data points.

[0179] The term "reference analyte values" and "reference data" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to data from a reference analyte monitor, such as a blood glucose meter, or the like, including one or more reference data points. In some embodiments, the reference glucose values are obtained from a self-monitored blood glucose (SMBG) test (for example, from a finger or forearm blood test) or an YSI (Yellow Springs Instruments) test, for example.

[0180] The term "matched data pairs" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to reference data (for example, one or more reference analyte data points) matched with substantially time corresponding sensor data (for example, one or more sensor data points).

[0181] The terms "interferants" and "interfering species" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to effects and/or species that interfere with the measurement of an analyte of interest in a sensor to produce a signal that does not accurately represent the analyte measurement. In one example of an electrochemical sensor, interfering species are compounds with an oxidation potential that overlaps with the analyte to be measured, producing a false positive signal. In another example of an electrochemical sensor, interfering species are substantially non-constant compounds (e.g., the concentration of an interfering species fluctuates over time). In yet another example of an electrochemical sensor, an interferent is a "noise-causing species" that causes noise on the sensor. Interfering species include but are not limited to compounds with electroactive acidic, amine or sulfhydryl groups, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors or break-down products, nitric oxide (NO), NO-donors, NO-precursors, acetaminophen, ascorbic acid, bilirubin, cholesterol, creatinine, dopamine, ephedrine, ibuprofen, L-dopa, methyl dopa, salicylate, tetracycline, tolazamide, tolbutamide, triglycerides,

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and uric acid electroactive species produced during cell metabolism and/or wound healing, electroactive species that arise during body pH changes and the like.

[0182] The term "bifunctional" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to having or serving two functions. For example, in a needle-type analyte sensor, a metal wire is bifunctional because it provides structural support and acts as an electrical conductor.

[0183] The term "function" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to an action or use for which something is suited or designed.

[0184] The term "electrical conductor" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning) and refers without limitation to materials that contain movable charges of electricity. When an electric potential difference is impressed across separate points on a conductor, the mobile charges within the conductor are forced to move, and an electric current between those points appears in accordance with Ohm's law.

[0185] Accordingly, the term "electrical conductance" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning) and refers without limitation to the propensity of a material to behave as an electrical conductor. In some embodiments, the term refers to a sufficient amount of electrical conductance (*e.g.*, material property) to provide a necessary function (electrical conduction).

[0186] The terms "insulative properties," "electrical insulator" and "insulator" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning) and refers without limitation to the tendency of materials that lack mobile charges to prevent movement of electrical charges between two points. In one exemplary embodiment, an electrically insulative material may be placed between two electrically conductive materials, to prevent movement of electricity between the two electrically conductive materials. In some

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embodiments, the terms refer to a sufficient amount of insulative property (e.g., of a material) to provide a necessary function (electrical insulation). The terms "insulator" and "non-conductive material" can be used interchangeably herein.

[0187] The term "structural support" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning) and refers without limitation to the tendency of a material to keep the sensor's structure stable or in place. For example, structural support can include "weight bearing" as well as the tendency to hold the parts or components of a whole structure together. A variety of materials can provide "structural support" to the sensor.

[0188] The term "diffusion barrier" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning) and refers without limitation to something that obstructs the random movement of compounds, species, atoms, molecules, or ions from one site in a medium to another. In some embodiments, a diffusion barrier is structural, such as a wall that separates two working electrodes and substantially prevents diffusion of a species from one electrode to the other. In some embodiments, a diffusion barrier is spatial, such as separating working electrodes by a distance sufficiently large enough to substantially prevent a species at a first electrode from affecting a second electrode. In other embodiments, a diffusion barrier can be temporal, such as by turning the first and second working electrodes on and off, such that a reaction at a first electrode will not substantially affect the function of the second electrode.

[0189] The terms "integral," "integrally," "integrally formed," integrally incorporated," "unitary" and "composite" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and they are not to be limited to a special or customized meaning), and refer without limitation to the condition of being composed of essential parts or elements that together make a whole. The parts are essential for completeness of the whole. In one exemplary embodiment, at least a portion (e.g., the *in vivo* portion) of the sensor is formed from at least one platinum wire at least partially covered with an insulative coating, which is at least partially helically wound with at least one additional wire, the exposed electroactive portions of which are covered by a membrane system

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(see description of Fig. 1B or 9B); in this exemplary embodiment, each element of the sensor is formed as an integral part of the sensor (e.g., both functionally and structurally).

[0190] The term "coaxial" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to having a common axis, having coincident axes or mounted on concentric shafts.

[0191] The term "twisted" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to united by having one part or end turned in the opposite direction to the other, such as, but not limited to the twisted strands of fiber in a string, yarn, or cable.

[0192] The term "helix" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a spiral or coil, or something in the form of a spiral or coil (e.g. a corkscrew or a coiled spring). In one example, a helix is a mathematical curve that lies on a cylinder or cone and makes a constant angle with the straight lines lying in the cylinder or cone. A "double helix" is a pair of parallel helices intertwined about a common axis, such as but not limited to that in the structure of DNA.

[0193] The term "*in vivo* portion" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a portion of a device that is to be implanted or inserted into the host. In one exemplary embodiment, an *in vivo* portion of a transcutaneous sensor is a portion of the sensor that is inserted through the host's skin and resides within the host.

[0194] The terms "background," "baseline," and "noise" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refer without limitation to a component of an analyte sensor signal that is not related to the analyte concentration. In one example of a glucose sensor, the background is composed substantially of signal contribution due to factors other than glucose (for example, interfering species, non-reaction-related hydrogen

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peroxide, or other electroactive species with an oxidation potential that overlaps with hydrogen peroxide). In some embodiments wherein a calibration is defined by solving for the equation $y=mx+b$, the value of b represents the background of the signal. In general, the background (noise) comprises components related to constant and non-constant factors.

[0195] The term "constant noise" and "constant background" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refer without limitation to the component of the background signal that remains relatively constant over time. For example, certain electroactive compounds found in the human body are relatively constant factors (e.g., baseline of the host's physiology) and do not significantly adversely affect accuracy of the calibration of the glucose concentration (e.g., they can be relatively constantly eliminated using the equation $y=mx+b$). In some circumstances, constant background noise can slowly drift over time (*e.g.*, increases or decreases), however this drift need not adversely affect the accuracy of a sensor, for example, because a sensor can be calibrated and re-calibrated and/or the drift measured and compensated for.

[0196] The term "non-constant noise" or non-constant background" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refer without limitation to a component of the background signal that is relatively non-constant, for example, transient and/or intermittent. For example, certain electroactive compounds, are relatively non-constant (e.g., intermittent interferents due to the host's ingestion, metabolism, wound healing, and other mechanical, chemical and/or biochemical factors), which create intermittent (e.g., non-constant) "noise" on the sensor signal that can be difficult to "calibrate out" using a standard calibration equations (e.g., because the background of the signal does not remain constant).

[0197] The terms "inactive enzyme" or "inactivated enzyme" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refer without limitation to an enzyme (e.g., glucose oxidase, GOx) that has been rendered inactive (e.g., "killed" or "dead") and has no enzymatic activity. Enzymes can be inactivated using a variety of

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techniques known in the art, such as but not limited to heating, freeze-thaw, denaturing in organic solvent, acids or bases, cross-linking, genetically changing enzymatically critical amino acids, and the like. In some embodiments, a solution containing active enzyme can be applied to the sensor, and the applied enzyme subsequently inactivated by heating or treatment with an inactivating solvent.

[0198] The term "non-enzymatic" as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a lack of enzyme activity. In some embodiments, a "non-enzymatic" membrane portion contains no enzyme; while in other embodiments, the "non-enzymatic" membrane portion contains inactive enzyme. In some embodiments, an enzyme solution containing inactive enzyme or no enzyme is applied. In one example of an electrochemical sensor, a non-enzymatic or inactive enzymatic portion of the membrane includes an enzyme domain formed of enzyme domain materials, as described elsewhere herein, and either inactivated enzyme or no enzyme.

[0199] The term "GOx" as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the enzyme Glucose Oxidase (e.g., GOx is an abbreviation).

[0200] The term "equivalent," as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the state of being substantially equal or well matched; having the same or similar quantity, value, amplitude or measure as another. In some embodiments, equivalent amounts are within 20% of each other (e.g., a number plus or minus 10%). In some embodiments, equivalent amounts are within 10% of each other (e.g., a number plus or minus 5%).

[0201] The term "measured/measurable species," as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a compound that can be or is detected by an analyte sensor, the amount of which is indicative of the amount of analyte present. The identity of the measure/measurable species is dependent upon

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what substance (e.g., glucose, urea, creatinine, cholesterol, phosphate) the biosensor in question is configured to detect. In one example, in the case of a diffusion-based glucose biosensor including glucose oxidase (GOx), the measured/measurable species is H_2O_2, which is produced by the reaction of glucose with the GOx, and is subsequently detected/measured at a working electrode.

[0202] The term "crosstalk" as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to the presence of (e.g., detection of) an unwanted signal *via* an accidental coupling. In one exemplary circumstance, crosstalk can occur on a glucose sensor having two working electrodes when a measured species (e.g., H_2O_2) produced at one working electrode diffuses to and is detected by the other working electrode.

[0203] The term "crosstalk diffusion distance," as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to, in a dual electrode biosensor, the maximum distance a measured species (e.g., H_2O_2 produced in the active enzymatic portion of the membrane) can diffuse from a first working electrode (e.g., having the active enzymatic portion of the membrane) toward/to a second working electrode (e.g., having the non-enzymatic/inactive enzymatic portion of the membrane) and cause a detectable signal on the second working electrode.

[0204] The term "physical diffusion barrier," as used herein is a broad term, and is to be given their ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to a structure that physically (e.g., other than or in addition to spacing of the electrodes) attenuates diffusion (of a substance/compound/species/molecule) from one side of the barrier to the other. In one example of an electrochemical sensor, a physical diffusion barrier is configured and arranged to attenuate diffusion of H_2O_2 from a first portion of the sensor to a second portion of the sensor.

[0205] The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

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[0206] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

Overview

[0207] The preferred embodiments provide a continuous analyte sensor that measures a concentration of the analyte of interest or a substance indicative of the concentration or presence of the analyte. In some embodiments, the analyte sensor is an invasive, minimally invasive, or non-invasive device, for example a subcutaneous, transdermal, or intravascular device. In some embodiments, the analyte sensor may analyze a plurality of intermittent biological samples. The analyte sensor may use any method of analyte-measurement, including enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, radiometric, or the like.

[0208] In general, analyte sensors provide at least one working electrode and at least one reference electrode, which are configured to measure a signal associated with a concentration of the analyte in the host, such as described in more detail below, and as appreciated by one skilled in the art. The output signal is typically a raw data stream that is used to provide a useful value of the measured analyte concentration in a host to the patient or doctor, for example. However, the analyte sensors of the preferred embodiments may further measure at least one additional signal. For example, in some embodiments, the additional signal is associated with the baseline and/or sensitivity of the analyte sensor, thereby enabling monitoring of baseline and/or sensitivity changes that may occur in a continuous analyte sensor over time.

[0209] In general, continuous analyte sensors define a relationship between sensor-generated measurements (for example, current in nA or digital counts after A/D conversion) and a reference measurement (for example, mg/dL or mmol/L) that are meaningful to a user (for example, patient or doctor). In the case of an implantable enzyme-based electrochemical glucose

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sensor, the sensing mechanism generally depends on phenomena that are linear with glucose concentration, for example: (1) diffusion of glucose through a membrane system (for example, biointerface membrane and membrane system) situated between implantation site and the electrode surface, (2) an enzymatic reaction within the membrane system (for example, membrane system), and (3) diffusion of the H_2O_2 to the sensor. Because of this linearity, calibration of the sensor can be understood by solving an equation:

$$y = mx + b$$

where y represents the sensor signal (counts), x represents the estimated glucose concentration (mg/dL), m represents the sensor sensitivity to glucose (counts/mg/dL), and b represents the baseline signal (counts). Because both sensitivity m and baseline (background) b change over time *in vivo*, calibration has conventionally required at least two independent, matched data pairs (x_1, y_1; x_2, y_2) to solve for m and b and thus allow glucose estimation when only the sensor signal, y is available. Matched data pairs can be created by matching reference data (for example, one or more reference glucose data points from a blood glucose meter, or the like) with substantially time corresponding sensor data (for example, one or more glucose sensor data points) to provide one or more matched data pairs, such as described in co-pending U.S. Patent Publication No. US-2005-0027463-A1.

[0210] Accordingly, in some embodiments, the sensing region is configured to measure changes in sensitivity of the analyte sensor over time, which can be used to trigger calibration, update calibration, avoid inaccurate calibration (for example, calibration during unstable periods), and/or trigger filtering of the sensor data. Namely, the analyte sensor is configured to measure a signal associated with a non-analyte constant in the host. Preferably, the non-analyte constant signal is measured beneath the membrane system on the sensor. In one example of a glucose sensor, a non-glucose constant that can be measured is oxygen, wherein a measured change in oxygen transport is indicative of a change in the sensitivity of the glucose signal, which can be measured by switching the bias potential of the working electrode, an auxiliary oxygen-measuring electrode, an oxygen sensor, or the like, as described in more detail elsewhere herein.

[0211] Alternatively or additionally, in some embodiments, the sensing region is configured to measure changes in the amount of background noise (e.g., baseline) in the signal,

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which can be used to trigger calibration, update calibration, avoid inaccurate calibration (for example, calibration during unstable periods), and/or trigger filtering of the sensor data. In one example of a glucose sensor, the baseline is composed substantially of signal contribution due to factors other than glucose (for example, interfering species, non-reaction-related hydrogen peroxide, or other electroactive species with an oxidation potential that overlaps with hydrogen peroxide). Namely, the glucose sensor is configured to measure a signal associated with the baseline (all non-glucose related current generated) measured by sensor in the host. In some embodiments, an auxiliary electrode located beneath a non-enzymatic portion of the membrane system is used to measure the baseline signal. In some embodiments, the baseline signal is subtracted from the glucose signal (which includes the baseline) to obtain the signal contribution substantially only due to glucose. Subtraction may be accomplished electronically in the sensor using a differential amplifier, digitally in the receiver, and/or otherwise in the hardware or software of the sensor or receiver as is appreciated by one skilled in the art, and as described in more detail elsewhere herein.

[0212] One skilled in the art appreciates that the above-described sensitivity and baseline signal measurements can be combined to benefit from both measurements in a single analyte sensor.

Preferred Sensor Components

[0213] In general, sensors of the preferred embodiments describe a variety of sensor configurations, wherein each sensor generally comprises two or more working electrodes, a reference and/or counter electrode, an insulator, and a membrane system. In general, the sensors can be configured to continuously measure an analyte in a biological sample, for example, in subcutaneous tissue, in a host's blood flow, and the like. Although a variety of exemplary embodiments are shown, one skilled in the art appreciates that the concepts and examples here can be combined, reduced, substituted, or otherwise modified in accordance with the teachings of the preferred embodiments and/or the knowledge of one skilled in the art.

[0214] Preferably, each exemplary sensor design (e.g., **Figs. 1A**, **2A**, **7A** through **9B**, and **11**) includes a first working electrode, wherein the working electrode is formed from known materials. In some embodiments, each electrode is formed from a fine wire with a diameter of from about 0.001 or less to about 0.010 inches or more, for example, and is formed from, *e.g.*, a

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plated insulator, a plated wire, or bulk electrically conductive material. In preferred embodiments, the working electrode comprises a wire formed from a conductive material, such as platinum, platinum-iridium, palladium, graphite, gold, carbon, conductive polymer, alloys, or the like. Although the electrodes can by formed by a variety of manufacturing techniques (bulk metal processing, deposition of metal onto a substrate, and the like), it can be advantageous to form the electrodes from plated wire (*e.g.*, platinum on steel wire) or bulk metal (*e.g.*, platinum wire). It is believed that electrodes formed from bulk metal wire provide superior performance (*e.g.*, in contrast to deposited electrodes), including increased stability of assay, simplified manufacturability, resistance to contamination (*e.g.*, which can be introduced in deposition processes), and improved surface reaction (*e.g.*, due to purity of material) without peeling or delamination.

[0215] Preferably, the working electrode is configured to measure the concentration of an analyte. In an enzymatic electrochemical sensor for detecting glucose, for example, the working electrode measures the hydrogen peroxide produced by an enzyme catalyzed reaction of the analyte being detected and creates a measurable electronic current. For example, in the detection of glucose wherein glucose oxidase produces hydrogen peroxide as a byproduct, hydrogen peroxide (H_2O_2) reacts with the surface of the working electrode producing two protons ($2H^+$), two electrons ($2e^-$) and one molecule of oxygen (O_2), which produces the electronic current being detected.

[0216] Preferably, each exemplary sensor design (e.g., **Figs. 1A**, **2A**, **7A** through **9B**, and **11**) includes at least one additional working electrode configured to measure a baseline (e.g., background noise) signal, to measure another analyte (e.g., oxygen), to generate oxygen, and/or as a transport-measuring electrode, all of which are described in more detail elsewhere herein. In general, the additional working electrode(s) can be formed as described with reference to the first working electrode. In one embodiment, the auxiliary (additional) working electrode is configured to measure a background signal, including constant and non-constant analyte signal components.

[0217] Preferably, each exemplary sensor design (e.g., **Figs. 1A**, **2A**, and **7A** through **9B**) includes a reference and/or counter electrode. In general, the reference electrode has a configuration similar to that described elsewhere herein with reference to the first working

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electrode, however may be formed from materials, such as silver, silver/silver chloride, calomel, and the like. In some embodiments, the reference electrode is integrally formed with the one or more working electrodes, however other configurations are also possible (*e.g.*, remotely located on the host's skin, or otherwise in bodily fluid contact). In some exemplary embodiments (e.g., **Figs. 1B** and **9B**, the reference electrode is helically wound around other component(s) of the sensor system. In some alternative embodiments, the reference electrode is disposed remotely from the sensor, such as but not limited to on the host's skin, as described herein.

[0218] Preferably, each exemplary sensor design (e.g., **Figs. 1A**, **2A**, **7A** through **9B**, and **11**) includes an insulator (e.g., non-conductive material) or similarly functional component. In some embodiments, one or more electrodes are covered with an insulating material, for example, a non-conductive polymer. Dip-coating, spray-coating, vapor-deposition, or other coating or deposition techniques can be used to deposit the insulating material on the electrode(s). In some embodiments, the insulator is a separate component of the system (e.g., see **Fig. 7E**) and can be formed as is appreciated by one skilled in the art. In one embodiment, the insulating material comprises parylene, which can be an advantageous polymer coating for its strength, lubricity, and electrical insulation properties. Generally, parylene is produced by vapor deposition and polymerization of para-xylylene (or its substituted derivatives). In alternative embodiments, any suitable insulating material can be used, for example, fluorinated polymers, polyethyleneterephthalate, polyurethane, polyimide, other nonconducting polymers, or the like. Glass or ceramic materials can also be employed. Other materials suitable for use include surface energy modified coating systems such as are marketed under the trade names AMC18, AMC148, AMC141, and AMC321 by Advanced Materials Components Express of Bellafonte, PA.

[0219] Preferably, each exemplary sensor design (e.g., **Figs. 1A**, **2A**, **7A** through **9B**, and **11**) includes exposed electroactive area(s). In embodiments wherein an insulator is disposed over one or more electrodes, a portion of the coated electrode(s) can be stripped or otherwise removed, for example, by hand, excimer lasing, chemical etching, laser ablation, grit-blasting (*e.g.*, with sodium bicarbonate or other suitable grit), and the like, to expose the electroactive surfaces. Alternatively, a portion of the electrode can be masked prior to depositing the insulator in order to maintain an exposed electroactive surface area. In one exemplary embodiment, grit

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blasting is implemented to expose the electroactive surfaces, preferably utilizing a grit material that is sufficiently hard to ablate the polymer material, while being sufficiently soft so as to minimize or avoid damage to the underlying metal electrode (*e.g.*, a platinum electrode). Although a variety of "grit" materials can be used (*e.g.*, sand, talc, walnut shell, ground plastic, sea salt, and the like), in some preferred embodiments, sodium bicarbonate is an advantageous grit-material because it is sufficiently hard to ablate, a coating (e.g., parylene) without damaging, an underlying conductor (e.g., platinum). One additional advantage of sodium bicarbonate blasting includes its polishing action on the metal as it strips the polymer layer, thereby eliminating a cleaning step that might otherwise be necessary. In some embodiments, the tip (e.g., end) of the sensor is cut to expose electroactive surface areas, without a need for removing insulator material from sides of insulated electrodes. In general, a variety of surfaces and surface areas can be exposed.

[0220] Preferably, each exemplary sensor design (e.g., **Figs. 1A**, **2A**, **7A** through **9B**, and **11**) includes a membrane system. Preferably, a membrane system is deposited over at least a portion of the electroactive surfaces of the sensor (working electrode(s) and optionally reference electrode) and provides protection of the exposed electrode surface from the biological environment, diffusion resistance (limitation) of the analyte if needed, a catalyst for enabling an enzymatic reaction, limitation or blocking of interferents, and/or hydrophilicity at the electrochemically reactive surfaces of the sensor interface. Some examples of suitable membrane systems are described in U.S. Patent Publication No. US-2005-0245799-A1.

[0221] In general, the membrane system includes a plurality of domains, for example, one or more of an electrode domain **24**, an optional interference domain **26**, an enzyme domain **28** (for example, including glucose oxidase), and a resistance domain **30**, as shown in **Figs. 2A** and **2B**, and can include a high oxygen solubility domain, and/or a bioprotective domain (not shown), such as is described in more detail in U.S. Patent Publication No. US-2005-0245799-A1, and such as is described in more detail below. The membrane system can be deposited on the exposed electroactive surfaces using known thin film techniques (for example, vapor deposition, spraying, electro-depositing, dipping, or the like). In alternative embodiments, however, other vapor deposition processes (e.g., physical and/or chemical vapor deposition processes) can be useful for providing one or more of the insulating and/or membrane layers, including ultrasonic

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vapor deposition, electrostatic deposition, evaporative deposition, deposition by sputtering, pulsed laser deposition, high velocity oxygen fuel deposition, thermal evaporator deposition, electron beam evaporator deposition, deposition by reactive sputtering molecular beam epitaxy, atmospheric pressure chemical vapor deposition (CVD), atomic layer CVD, hot wire CVD, low-pressure CVD, microwave plasma-assisted CVD, plasma-enhanced CVD, rapid thermal CVD, remote plasma-enhanced CVD, and ultra-high vacuum CVD, for example. However, the membrane system can be disposed over (or deposited on) the electroactive surfaces using any known method, as will be appreciated by one skilled in the art.

[0222] In some embodiments, one or more domains of the membrane systems are formed from materials such as silicone, polytetrafluoroethylene, polyethylene-co-tetrafluoroethylene, polyolefin, polyester, polycarbonate, biostable polytetrafluoroethylene, homopolymers, copolymers, terpolymers of polyurethanes, polypropylene (PP), polyvinylchloride (PVC), polyvinylidene fluoride (PVDF), polybutylene terephthalate (PBT), polymethylmethacrylate (PMMA), polyether ether ketone (PEEK), polyurethanes, cellulosic polymers, polysulfones and block copolymers thereof including, for example, di-block, tri-block, alternating, random and graft copolymers. U.S. Patent Publication No. US-2005-0245799-A1 describes biointerface and membrane system configurations and materials that may be applied to the preferred embodiments.

Electrode Domain

[0223] In some embodiments, the membrane system comprises an optional electrode domain **24** (**Figs. 2A-2B**). The electrode domain is provided to ensure that an electrochemical reaction occurs between the electroactive surfaces of the working electrode and the reference electrode, and thus the electrode domain is preferably situated more proximal to the electroactive surfaces than the interference and/or enzyme domain. Preferably, the electrode domain includes a coating that maintains a layer of water at the electrochemically reactive surfaces of the sensor. In other words, the electrode domain is present to provide an environment between the surfaces of the working electrode and the reference electrode, which facilitates an electrochemical reaction between the electrodes. For example, a humectant in a binder material can be employed as an electrode domain; this allows for the full transport of ions in the aqueous environment. The electrode domain can also assist in stabilizing the operation of the sensor by accelerating

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electrode start-up and drifting problems caused by inadequate electrolyte. The material that forms the electrode domain can also provide an environment that protects against pH-mediated damage that can result from the formation of a large pH gradient due to the electrochemical activity of the electrodes.

[0224] In one embodiment, the electrode domain includes a flexible, water-swellable, hydrogel film having a "dry film" thickness of from about 0.05 micron or less to about 20 microns or more, more preferably from about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5 microns to about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 19.5 microns, and more preferably still from about 2, 2.5 or 3 microns to about 3.5, 4, 4.5, or 5 microns. "Dry film" thickness refers to the thickness of a cured film cast from a coating formulation by standard coating techniques.

[0225] In certain embodiments, the electrode domain is formed of a curable mixture of a urethane polymer and a hydrophilic polymer. Particularly preferred coatings are formed of a polyurethane polymer having carboxylate or hydroxyl functional groups and non-ionic hydrophilic polyether segments, wherein the polyurethane polymer is crosslinked with a water-soluble carbodiimide (*e.g.*, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)) in the presence of polyvinylpyrrolidone and cured at a moderate temperature of about 50°C.

[0226] In some preferred embodiments, the electrode domain is formed from a hydrophilic polymer such as polyvinylpyrrolidone (PVP). An electrode domain formed from PVP has been shown to reduce break-in time of analyte sensors; for example, a glucose sensor utilizing a cellulosic-based interference domain such as described in more detail below.

[0227] Preferably, the electrode domain is deposited by vapor deposition, spray coating, dip coating, or other thin film techniques on the electroactive surfaces of the sensor. In one preferred embodiment, the electrode domain is formed by dip-coating the electroactive surfaces in an electrode layer solution and curing the domain for a time of from about 15 minutes to about 30 minutes at a temperature of from about 40°C to about 55°C (and can be accomplished under vacuum (*e.g.*, 20 to 30 mmHg)). In embodiments wherein dip-coating is used to deposit the electrode domain, a preferred insertion rate of from about 1 to about 3 inches per minute into the electrode layer solution, with a preferred dwell time of from about 0.5 to about 2 minutes in the electrode layer solution, and a preferred withdrawal rate of from about

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0.25 to about 2 inches per minute from the electrode layer solution provide a functional coating. However, values outside of those set forth above can be acceptable or even desirable in certain embodiments, for example, depending upon solution viscosity and solution surface tension, as is appreciated by one skilled in the art. In one embodiment, the electroactive surfaces of the electrode system are dip-coated one time (one layer) and cured at 50°C under vacuum for 20 minutes.

[0228] Although an independent electrode domain is described herein, in some embodiments sufficient hydrophilicity can be provided in the interference domain and/or enzyme domain (the domain adjacent to the electroactive surfaces) so as to provide for the full transport of ions in the aqueous environment (*e.g.* without a distinct electrode domain). In these embodiments, an electrode domain is not necessary.

Interference Domain

[0229] Interferents are molecules or other species that are reduced or oxidized at the electrochemically reactive surfaces of the sensor, either directly or via an electron transfer agent, to produce a false positive analyte signal. In preferred embodiments, an optional interference domain **26** is provided that substantially restricts, resists, or blocks the flow of one or more interfering species (**Figs. 2A-2B**). Some known interfering species for a glucose sensor, as described in more detail above, include acetaminophen, ascorbic acid, bilirubin, cholesterol, creatinine, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, triglycerides, and uric acid. In general, the interference domain of the preferred embodiments is less permeable to one or more of the interfering species than to the analyte, e.g., glucose.

[0230] In one embodiment, the interference domain is formed from one or more cellulosic derivatives. In general, cellulosic derivatives include polymers such as cellulose acetate, cellulose acetate butyrate, 2-hydroxyethyl cellulose, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate trimellitate, and the like.

[0231] In one preferred embodiment, the interference domain is formed from cellulose acetate butyrate. Cellulose acetate butyrate with a molecular weight of about 10,000 daltons to about 75,000 daltons, preferably from about 15,000, 20,000, or 25,000 daltons to about 50,000, 55,000, 60,000, 65,000, or 70,000 daltons, and more preferably about 20,000 daltons is

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employed. In certain embodiments, however, higher or lower molecular weights can be preferred. Additionally, a casting solution or dispersion of cellulose acetate butyrate at a weight percent of about 15% to about 25%, preferably from about 15%, 16%, 17%, 18%, 19% to about 20%, 21%, 22%, 23%, 24% or 25%, and more preferably about 18% is preferred. Preferably, the casting solution includes a solvent or solvent system, for example an acetone:ethanol solvent system. Higher or lower concentrations can be preferred in certain embodiments. A plurality of layers of cellulose acetate butyrate can be advantageously combined to form the interference domain in some embodiments, for example, three layers can be employed. It can be desirable to employ a mixture of cellulose acetate butyrate components with different molecular weights in a single solution, or to deposit multiple layers of cellulose acetate butyrate from different solutions comprising cellulose acetate butyrate of different molecular weights, different concentrations, and/or different chemistries (e.g., functional groups). It can also be desirable to include additional substances in the casting solutions or dispersions, e.g., functionalizing agents, crosslinking agents, other polymeric substances, substances capable of modifying the hydrophilicity/hydrophobicity of the resulting layer, and the like.

[0232] In one alternative embodiment, the interference domain is formed from cellulose acetate. Cellulose acetate with a molecular weight of about 30,000 daltons or less to about 100,000 daltons or more, preferably from about 35,000, 40,000, or 45,000 daltons to about 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, or 95,000 daltons, and more preferably about 50,000 daltons is preferred. Additionally, a casting solution or dispersion of cellulose acetate at a weight percent of about 3% to about 10%, preferably from about 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, or 6.5% to about 7.5%, 8.0%, 8.5%, 9.0%, or 9.5%, and more preferably about 8% is preferred. In certain embodiments, however, higher or lower molecular weights and/or cellulose acetate weight percentages can be preferred. It can be desirable to employ a mixture of cellulose acetates with molecular weights in a single solution, or to deposit multiple layers of cellulose acetate from different solutions comprising cellulose acetates of different molecular weights, different concentrations, or different chemistries (e.g., functional groups). It can also be desirable to include additional substances in the casting solutions or dispersions such as described in more detail above.

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[0233] Layer(s) prepared from combinations of cellulose acetate and cellulose acetate butyrate, or combinations of layer(s) of cellulose acetate and layer(s) of cellulose acetate butyrate can also be employed to form the interference domain.

[0234] In some alternative embodiments, additional polymers, such as Nafion®, can be used in combination with cellulosic derivatives to provide equivalent and/or enhanced function of the interference domain. As one example, a 5 wt % Nafion® casting solution or dispersion can be used in combination with a 8 wt % cellulose acetate casting solution or dispersion, e.g., by dip coating at least one layer of cellulose acetate and subsequently dip coating at least one layer Nafion® onto a needle-type sensor such as described with reference to the preferred embodiments. Any number of coatings or layers formed in any order may be suitable for forming the interference domain of the preferred embodiments.

[0235] In some alternative embodiments, more than one cellulosic derivative can be used to form the interference domain of the preferred embodiments. In general, the formation of the interference domain on a surface utilizes a solvent or solvent system in order to solvate the cellulosic derivative (or other polymer) prior to film formation thereon. In preferred embodiments, acetone and ethanol are used as solvents for cellulose acetate; however one skilled in the art appreciates the numerous solvents that are suitable for use with cellulosic derivatives (and other polymers). Additionally, one skilled in the art appreciates that the preferred relative amounts of solvent can be dependent upon the cellulosic derivative (or other polymer) used, its molecular weight, its method of deposition, its desired thickness, and the like. However, a percent solute of from about 1% to about 25% is preferably used to form the interference domain solution so as to yield an interference domain having the desired properties. The cellulosic derivative (or other polymer) used, its molecular weight, method of deposition, and desired thickness can be adjusted, depending upon one or more other of the parameters, and can be varied accordingly as is appreciated by one skilled in the art.

[0236] In some alternative embodiments, other polymer types that can be utilized as a base material for the interference domain including polyurethanes, polymers having pendant ionic groups, and polymers having controlled pore size, for example. In one such alternative embodiment, the interference domain includes a thin, hydrophobic membrane that is non-swellable and restricts diffusion of low molecular weight species. The interference domain is

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permeable to relatively low molecular weight substances, such as hydrogen peroxide, but restricts the passage of higher molecular weight substances, including glucose and ascorbic acid. Other systems and methods for reducing or eliminating interference species that can be applied to the membrane system of the preferred embodiments are described in U.S. Patent Publication No. US-2005-0115832-A1, U.S. Patent Publication No. US-2005-0176136-A1, U.S. Patent Publication No. US-2005-0161346-A1, and U.S. Patent Publication No. US-2005-0143635-A1. In some alternative embodiments, a distinct interference domain is not included.

[0237] In preferred embodiments, the interference domain is deposited directly onto the electroactive surfaces of the sensor for a domain thickness of from about 0.05 micron or less to about 20 microns or more, more preferably from about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5 microns to about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 19.5 microns, and more preferably still from about 1, 1.5 or 2 microns to about 2.5 or 3 microns. Thicker membranes can also be desirable in certain embodiments, but thinner membranes are generally preferred because they have a lower impact on the rate of diffusion of hydrogen peroxide from the enzyme membrane to the electrodes.

[0238] In general, the membrane systems of the preferred embodiments can be formed and/or deposited on the exposed electroactive surfaces (*e.g.*, one or more of the working and reference electrodes) using known thin film techniques (for example, casting, spray coating, drawing down, electro-depositing, dip coating, and the like), however casting or other known application techniques can also be utilized. Preferably, the interference domain is deposited by vapor deposition, spray coating, or dip coating. In one exemplary embodiment of a needle-type (transcutaneous) sensor such as described herein, the interference domain is formed by dip coating the sensor into an interference domain solution using an insertion rate of from about 20 inches/min to about 60 inches/min, preferably 40 inches/min, a dwell time of from about 0 minute to about 5 seconds, preferably 0 seconds, and a withdrawal rate of from about 20 inches/minute to about 60 inches/minute, preferably about 40 inches/minute, and curing (drying) the domain from about 1 minute to about 30 minutes, preferably from about 3 minutes to about 15 minutes (and can be accomplished at room temperature or under vacuum (*e.g.*, 20 to 30 mmHg)). In one exemplary embodiment including cellulose acetate butyrate interference domain, a 3-minute cure (i.e., dry) time is preferred between each layer applied. In another

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exemplary embodiment employing a cellulose acetate interference domain, a 15-minute cure (i.e., dry) time is preferred between each layer applied.

[0239] The dip process can be repeated at least one time and up to 10 times or more. The preferred number of repeated dip processes depends upon the cellulosic derivative(s) used, their concentration, conditions during deposition (e.g., dipping) and the desired thickness (*e.g.*, sufficient thickness to provide functional blocking of (or resistance to) certain interferents), and the like. In some embodiments, 1 to 3 microns may be preferred for the interference domain thickness; however, values outside of these can be acceptable or even desirable in certain embodiments, for example, depending upon viscosity and surface tension, as is appreciated by one skilled in the art. In one exemplary embodiment, an interference domain is formed from three layers of cellulose acetate butyrate. In another exemplary embodiment, an interference domain is formed from 10 layers of cellulose acetate. In another exemplary embodiment, an interference domain is formed of one relatively thicker layer of cellulose acetate butyrate. In yet another exemplary embodiment, an interference domain is formed of four relatively thinner layers of cellulose acetate butyrate. In alternative embodiments, the interference domain can be formed using any known method and combination of cellulose acetate and cellulose acetate butyrate, as will be appreciated by one skilled in the art.

[0240] In some embodiments, the electroactive surface can be cleaned prior to application of the interference domain. In some embodiments, the interference domain of the preferred embodiments can be useful as a bioprotective or biocompatible domain, namely, a domain that interfaces with host tissue when implanted in an animal (*e.g.*, a human) due to its stability and biocompatibility.

Enzyme Domain

[0241] In preferred embodiments, the membrane system further includes an enzyme domain **28** disposed more distally from the electroactive surfaces than the interference domain; however other configurations can be desirable (**Figs. 2A-2B**). In the preferred embodiments, the enzyme domain provides an enzyme to catalyze the reaction of the analyte and its co-reactant, as described in more detail below. In the preferred embodiments of a glucose sensor, the enzyme domain includes glucose oxidase; however other oxidases, for example, galactose oxidase or uricase oxidase, can also be used.

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[0242] For an enzyme-based electrochemical glucose sensor to perform well, the sensor's response is preferably limited by neither enzyme activity nor co-reactant concentration. Because enzymes, including glucose oxidase (GOx), are subject to deactivation as a function of time even in ambient conditions, this behavior is compensated for in forming the enzyme domain. Preferably, the enzyme domain is constructed of aqueous dispersions of colloidal polyurethane polymers including the enzyme. However, in alternative embodiments the enzyme domain is constructed from an oxygen enhancing material, for example, silicone, or fluorocarbon, in order to provide a supply of excess oxygen during transient ischemia. Preferably, the enzyme is immobilized within the domain. See, e.g., U.S. Patent Publication No. US-2005-0054909-A1.

[0243] In preferred embodiments, the enzyme domain is deposited onto the interference domain for a domain thickness of from about 0.05 micron or less to about 20 microns or more, more preferably from about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5 microns to about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 19.5 microns, and more preferably still from about 2, 2.5 or 3 microns to about 3.5, 4, 4.5, or 5 microns. However in some embodiments, the enzyme domain can be deposited directly onto the electroactive surfaces. Preferably, the enzyme domain is deposited by spray or dip coating. In one embodiment of needle-type (transcutaneous) sensor such as described herein, the enzyme domain is formed by dip coating the interference domain coated sensor into an enzyme domain solution and curing the domain for from about 15 to about 30 minutes at a temperature of from about 40°C to about 55°C (and can be accomplished under vacuum (*e.g.*, 20 to 30 mmHg)). In embodiments wherein dip coating is used to deposit the enzyme domain at room temperature, a preferred insertion rate of from about 0.25 inch per minute to about 3 inches per minute, with a preferred dwell time of from about 0.5 minutes to about 2 minutes, and a preferred withdrawal rate of from about 0.25 inch per minute to about 2 inches per minute provides a functional coating. However, values outside of those set forth above can be acceptable or even desirable in certain embodiments, for example, depending upon viscosity and surface tension, as is appreciated by one skilled in the art. In one embodiment, the enzyme domain is formed by dip coating two times (namely, forming two layers) in an enzyme domain solution and curing at 50°C under vacuum for 20 minutes. However, in some embodiments, the enzyme domain can be

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formed by dip coating and/or spray coating one or more layers at a predetermined concentration of the coating solution, insertion rate, dwell time, withdrawal rate, and/or desired thickness.

Resistance Domain

[0244] In preferred embodiments, the membrane system includes a resistance domain **30** disposed more distal from the electroactive surfaces than the enzyme domain (**Figs. 2A-2B**). In general, the resistance domain is configured and arranged to attenuate flux (e.g., diffusion) of a measured/measurable species (e.g., an analyte and/or co-reactant, such as but not limited to glucose, H_2O_2 or other species) therethrough. `Although the following description is directed to a resistance domain for a glucose sensor, the resistance domain can be modified for other analytes and co-reactants as well.

[0245] There exists a molar excess of glucose relative to the amount of oxygen in blood; that is, for every free oxygen molecule in extracellular fluid, there are typically more than 100 glucose molecules present (see Updike *et al.*, Diabetes Care 5:207-21(1982)). However, an immobilized enzyme-based glucose sensor employing oxygen as co-reactant is preferably supplied with oxygen in non-rate-limiting excess in order for the sensor to respond linearly to changes in glucose concentration, while not responding to changes in oxygen concentration. Specifically, when a glucose-monitoring reaction is oxygen limited, linearity is not achieved above minimal concentrations of glucose. Without a semipermeable membrane situated over the enzyme domain to control the flux of glucose and oxygen, a linear response to glucose levels can be obtained only for glucose concentrations of up to about 40 mg/dL. However, in a clinical setting, a linear response to glucose levels is desirable up to at least about 400 mg/dL.

[0246] The resistance domain includes a semipermeable membrane that controls the flux of oxygen and glucose to the underlying enzyme domain, preferably rendering oxygen in a non-rate-limiting excess (e.g., by attenuating glucose flux). As a result, the upper limit of linearity of glucose measurement is extended to a much higher value than that which is achieved without the resistance domain. In one embodiment, the resistance domain exhibits an oxygen to glucose permeability ratio of from about 50:1 or less to about 400:1 or more, preferably about 200:1. As a result, one-dimensional reactant diffusion is adequate to provide excess oxygen at all reasonable glucose and oxygen concentrations found in the subcutaneous matrix (See Rhodes *et al.*, Anal. Chem., 66:1520-1529 (1994)).

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[0247] In alternative embodiments, a lower ratio of oxygen-to-glucose can be sufficient to provide excess oxygen by using a high oxygen solubility domain (for example, a silicone or fluorocarbon-based material or domain) to enhance the supply/transport of oxygen to the enzyme domain. If more oxygen is supplied to the enzyme, then more glucose can also be supplied to the enzyme without creating an oxygen rate-limiting excess. In alternative embodiments, the resistance domain is formed from a silicone composition, such as is described in U.S. Patent Publication No. US-2005-0090607-A1.

[0248] In a preferred embodiment, the resistance domain includes a polyurethane membrane with both hydrophilic and hydrophobic regions to control the diffusion of glucose and oxygen to an analyte sensor, the membrane being fabricated easily and reproducibly from commercially available materials. A suitable hydrophobic polymer component is a polyurethane, or polyetherurethaneurea. Polyurethane is a polymer produced by the condensation reaction of a diisocyanate and a difunctional hydroxyl-containing material. A polyurethaneurea is a polymer produced by the condensation reaction of a diisocyanate and a difunctional amine-containing material. Preferred diisocyanates include aliphatic diisocyanates containing from about 4 to about 8 methylene units. Diisocyanates containing cycloaliphatic moieties can also be useful in the preparation of the polymer and copolymer components of the membranes of preferred embodiments. The material that forms the basis of the hydrophobic matrix of the resistance domain can be any of those known in the art as appropriate for use as membranes in sensor devices and as having sufficient permeability to allow relevant compounds to pass through it, for example, to allow an oxygen molecule to pass through the membrane from the sample under examination in order to reach the active enzyme or electrochemical electrodes. Examples of materials which can be used to make non-polyurethane type membranes include vinyl polymers, polyethers, polyesters, polyamides, inorganic polymers such as polysiloxanes and polycarbosiloxanes, natural polymers such as cellulosic and protein based materials, and mixtures or combinations thereof.

[0249] In a preferred embodiment, the hydrophilic polymer component is polyethylene oxide. For example, one useful hydrophobic-hydrophilic copolymer component is a polyurethane polymer that includes about 20% hydrophilic polyethylene oxide. The polyethylene oxide portions of the copolymer are thermodynamically driven to separate from the hydrophobic

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portions of the copolymer and the hydrophobic polymer component. The 20% polyethylene oxide-based soft segment portion of the copolymer used to form the final blend affects the water pick-up and subsequent glucose permeability of the membrane.

[0250] In some embodiments, the resistance domain is formed from a silicone polymer modified to allow analyte (e.g., glucose) transport.

[0251] In some embodiments, the resistance domain is formed from a silicone polymer/hydrophobic-hydrophilic polymer blend. In one embodiment, The hydrophobic-hydrophilic polymer for use in the blend may be any suitable hydrophobic-hydrophilic polymer, including but not limited to components such as polyvinylpyrrolidone (PVP), polyhydroxyethyl methacrylate, polyvinylalcohol, polyacrylic acid, polyethers such as polyethylene glycol or polypropylene oxide, and copolymers thereof, including, for example, di-block, tri-block, alternating, random, comb, star, dendritic, and graft copolymers (block copolymers are discussed in U.S. Patent Nos. 4,803,243 and 4,686,044, which are incorporated herein by reference). In one embodiment, the hydrophobic-hydrophilic polymer is a copolymer of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO). Suitable such polymers include, but are not limited to, PEO-PPO diblock copolymers, PPO-PEO-PPO triblock copolymers, PEO-PPO-PEO triblock copolymers, alternating block copolymers of PEO-PPO, random copolymers of ethylene oxide and propylene oxide, and blends thereof. In some embodiments, the copolymers may be optionally substituted with hydroxy substituents. Commercially available examples of PEO and PPO copolymers include the PLURONIC® brand of polymers available from BASF®. In one embodiment, PLURONIC® F-127 is used. Other PLURONIC® polymers include PPO-PEO-PPO triblock copolymers (e.g., PLURONIC® R products). Other suitable commercial polymers include, but are not limited to, SYNPERONICS® products available from UNIQEMA®.

[0252] In preferred embodiments, the resistance domain is deposited onto the enzyme domain to yield a domain thickness of from about 0.05 microns or less to about 20 microns or more, more preferably from about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5 microns to about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 19.5 microns, and more preferably still from about 2, 2.5 or 3 microns to about 3.5, 4, 4.5, or 5 microns. Preferably, the resistance domain is deposited onto the enzyme domain by vapor deposition, spray coating, or dip coating. In one preferred embodiment, spray coating is the

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preferred deposition technique. The spraying process atomizes and mists the solution, and therefore most or all of the solvent is evaporated prior to the coating material settling on the underlying domain, thereby minimizing contact of the solvent with the enzyme.

[0253] In a preferred embodiment, the resistance domain is deposited on the enzyme domain by spray coating a solution of from about 1 wt. % to about 5 wt. % polymer and from about 95 wt. % to about 99 wt. % solvent. In spraying a solution of resistance domain material, including a solvent, onto the enzyme domain, it is desirable to mitigate or substantially reduce any contact with enzyme of any solvent in the spray solution that can deactivate the underlying enzyme of the enzyme domain. Tetrahydrofuran (THF) is one solvent that minimally or negligibly affects the enzyme of the enzyme domain upon spraying. Other solvents can also be suitable for use, as is appreciated by one skilled in the art.

[0254] Preferably, each exemplary sensor design (e.g., Figs. 1A, 2A, and 7A through 9B) includes electronic connections, for example, one or more electrical contacts configured to provide secure electrical contact between the sensor and associated electronics. In some embodiments, the electrodes and membrane systems of the preferred embodiments are coaxially formed, namely, the electrodes and/or membrane system all share the same central axis. While not wishing to be bound by theory, it is believed that a coaxial design of the sensor enables a symmetrical design without a preferred bend radius. Namely, in contrast to prior art sensors comprising a substantially planar configuration that can suffer from regular bending about the plane of the sensor, the coaxial design of the preferred embodiments do not have a preferred bend radius and therefore are not subject to regular bending about a particular plane (which can cause fatigue failures and the like). However, non-coaxial sensors can be implemented with the sensor system of the preferred embodiments.

[0255] In addition to the above-described advantages, the coaxial sensor design of the preferred embodiments enables the diameter of the connecting end of the sensor (proximal portion) to be substantially the same as that of the sensing end (distal portion) such that a needle is able to insert the sensor into the host and subsequently slide back over the sensor and release the sensor from the needle, without slots or other complex multi-component designs, as described in detail in U.S. Patent Publication No. US-2006-0063142-A1 and U.S. Patent

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Publication No. US-2007-0197889-A1 which are incorporated in their entirety herein by reference.

Exemplary Continuous Sensor Configurations

[0256] In some embodiments, the sensor is an enzyme-based electrochemical sensor, wherein the glucose-measuring working electrode **16** (e.g., **Figs. 1A-1B)** measures the hydrogen peroxide produced by the enzyme catalyzed reaction of glucose being detected and creates a measurable electronic current (for example, detection of glucose utilizing glucose oxidase produces hydrogen peroxide (H_2O_2) as a by product, H_2O_2 reacts with the surface of the working electrode producing two protons ($2H^+$), two electrons ($2e^-$) and one molecule of oxygen (O_2) which produces the electronic current being detected, see **Fig. 10**), such as described in more detail elsewhere herein and as is appreciated by one skilled in the art. Preferably, one or more potentiostat is employed to monitor the electrochemical reaction at the electroactive surface of the working electrode(s). The potentiostat applies a constant potential to the working electrode and its associated reference electrode to determine the current produced at the working electrode. The current that is produced at the working electrode (and flows through the circuitry to the counter electrode) is substantially proportional to the amount of H_2O_2 that diffuses to the working electrodes. The output signal is typically a raw data stream that is used to provide a useful value of the measured analyte concentration in a host to the patient or doctor, for example.

[0257] Some alternative analyte sensors that can benefit from the systems and methods of the preferred embodiments include U.S. Patent No. 5,711,861 to Ward et al., U.S. Patent No. 6,642,015 to Vachon et al., U.S. Patent No. 6,654,625 to Say et al., U.S. Patent 6,565,509 to Say et al., U.S. Patent No. 6,514,718 to Heller, U.S. Patent No. 6,465,066 to Essenpreis et al., U.S. Patent No. 6,214,185 to Offenbacher et al., U.S. Patent No. 5,310,469 to Cunningham et al., and U.S. Patent No. 5,683,562 to Shaffer et al., .S. Patent 6,579,690 to Bonnecaze et al., U.S. Patent 6,484,046 to Say et al. , U.S. Patent 6,512,939 to Colvin et al., U.S. Patent 6,424,847 to Mastrototaro et al., U.S. Patent 6,424,847 to Mastrototaro et al, for example. All of the above patents are incorporated in their entirety herein by reference and are not inclusive of all applicable analyte sensors; in general, it should be understood that the disclosed embodiments are applicable to a variety of analyte sensor configurations.

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[0258] Although some exemplary glucose sensor configurations are described in detail below, it should be understood that the systems and methods described herein can be applied to any device capable of continually or continuously detecting a concentration of analyte of interest and providing an output signal that represents the concentration of that analyte, for example oxygen, lactose, hormones, cholesterol, medicaments, viruses, or the like.

[0259] **Fig. 1A** is a perspective view of an analyte sensor, including an implantable body with a sensing region including a membrane system disposed thereon. In the illustrated embodiment, the analyte sensor **10a** includes a body **12** and a sensing region **14** including membrane and electrode systems configured to measure the analyte. In this embodiment, the sensor **10a** is preferably wholly implanted into the subcutaneous tissue of a host, such as described in U.S. Patent Publication No. US-2006-0015020-A1; U.S. Patent Publication No. US-2005-0245799-A1; U.S. Patent Publication No. US-2005-0192557-A1; U.S. Patent Publication No. US-2004-0199059-A1; U.S. Patent Publication No. US-2005-0027463-A1; and U.S. Patent Number 6,001,067 issued December 14, 1999 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS," each of which are incorporated herein by reference in their entirety.

[0260] The body **12** of the sensor **10a** can be formed from a variety of materials, including metals, ceramics, plastics, or composites thereof. In one embodiment, the sensor is formed from thermoset molded around the sensor electronics. U.S. Patent Publication No. US-2004-0199059-A1 discloses suitable configurations for the body, and is incorporated by reference in its entirety.

[0261] In some embodiments, the sensing region **14** includes a glucose-measuring working electrode **16**, an optional auxiliary working electrode **18**, a reference electrode **20**, and a counter electrode **24**. Generally, the sensing region **14** includes means to measure two different signals, 1) a first signal associated with glucose and non-glucose related electroactive compounds having a first oxidation potential, wherein the first signal is measured at the glucose-measuring working electrode disposed beneath an active enzymatic portion of a membrane system, and 2) a second signal associated with the baseline and/or sensitivity of the glucose sensor. In some embodiments, wherein the second signal measures sensitivity, the signal is associated with at least one non-glucose constant data point, for example, wherein the auxiliary working electrode

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18 is configured to measure oxygen. In some embodiments, wherein the second signal measures baseline, the signal is associated with non-glucose related electroactive compounds having the first oxidation potential, wherein the second signal is measured at an auxiliary working electrode **18** and is disposed beneath a non-enzymatic portion of the membrane system, such as described in more detail elsewhere herein.

[0262] Preferably, a membrane system (see **Fig. 2A**) is deposited over the electroactive surfaces of the sensor **10a** and includes a plurality of domains or layers, such as described in more detail below, with reference to **Figs. 2A** and **2B**. In general, the membrane system may be disposed over (deposited on) the electroactive surfaces using methods appreciated by one skilled in the art. See U.S. Patent Publication No. US-2006-0015020-A1.

[0263] The sensing region **14** comprises electroactive surfaces, which are in contact with an electrolyte phase (not shown), which is a free-flowing fluid phase disposed between the membrane system **22** and the electroactive surfaces. In this embodiment, the counter electrode is provided to balance the current generated by the species being measured at the working electrode. In the case of glucose oxidase based analyte sensors, the species being measured at the working electrode is H_2O_2. Glucose oxidase catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate according to the following reaction:

$$\text{Glucose} + O_2 \rightarrow \text{Gluconate} + H_2O_2$$

[0264] The change in H_2O_2 can be monitored to determine glucose concentration because for each glucose molecule metabolized, there is a proportional change in the product H_2O_2 (see **Fig. 10**). Oxidation of H_2O_2 by the working electrode is balanced by reduction of ambient oxygen, enzyme generated H_2O_2, or other reducible species at the counter electrode. The H_2O_2 produced from the glucose oxidase reaction further reacts at the surface of the working electrode and produces two protons ($2H^+$), two electrons ($2e^-$), and one oxygen molecule (O_2). Preferably, one or more potentiostats are employed to monitor the electrochemical reaction at the electroactive surface of the working electrode(s). The potentiostat applies a constant potential to the working electrode and its associated reference electrode to determine the current produced at the working electrode. The current that is produced at the working electrode (and flows through the circuitry to the counter electrode) is substantially proportional to the amount of H_2O_2 that diffuses to the working electrodes. The output signal is typically a raw data stream that is used to

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provide a useful value of the measured analyte concentration in a host to the patient or doctor, for example.

[0265] **Fig. 1B** is a schematic view of an alternative exemplary embodiment of a continuous analyte sensor **10b**, also referred to as an in-dwelling or transcutaneous analyte sensor in some circumstances, particularly illustrating the *in vivo* portion of the sensor. In this embodiment, the *in vivo* portion of the sensor **10b** is the portion adapted for insertion under the host's skin, in a host's blood stream, or other biological sample, while an *ex vivo* portion of the sensor (not shown) is the portion that remains above the host's skin after sensor insertion and operably connects to an electronics unit. In the illustrated embodiment, the analyte sensor **10b** is coaxial and includes three electrodes: a glucose-measuring working electrode **16**, an optional auxiliary working electrode **18**, and at least one additional electrode **20**, which may function as a counter and/or reference electrode, hereinafter referred to as the reference electrode **20**. Generally, the sensor **10b** may include the ability to measure two different signals, 1) a first signal associated with glucose and non-glucose related electroactive compounds having a first oxidation potential, wherein the first signal is measured at the glucose-measuring working electrode disposed beneath an active enzymatic portion of a membrane system, and 2) a second signal associated with the baseline and/or sensitivity of the glucose sensor, such as described in more detail above with reference to **Fig. 1A**.

[0266] One skilled in the art appreciates that the analyte sensor of **Fig. 1B** can have a variety of configurations. In one exemplary embodiment, the sensor is generally configured of a first working electrode, a second working electrode, and a reference electrode. In one exemplary configuration, the first working electrode **16** is a central metal wire or plated non-conductive rod/filament/fiber and the second working and reference electrodes (**20** and **18**, respectively OR **18** and **20**, respectively) are coiled around the first working electrode **16**. In another exemplary configuration, the first working electrode is a central wire, as depicted in **Fig. 1B**, the second working electrode is coiled around the first working electrode, and the reference electrode is disposed remotely from the sensor, as described herein. In another exemplary configuration, the first and second working electrodes (**20** and **18**) are coiled around a supporting rod **16** of insulating material. The reference electrode (not shown) can be disposed remotely from the sensor, as described herein, or disposed on the non-conductive supporting rod **16**. In still another

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exemplary configuration, the first and second working electrodes (**20** and **18**) are coiled around a reference electrode **16** (not to scale).

[0267] Preferably, each electrode is formed from a fine wire, with a diameter in the range of 0.001 to 0.010 inches, for example, and may be formed from plated wire or bulk material, however the electrodes may be deposited on a substrate or other known configurations as is appreciated by one skilled in the art.

[0268] In one embodiment, the glucose-measuring working electrode **16** comprises a wire formed from a conductive material, such as platinum, palladium, graphite, gold, carbon, conductive polymer, or the like. Alternatively, the glucose-measuring working electrode **16** can be formed of a non-conductive fiber or rod that is plated with a conductive material. The glucose-measuring working electrode **16** is configured and arranged to measure the concentration of glucose. The glucose-measuring working electrode **16** is covered with an insulating material, for example a non-conductive polymer. Dip-coating, spray-coating, or other coating or deposition techniques can be used to deposit the insulating material on the working electrode, for example. In one preferred embodiment, the insulating material comprises Parylene, which can be an advantageous conformal coating for its strength, lubricity, and electrical insulation properties, however, a variety of other insulating materials can be used, for example, fluorinated polymers, polyethyleneterephthalate, polyurethane, polyimide, or the like.

[0269] In this embodiment, the auxiliary working electrode **18** comprises a wire formed from a conductive material, such as described with reference to the glucose-measuring working electrode **16** above. Preferably, the reference electrode **20**, which may function as a reference electrode alone, or as a dual reference and counter electrode, is formed from silver, Silver/Silver chloride, or the like.

[0270] Preferably, the electrodes are juxtapositioned and/or twisted with or around each other; however other configurations are also possible. In one example, the auxiliary working electrode **18** and reference electrode **20** may be helically wound around the glucose-measuring working electrode **16** as illustrated in **Fig. 1B**. Alternatively, the auxiliary working electrode **18** and reference electrode **20** may be formed as a double helix around a length of the glucose-measuring working electrode **16**. In some embodiments, the working electrode, auxiliary working electrode and reference electrodes may be formed as a triple helix. The

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assembly of wires may then be optionally coated together with an insulating material, similar to that described above, in order to provide an insulating attachment. Some portion of the coated assembly structure is then stripped, for example using an excimer laser, chemical etching, or the like, to expose the necessary electroactive surfaces. In some alternative embodiments, additional electrodes may be included within the assembly, for example, a three-electrode system (including separate reference and counter electrodes) as is appreciated by one skilled in the art.

[0271] **Figs. 2A** and **2B** are schematic views membrane systems in some embodiments that may be disposed over the electroactive surfaces of an analyte sensors of **Fig. 1A** and **1B**, respectively, wherein the membrane system includes one or more of the following domains: a resistance domain **30**, an enzyme domain **28**, an optional interference domain **26**, and an electrolyte domain **24**, such as described in more detail below. However, it is understood that the membrane system **22** can be modified for use in other sensors, by including only one or more of the domains, additional domains not recited above, or for other sensor configurations. For example, the interference domain can be removed when other methods for removing interferants are utilized, such as an auxiliary electrode for measuring and subtracting out signal due to interferants. As another example, an "oxygen antenna domain" composed of a material that has higher oxygen solubility than aqueous media so that it concentrates oxygen from the biological fluid surrounding the biointerface membrane can be added. The oxygen antenna domain can then act as an oxygen source during times of minimal oxygen availability and has the capacity to provide on demand a higher rate of oxygen delivery to facilitate oxygen transport to the membrane. This enhances function in the enzyme reaction domain and at the counter electrode surface when glucose conversion to hydrogen peroxide in the enzyme domain consumes oxygen from the surrounding domains. Thus, this ability of the oxygen antenna domain to apply a higher flux of oxygen to critical domains when needed improves overall sensor function.

[0272] In some embodiments, the membrane system generally provides one or more of the following functions: 1) protection of the exposed electrode surface from the biological environment, 2) diffusion resistance (limitation) of the analyte, 3) a catalyst for enabling an enzymatic reaction, 4) optionally limitation or blocking of interfering species, and 5) hydrophilicity at the electrochemically reactive surfaces of the sensor interface, such as described in U.S. Patent Publication No. US-2005-0245799-A1. In some embodiments, the membrane

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system additionally includes a cell disruptive domain, a cell impermeable domain, and/or an oxygen domain (not shown), such as described in more detail in U.S. Patent Publication No. US-2005-0245799-A1. However, it is understood that a membrane system modified for other sensors, for example, by including fewer or additional domains is within the scope of the preferred embodiments.

[0273] One aspect of the preferred embodiments provides for a sensor (for transcutaneous, wholly implantable, or intravascular short-term or long-term use) having integrally formed parts, such as but not limited to a plurality of electrodes, a membrane system and an enzyme. For example, the parts may be coaxial, juxtapositioned, helical, bundled and/or twisted, plated and/or deposited thereon, extruded, molded, held together by another component, and the like. In another example, the components of the electrode system are integrally formed, (e.g., without additional support, such as a supporting substrate), such that substantially all parts of the system provide essential functions of the sensor (e.g., the sensing mechanism or "*in vivo*" portion). In a further example, a first electrode can be integrally formed directly on a second electrode (*e.g.*, electrically isolated by an insulator), such as by vapor deposition of a conductive electrode material, screen printing a conductive electrode ink or twisting two electrode wires together in a coiled structure.

[0274] Some embodiments provide an analyte sensor that is configured for insertion into a host and for measuring an analyte in the host, wherein the sensor includes a first working electrode disposed beneath an active enzymatic portion of a membrane (e.g., membrane system) on the sensor and a second working electrode disposed beneath an inactive- or non-enzymatic portion of the membrane on the sensor. In these embodiments, the first and second working electrodes integrally form at least a portion of the sensor.

Exemplary Sensor Configurations

[0275] **Fig. 1B** is a schematic view of a sensor in one embodiment. In some preferred embodiments, the sensor is configured to be integrally formed and coaxial. In this exemplary embodiment, one or more electrodes are helically wound around a central core, all of which share axis A-A. The central core **16** can be an electrode (e.g., a wire or metal-plated insulator) or a support made of insulating material. The coiled electrodes **18**, **20** are made of conductive material (e.g., plated wire, metal-plated polymer filaments, bulk metal wires, etc.) that is helically

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wound or twisted about the core **16**. Generally, at least the working electrodes are coated with an insulator **I** of non-conductive or dielectric material.

[0276] One skilled in the art will recognize that various electrode combinations are possible. For example, in one embodiment, the core **16** is a first working electrode and can be substantially straight. One of the coiled electrodes (**18** or **20**) is a second working electrode and the remaining coiled electrode is a reference or counter electrode. In a further embodiment, the reference electrode can be disposed remotely from the sensor, such as on the host's skin or on the exterior of the sensor, for example. Although this exemplary embodiment illustrates an integrally formed coaxial sensor, one skilled in the art appreciates a variety of alternative configurations. In one exemplary embodiment, the arrangement of electrodes is reversed, wherein the first working electrode is helically wound around the second working electrode core **16**. In another exemplary embodiment, the reference electrode can form the central core **16** with the first and second working electrodes coiled there around. In some exemplary embodiments, the sensor can have additional working, reference and/or counter electrodes, depending upon the sensor's purpose. Generally, one or more of the electrode wires are coated with an insulating material, to prevent direct contact between the electrodes. Generally, a portion of the insulating material can be removed (e.g., etched, scraped or grit-blasted away) to expose an electroactive surface of the electrode. An enzyme solution can be applied to the exposed electroactive surface, as described herein.

[0277] The electrodes each have first and second ends. The electrodes can be of any geometric solid shape, such as but not limited to a cylinder having a circular or oval cross-section, a rectangle (e.g., extruded rectangle), a triangle (e.g., extruded triangle), an X-cross section, a Y-cross section, flower petal-cross sections, star-cross sections, melt-blown fibers loaded with conductive material (e.g., conductive polymers) and the like. The first ends (e.g., an *in vivo* portion, "front end") of the electrodes are configured for insertion in the host and the second ends (e.g., an *ex vivo* portion, "back end") are configured for electrical connection to sensor electronics. In some embodiments, the sensor includes sensor electronics that collect data from the sensor and provide the data to the host in various ways. Sensor electronics are discussed in detail elsewhere herein.

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[0278] **Figs. 7A1** and **7A2** are schematics of an analyte sensor in another embodiment. **Fig. 7A1** is a side view and **Fig. 7A2** is a side-cutaway view. In some preferred embodiments, the sensor is configured to be integrally formed and coaxial, with an optional stepped end. In this exemplary embodiment, the sensor includes a plurality of electrodes **E1**, **E2**, **E3** to **E*n***, wherein ***n*** equals any number of electrode layers. Layers of insulating material **I** (e.g., non-conductive material) separate the electrode layers. All of the electrode and insulating material layers share axis **A-A**. The layers can be applied by any technique known in the art, such as but not limited to spraying, dipping, spraying, etc. For example, a bulk metal wire electrode **E1** can be dipped into a solution of insulating polymer that is vulcanized to form a layer of non-conductive, electrically insulating material **I**. A second electrode **E2** can be plated (e.g., by electroplating or other plating technique used in the art) on the first insulating layer, followed by application of a second insulating layer **I** applied in the same manner as the first layer. Additional electrode layers (e.g., **E3** to **E*n***) and insulating layers can be added to the construct, to create the desired number of electrodes and insulating layers. As an example, multiple sensors can be formed from a long wire (with insulating and electrode layers applied) that can be cut to yield a plurality of sensors of the desired length. After the sensor has been cut to size, it can be polished or otherwise treated to prepare the electrodes for use. In some embodiments, the various electrode and/or insulator layers can be applied by dipping, spraying, printing, vapor deposition, plating, spin coating or any other method known in the art. Although this exemplary embodiment illustrates an integrally formed coaxial sensor, one skilled in the art appreciates a variety of alternative configurations. For example, in some embodiments, the sensor can have two, three, four or more electrodes separated by insulating material **I**. In another embodiment, the analyte sensor has two or more electrodes, such as but not limited to a first working electrode, an auxiliary working electrode, a reference electrode and/or counter electrode. **Fig. 7B** is a schematic view of an integrally formed, coaxial sensor in another embodiment. In this exemplary embodiment, a coiled first electrode **E1** is manufactured from an electrically conductive tube or cylinder, such as but not limited to a silver Hypotube. A portion of the Hypotube is trimmed or carved into a helix or coil **702**. A second electrode **E2** that is sized to fit (e.g., with minimal tolerance) within the first electrode **E1** mates (e.g., slides into) with the first electrode **E1**, to form the sensor. In general, the surfaces of the electrodes are coated with an

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insulator, to prevent direct contact between the electrodes. As described herein, portion of the insulator can be stripped away to expose the electroactive surfaces. Although this exemplary embodiment illustrates one configuration of a coaxial, integrally formed sensor, one skilled in the art appreciates a variety of alternative configurations. For example, in some embodiments, the first electrode **E1** is a reference or auxiliary electrode, and the second electrode **E2** is a working electrode. However, the first electrode **E1** can be a working electrode and the second electrode **E2** can be a reference or auxiliary electrode. In some embodiments, additional electrodes are applied to the construct (e.g., after **E2** is inserted into **E1**). One advantage of this configuration is that the silver Hypotube can be cut to increase or decrease the flexibility of the sensor. For example, the spiral cut can space the coils farther apart to increase the sensor's flexibility. Another example of this configuration is that it is easier to construct the sensor in this manner, rather than winding one electrode around another (e.g., as is done for the embodiment shown in **Fig. 1B**).

[0279] **Figs. 7C** to **7E** are schematics of three embodiments of bundled analyte sensors. In these embodiments, of the sensors are configured to be integrally formed sensors, wherein a plurality (**E1**, **E2**, **E3**, to **E*n***) of electrodes are bundled, coiled or twisted to form a portion of the sensor. In some embodiments, the electrodes can be twisted or helically coiled to form a coaxial portion of the sensor, which share the same axis. In one embodiment, the first and second working electrodes are twisted or helically wound together, to form at least a portion of the sensor (e.g., a glucose sensor). For example, the electrodes can be twisted in a double helix. In some embodiments, additional electrodes are provided and twisted, coiled or wound with the first and second electrodes to form a larger super helix, such as a triple helix, a quadruple helix, or the like. For example, three wires (**E1**, **E2**, and **E3**) can be twisted to form a triple helix. In still other embodiments, at least one reference electrode can be disposed remotely from the working electrodes, as described elsewhere herein. In some embodiments, the tip of the sensor can be cut at an angle (90° or other angle) to expose the electrode tips to varying extents, as described herein.

[0280] **Fig. 7C** is a schematic of an exemplary embodiment of a sensor having three bundled electrodes **E1**, **E2**, and **E3**. In some preferred embodiments of the sensor, two or all of the electrodes can be identical. Alternatively, the electrodes can be non-identical. For example,

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the sensor can have a glucose-sensing electrode, an oxygen-sensing electrode and a reference electrode. Although this exemplary embodiment illustrates a bundled sensor, one skilled in the art appreciates a variety of alternative sensor configurations. For example, only two electrodes can be used or more than three electrodes can be used. In another example, holding one end of the bundled wires in a clamp and twisting the other end of the wires, to form a cable-like structure, can coil the electrodes together. Such a coiled structure can hold the electrodes together without additional structure (e.g., bound by a wire or coating). In another example, non-coiled electrodes can be bundled and held together with a wire or fiber coiled there around, or by applying a coating of insulating material to the electrode bundle. In still another example, the reference electrode can be disposed remotely from the working electrodes, as described elsewhere herein.

[0281] **Fig. 7D** is a schematic view of a sensor in one embodiment. In some preferred embodiments, the sensor is designed to be integrally formed and bundled and/or coaxial. In this exemplary embodiment, the sensor includes seven electrodes, wherein three electrodes of a first type (e.g., 3 x **E1**) and three electrodes of a second type (e.g., 3 x **E2**) are bundled around one electrode of a third type (e.g., **E3**). Those skilled in the art appreciate a variety of configurations possible with this embodiment. For example, the different types of electrodes can be alternated or not alternated. For example, in Fig. 7D, the two types of electrodes are alternately disposed around E3. However, the two types of electrodes can be grouped around the central structure. As described herein, some or all of the electrodes can be coated with a layer of insulating material, to prevent direct contact between the electrodes. The electrodes can be coiled together, as in a cable, or held together by a wire or fiber wrapping or a coating of insulating material. The sensor can be cut, to expose the electroactive surfaces of the electrodes, or portions of the insulating material coating can be stripped away, as described elsewhere herein. In another example, the sensor can include additional (or fewer) electrodes. In one exemplary embodiment, the **E1** and **E2** electrodes are bundled around a non-conductive core (e.g., instead of electrode **E3**), such as an insulated fiber. In another embodiment, different numbers of **E1**, **E2**, and **E3** electrodes can be used (e.g., two **E1** electrodes, two **E2** electrodes, and three **E3** electrodes). In another embodiment, additional electrode type can be included in the sensor (e.g., an electrode of type **E4**, **E5** or **E6**, etc.). In still another exemplary embodiment, three glucose-detecting

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electrodes (e.g., **E1**) and three reference electrodes (e.g., **E2**) are bundled and (optionally) coiled around a central auxiliary working electrode (e.g., **E3**).

[0282] **Fig. 7E** is a schematic of a sensor in another embodiment. In this exemplary embodiment of an integrally formed sensor, two pairs of electrodes (e.g., 2 x **E1** and 2 x **E2**) are bundled around a core of insulating material **I**. Fibers or strands of insulating material **I** also separate the electrodes from each other. Although this exemplary embodiment illustrates an integrally formed sensor, one skilled in the art appreciates a variety of alternative configurations. For example, the pair of **E1** electrodes can be working electrodes and the pair of **E2** electrodes can be reference and/or auxiliary electrodes. In one exemplary embodiment, the **E1** electrodes are both glucose-detecting electrodes, a first **E2** electrode is a reference electrode and a second **E2** electrode is an auxiliary electrode. In another exemplary embodiment, one **E1** electrode includes active GOx and measures a glucose-related signal; the other **E1** electrode lacks active GOx and measures a non-glucose-related signal, and the **E2** electrodes are reference electrodes. In yet another exemplary embodiment, one **E1** electrode detects glucose and the other **E1** electrode detects urea, and both **E2** electrodes are reference electrodes. One skilled in the art of electrochemical sensors will recognized that the size of the various electrodes can be varied, depending upon their purpose and the current and/or electrical potential used. Electrode size and insulating material size/shape are not constrained by their depiction of relative size in the Figures, which are schematic schematics intended for only illustrative purposes.

[0283] **Fig. 7F** is a schematic view of a cross-section of an integrally formed sensor in another embodiment. In some preferred embodiments, the sensor is configured to be bifunctional. In this exemplary embodiment, the sensor includes two working electrodes **E1/E2** separated by either a reference electrode **R** or an insulating material **I**. The electrodes **E1**, **E2** and optionally the reference electrode **R** are conductive and support the sensor's shape. In addition, the reference electrode **R** (or the insulating material **I**) can act as a diffusion barrier (***D***, described herein) between the working electrodes **E1**, **E2** and support the sensor's structure. Although this exemplary embodiment illustrates one configuration of an integrally formed sensor having bifunctional components, one skilled in the art appreciates a variety of alternative configurations. Namely, **Fig. 7F** is not to scale and the working electrodes **E1**, **E2** can be relatively larger or smaller in scale, with regard to the reference electrode/insulator **R/I** separating them. For

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example, in one embodiment, the working electrodes **E1**, **E2** are separated by a reference electrode that has at least 6-times the surface area of the working electrodes, combined. While the working electrodes **E1**, **E2** and reference electrode/insulator **R/I** are shown and semi-circles and a rectangle, respectively, one skilled in the art recognizes that these components can take on any geometry know in the art, such as but not limited to rectangles, cubes, cylinders, cones, and the like.

[0284] **Fig. 7G** is a schematic view of a sensor in yet another embodiment. In some preferred embodiments, the sensor is configured to be integrally formed with a diffusion barrier ***D***, as described herein. In this exemplary embodiment, the working electrodes **E1**, **E2** (or one working electrode and one counter electrode) are integrally formed on a substantially larger reference electrode **R** or an insulator **I** that substantially prevents diffusion of analyte or other species from one working electrode to another working electrode (e.g., from the enzymatic electrode (e.g., coated with active enzyme) to the non-enzymatic electrode (e.g., no enzyme or inactive enzyme)). Although this exemplary embodiment illustrates an integrally formed sensor having a diffusion barrier, one skilled in the art appreciates a variety of alternative configurations. For example, in one embodiment, the reference electrode is designed to include an exposed electroactive surface area that is at least equal to, greater than, or more than about 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times greater than the surface area of the working electrodes (e.g., combined). In other embodiments, the surface of the reference electrode is about 6 (e.g., about 6 to 20) or more times greater than the working electrodes. In some embodiments, each working electrode detects a separate analyte (e.g., glucose, oxygen, uric acid, nitrogen, pH, and the like). In other embodiments, one of the working electrodes is a counter electrode. In still another exemplary embodiment, an enzyme solution containing active GOx is applied to the **E1** electroactive surface, while an enzyme solution containing inactive GOx (or no GOx at all) is applied to the **E2** electroactive surface. As described herein, this configuration allows the measurement of two signals. Electrode **E1** measures both a signal related to glucose concentration and a signal that is not related to glucose concentration. Electrode **E2** measures a signal that is not related to glucose concentration. The sensor electronics, as described herein, can use these data to calculate glucose concentration without signal due to non-glucose-related contributions.

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[0285] **Fig. 7H** is a schematic view of a sensor in another embodiment. In some preferred embodiments, the sensor is configured of a geometric solid (e.g., cylindrical) reference electrode **R** having two or more working electrodes **E1**, **E2** to **En** disposed within two or more grooves or channels carved in the sides of the reference electrode **R** (parallel to the axis of the reference electrode **R**). The grooves are sized such that the electrodes **E1**, **E2** can snuggly fit therein. Additionally, the depth of the grooves can be configured that the electrode placed therein is externally exposed to a greater or lesser degree. For example, the opening to the groove may be wider or narrower. In some embodiments, a portion of an electrode protrudes from the groove in which the electrode has been disposed. In some embodiments, an insulator (e.g., **I**) takes the place of a reference electrode (which can be disposed elsewhere, such remotely as described in more detail elsewhere herein). The reference electrode/insulator **R/I** can take any geometric structure known in the art, such as but not limited to cylinders, rectangles, cones, and the like. Similarly, the relative sizes of the working electrodes **E1**, **E2** and the reference electrode/insulator **R/I** can be varied to achieve a desired signal level, to enable the use of the desired voltage (e.g., to bias the sensor), and the like, as described herein.

[0286] In one exemplary embodiment, a diffusion barrier ***D*** (described in greater detail below) separates the working electrodes. The diffusion barrier can be spatial, physical, or temporal. For example, the distance around the reference electrode (e.g., from the first working electrode **E1** to the second working electrode **E2**, around a portion of the circumference of the reference electrode **R**) acts as a spatial diffusion barrier. In one exemplary embodiment, the working electrodes are coated with a layer of insulating material **I** (e.g., non-conductive material or dielectric) to prevent direct contact between the working electrodes **E1**, **E2** and the reference electrode **R**. A portion of the insulator **I** on an exterior surface of each working electrode is etched away, to expose the electrode's electroactive surface. In some embodiments, an enzyme solution (e.g., containing active GOx) is applied to the electroactive surfaces of both electrodes, and dried. Thereafter, the enzyme applied to one of the electroactive surfaces is inactivated. As is known in the art, enzymes can be inactivated by a variety of means, such as heat, treatment with inactivating (e.g., denaturing) solvents, proteolysis, laser irradiation or UV irradiation (e.g., at 254-320 nm). For example, the enzyme coating one of the electroactive surfaces can be inactivated by masking one of the electroactive surfaces/electrodes (e.g., **E1**, temporarily covered

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with a UV-blocking material); irradiating the sensor with UV light (e.g., 254-320 nm; a wavelength that inactivates the enzyme, such as by cross-linking amino acid residues) and removing the mask. Accordingly, the GOx on **E2** is inactivated by the UV treatment, but the **E1** GOx is still active due to the protective mask. In other embodiments, an enzyme solution containing active enzyme is applied to a first electroactive surface (e.g., **E1**) and an enzyme solution containing either inactivated enzyme or no enzyme is applied to the second electroactive surface (e.g., **E2**). Accordingly, the enzyme-coated first electroactive surface (e.g., **E1**) detects analyte-related signal and non-analyte-related signal; while the second electroactive surface (e.g., **E2**), which lacks active enzyme, detects non-analyte-related signal. As described herein, the sensor electronics can use the data collected from the two working electrodes to calculate the analyte-only signal.

[0287] Although this exemplary embodiment illustrates one embodiment of an integrally-formed sensor having a diffusion barrier ***D***, one skilled in the art appreciates a variety of alternative configurations, such as but not limited to the embodiment shown in **Fig. 7I**. In this exemplary embodiment, the reference electrode is formed of at least two adjacent pieces shaped such that the working electrodes fill at least some space between them. The at least two pieces can be any shape known in the art, as described herein. In some embodiments, the at least two pieces are symmetrical and/or mirror images of each other, but one skilled in the art will recognize that this is not a requirement. In various embodiments, an insulating material can be coated on the working electrodes and/or the reference electrode(s) to prevent contact there between. As described elsewhere herein, the working electrodes can detect the same analyte or separate analytes, or one of the working electrodes may act as a counter electrode (e.g., auxiliary electrode). Although this exemplary embodiment illustrates one example of a sensor having a reference electrode **R** that is formed of at least two pieces shaped such that the working electrodes fill at least some space between the pieces, one skilled in the art appreciates that a variety of sensor configurations are possible. For example, the reference electrode can be formed of three or more pieces. In other example, the sensor can be configured with more than two working electrodes (e.g., 3, 4, or 5 working electrodes, or more).

[0288] **Fig. 7J** is a schematic view of an integrally formed sensor in yet another embodiment. In this exemplary embodiment, the reference electrode **R** is formed in any desired

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extruded geometry, such as an approximate X-shape. Two or more working electrodes **E1**, **E2** are disposed on substantially opposing sides of the reference electrode, with a diffusion barrier ***D*** between them. In this embodiment, the diffusion barrier is a physical diffusion barrier, namely the distance between the two working electrodes (e.g., around the reference electrode). In some embodiments, the electrodes are bundled and held together by a wrapping of wire or fiber. In other embodiments, the electrodes are twisted around the lengthwise axis of the extruded X-shaped reference electrode, to form a coaxial sensor. Although this exemplary embodiment illustrates an integrally formed sensor, one skilled in the art appreciates a variety of alternative configurations. For example, furthering some embodiments, three or four working electrodes can be disposed around the reference electrode (e.g., in the indentations between the legs/arms of the X-shaped electrode). In other embodiments, the reference electrode can be Y-shapes, star-shaped, flower-shaped, scalloped, or any other convenient shape with multiple substantially isolated sides. In some embodiments, an insulating material **I** takes the place of the reference electrode of **Fig. 7J**, which is remotely located. In an alternative embodiment, a working electrode is replaced with a counter electrode. As described elsewhere herein, the sensor components are bifunctional. Namely, the electrodes and reference electrode provide electrical conduction and the sensor's structure. The reference electrode (or insulating material) provides a physical diffusion barrier ***D***. In addition to providing shape to the sensor, the insulating material acts as insulator by preventing direct electrical contact between the electrodes. Similarly, the materials selected to construct the sensor determine the sensor's flexibility. As described elsewhere, active enzyme is applied to the electroactive surface of at least one working electrode (e.g., **E1**). In some embodiments, no enzyme (or inactivated enzyme) is applied to the electroactive surface of a second working electrode (e.g., **E2**). In an alternative embodiment, a second enzyme is applied to the second working electrode (e.g., E2) such that the sensor can measure the signals of two different analytes (e.g., glucose and aureate or oxygen). **Fig. 7K** is a schematic of a sensor in another embodiment. In some preferred embodiments, the sensor is configured to be integrally formed of two working electrodes. In this exemplary embodiment, the sensor includes two electrodes **E1**, **E2** (e.g., metal wires), wherein each electrode is coated with a non-conductive material **I** (e.g., and insulator). As is shown in **Fig. 7K**, the first working electrode **E1** formed within the insulator **I** leaving space for an enzyme. For example, an enzyme

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solution **702** (e.g., GOx for detecting glucose) is disposed within the space **701**. In contrast, the second working electrode **E2** extends substantially flush with the insulator **I**. A membrane system **703** coats the electrodes. A diffusion barrier ***D*** separates the working electrodes. In some embodiments, the first and second electrodes are separated by a distance ***D*** that substantially prevents diffusion of H_2O_2 from the first electrode (e.g., with active enzyme) to the second electrode (e.g., without active enzyme). Although this exemplary embodiment illustrates one integrally formed sensor, one skilled in the art appreciates a variety of alternative configurations. For example, the use of more than two working electrodes and wrapping the construct with a reference electrode wire **R** or disposing the reference electrode remotely from the sensor.

[0289] **Fig. 7L** is a schematic of a sensor in one embodiment. In some preferred embodiments, the sensor is designed to be integrally formed. In this exemplary embodiment, two electrodes **E1**, **E2** are embedded within an insulator **I**. The sensor can be formed by embedding conductive wires within a dielectric, curing the dielectric and then cutting sensors of the desired length. The cut end provides the exposed electroactive electrode surfaces and can be polished or otherwise treated. Although this exemplary embodiment illustrates one integrally formed sensor, one skilled in the art appreciates a variety of alternative configurations. For example, additional electrode wires can be embedded in the dielectric material. In another example, a reference electrode (e.g., wire or cylinder) can be coiled or wrapped around the sensor (e.g., on the surface of the insulator). Alternatively, as described elsewhere herein, the reference electrode can be disposed remotely from the working electrodes **E1**, **E2**, such as on the host's skin or on another portion of the sensor. One advantage of this configuration is that it is relatively simple to embed electrode wires in a long cylinder of insulating material and then cut the sensors to any desired size and/or shape.

[0290] **Fig. 7M** is a schematic cross-sectional view of a sensor having multiple working and reference electrodes, in one embodiment. In some preferred embodiments, the sensor is integrally formed. In this exemplary embodiment, the sensor includes a plurality of working electrodes (e.g., **E1**, **E2**, **E3**) that are layered with a plurality of reference electrodes (e.g., **R1**, **R2**, **R*n***). In some embodiments, the working electrodes are coated with an insulating material to prevent direct contact with adjacent reference electrodes. In some embodiments, the reference electrodes are also coated with insulative material. In some embodiments, layers of

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insulating material separate the layers. In some embodiments, at least one of the working electrodes is a counter electrode. As described herein, in some embodiments, electroactive surfaces are exposed on one or more electrodes, such as by stripping away a portion of an insulating coating, such as on the sides of the sensor. In other embodiments, an extended electrode structure (e.g., a long sandwich of electrode layers) that is cut to the desired length, and the cut end includes the exposed electroactive surfaces of the electrodes. An enzyme layer can be applied to one or more of the electroactive surfaces, as described herein. Depending upon the desired sensor function, the working electrodes can be configured to detect the same analyte (e.g., all electroactive surfaces coated with GOx glucose) or different analytes (e.g., one working electrode detects glucose, another detects oxygen and the third detects ureate), as described herein. Although this exemplary embodiment illustrates a sensor having a plurality of working and reference electrodes, one skilled in the art appreciates a variety of alternative configurations. For example, in some embodiments, the electrodes can be of various sizes, depending upon their purpose. For example, in one sensor, it may be preferred to use a 3 mm oxygen electrode, a 10 mm glucose electrode and a 4 mm counter electrode, all separated by reference electrodes. In another embodiment, each reference electrode can be functionally paired with a working electrode. For example, the electrodes can be pulsed on and off, such that a first reference electrode **R1** is active only when the first working electrode **E1** is active, and a second reference electrode **R2** is active only when the second working electrode **E2** is active. In another embodiment, a flat sensor (e.g., disk-shaped) can be manufactured by sandwiching reference electrodes between working electrodes, cutting the sandwich into a cylinder, and the cutting the cylinder cross-wise (perpendicularly or at an angle) into disks.

[0291] **Fig. 7N** is a schematic cross-sectional view of the manufacture of an integrally formed sensor, in one embodiment. In some preferred embodiments, at least two working electrodes (**E1**, **E2**) and optionally a reference electrode **R** are embedded in a quantity **704** of insulating material **I**. The working electrodes are separated by a diffusion barrier ***D***. After the insulator has been cured (e.g., vulcanized or solidified) the structure is shaped (e.g., carved, scraped or cut etc.) to the final sensor shape **705**, such that excess insulation material is removed. In some embodiments, multiple sensors can be formed as an extended structure of electrode wires embedded in insulator, which is subsequently cut to the desired length, wherein the

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exposed electrode ends (e.g., at the cut surface) become the electroactive surfaces of the electrodes. In other embodiments, portions of the insulator adjacent to the electrodes (e.g., windows) can be removed (e.g., by cutting or scraping, etc.) to expose the electroactive surfaces. Depending upon the sensor's configuration and purpose, an enzyme solution can be applied to one or more of the electroactive surfaces, as described elsewhere herein. Although this exemplary embodiment illustrates one technique of manufacturing a sensor having insulation-embedded electrodes, one skilled in the art appreciates a variety of alternative configurations. For example, a diffusion barrier ***D***, can comprise both the reference electrode **R** and the insulating material **I**, or only the reference electrode. In another example, windows exposing the electroactive surfaces can be formed adjacent to each other (e.g., on the same side of the reference electrode) or on opposite sides of the reference electrode. Still, in other embodiments, more working or reference electrodes can be included, and the working and reference electrodes can be of relatively larger or smaller size, depending upon the sensor's configuration and operating requirements (e.g., voltage and/or current requirements).

[0292] **Figs. 8A** and **8B** are schematic views of a sensor in yet another embodiment. **Fig. 8A** is a view of the cross-section and side of an *in vivo* portion of the sensor. **Fig. 8B** is a side view of the *ex vivo* portion of the sensor (e.g., the portion that is connected to the sensor electronics, as described elsewhere herein). Namely, two working electrodes **E1**, **E2** that are coated with insulator **I** and then disposed on substantially opposing sides of a reference electrode **R**, such as a silver or silver/silver chloride electrode (see **Fig. 8A**). The working electrodes are separated by a diffusion barrier ***D*** that can include a physical barrier (provided by the reference electrode and/or the insulating material coatings), a spatial barrier (provided by staggering the electroactive surfaces of the working electrodes), or a temporal barrier (provided by oscillating the potentials between the electrodes). In some embodiments, the reference electrode **R** has a surface area at least 6-times the surface area of the working electrodes. Additionally, the reference electrode substantially can act as a spatial diffusion barrier between the working electrodes due to its larger size (e.g., the distance across the reference electrode, from one working electrode to another).

[0293] The electrodes can be held in position by wrapping with wire or a non-conductive fiber, a non-conductive sheath, a biointerface membrane coating, or the like. The

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electroactive surfaces of the working electrodes are exposed. In some embodiments, the end of the sensor is cut off, to expose the ends of the wires. In other embodiments, the ends of the wires are coated with insulating material; and the electroactive surfaces are exposed by removing a portion of the insulating material (e.g., a window **802** cut into the side of the insulation coating the electrode). In some embodiments, the windows exposing the electroactive surfaces of the electrodes can be staggered (e.g., spaced such that one or more electrodes extends beyond the other one or more electrodes), symmetrically arranged or rotated to any degree; for example, to substantially prevent diffusion of electroactive species from one working electrode (e.g., **802a**) to the other working electrode (e.g., **802b**), as will be discussed in greater detail elsewhere herein. In various embodiments, the reference electrode is not coated with a nonconductive material. The reference electrode can have a surface area that is at least 6 times the surface area of the exposed working electrode electroactive surfaces. In some embodiments, the reference electrode **R** surface area is 7-10 times (or larger) than the surface area of the working electrode electroactive surfaces. In still other embodiments, the reference electrode can be only 1-5 times the surface area of working electrode electroactive surfaces (e.g., (**E1** + **E2**) x 1 = **R** or (**E1** + **E2**) x 2 = **R**, etc.).

[0294] The *ex vivo* end of the sensor is connected to the sensor electronics (not shown) by electrical connectors **804a**, **804b**, **804c**. In some embodiments, the *ex vivo* end of the sensor is stepped. For example, the *ex vivo* end of the reference electrode **R** terminates within electrical connector **804a**. The *ex vivo* end of the first working electrode **E1** is exposed (e.g., nonconductive material removed therefrom) and terminates a small distance past the reference electrode **R**, within electrical connector **804b**. Similarly, the *ex vivo* end of the second working electrode **E2** is exposed (e.g., nonconductive material removed therefrom) and terminates a small distance past the termination of the first working electrode **E1**, within electrical connector **804c**.

[0295] Although this exemplary embodiment illustrates one configuration of an integrally formed sensor, one skilled in the art appreciates a variety of alternative configurations. For example, in some embodiments, a portion of the *in vivo* portion of the sensor can be twisted and/or stepped. More working, reference, and/or counter electrodes, as well as insulators, can be included. The electrodes can be of relatively larger or smaller size, depending upon the sensor's intended function. In some embodiments, the electroactive surfaces can be staggered. In still

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other embodiments, the reference electrode can be disposed remotely from the sensor, as described elsewhere herein. For example, the reference electrode shown in **Fig. 8A** can be replaced with a non-conductive support and the reference electrode disposed on the host's skin.

[0296] With reference to the *ex vivo* portion of the sensor, one skilled in the art appreciates additional alternative configurations. For example, in one embodiment, a portion of the *ex vivo* portion of the sensor can be twisted or coiled. In some embodiments, the working and reference electrodes can be of various lengths and configurations not shown in **Fig. 8B**. For example, the reference electrode **R** can be the longest (e.g., connect to electrical contact **804c**) and the first second working electrode **E2** can be the shortest (e.g., connect to electrical contact **804a**). In other embodiments, the first working electrode E1 may be either the longest electrode (e.g., connect to electrical contact **804c**) or the shortest electrode (e.g., connect to electrical contact **804a**).

[0297] **Fig. 9A** is a schematic view that illustrates yet another exemplary embodiment of an integrally formed analyte sensor. Namely, two working electrodes **E1**, **E2** are bundled together and substantially encircled with a cylindrical silver or silver/silver chloride reference electrode **R** (or the like). The reference electrode can be crimped at a location **902**, to prevent movement of the working electrodes **E1**, **E2** within the reference electrode **R** cylinder. In alternative embodiments, a reference electrode can be rolled or coiled around the working electrodes **E1**, **E2**, to form the reference electrode **R**. Preferably, the working electrodes are at least partially insulated as described in more detail elsewhere herein; such as by coating with a non-conductive material, such as but not limited to Parylene. One skilled in the art appreciates that a variety of alternative configurations are possible.

[0298] **Fig. 9B** illustrates another embodiment of an integrally formed analyte sensor. Namely, two working electrodes **E1**, **E2** are bundled together with a silver or silver/silver chloride wire reference electrode **R** coiled there around. The reference electrode can be coiled tightly, to prevent movement of the working electrodes **E1**, **E2** within the reference electrode **R** coil.

[0299] Referring again to **Figs. 9A** to **9B**, near the tip of the *in vivo* portion of the sensor, windows **904a** and **904b** are formed on the working electrodes **E1**, **E2**. Portions of the non-conductive material (e.g., insulator) coating each electrode is removed to form windows

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904a and **904b**. The electroactive surfaces of the electrodes are exposed *via* windows **904a** and **904b.** As described elsewhere herein, the electrode electroactive surfaces exposed through windows **904a** and **904b** are coated with a membrane system. An active enzyme (e.g., GOx is used if glucose is the analyte) is disposed within or beneath or within the membrane covering one of the windows (e.g., **904a** or **904b**). The membrane covering the other window can include inactivated enzyme (e.g., GOx inactivated by heat, solvent, UV or laser irradiation, etc., as described herein) or no enzyme. The electrode having active enzyme detects a signal related to the analyte concentration and non-analyte related signal (e.g., due to background, etc.). In contrast, the electrode having inactive enzyme or no enzyme detects substantially only the non-analyte related signal. These signals are transmitted to sensor electronics (discussed elsewhere herein) to calculate an analyte concentration based on only the signal component related to only the analyte (described elsewhere herein).

[0300] In general, the windows **904a** and **904b** are separated or staggered by a distance ***D***, which is selected to be sufficiently large that electroactive species (e.g., H_2O_2) do not substantially diffuse from one window to the other (e.g., from **904a** to **904b**). In an exemplary embodiment of a glucose-oxidase-based sensor, active enzyme is included in the membrane covering window **904a** and inactive enzyme is included in the membrane covering window **904b**. Distance ***D*** is configured to be large enough that H_2O_2 cannot diffuse from window **904a** to window **904b**, which lacks active enzyme (as discussed elsewhere herein). In some embodiments, the distance ***D*** is at least about 0.020 inches or less to about 0.120 inches or more. In some embodiments, ***D*** is at least about 0.030 to about 0.050 inches. In other embodiments, ***D*** is at least about 0.090 to about 0.095 inches. One skilled in the art appreciates alternative embodiments of the diffusion barrier ***D***. Namely, the diffusion barrier ***D*** can be spatial (discussed herein with relation to **Figs. 9A** and **9B**), physical or temporal (see discussion of Diffusion Barriers herein and **Fig. 10**). In some embodiments, a physical diffusion barrier ***D***, such as but not limited to an extended non-conductive structure placed between the working electrodes (e.g., Fig. 8A), substantially prevents diffusion of H_2O_2 from one working electrode (having active enzyme) to another working electrode (having no active enzyme). In other embodiments, a temporal diffusion barrier ***D*** is created by pulsing or oscillating the electrical potential, such that only one working electrode is activated at a time.

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[0301] In various embodiments, one of the windows **904a** or **904b** comprises an enzyme system configured to detect the analyte of interest (e.g., glucose or oxygen). The other window comprises no active enzyme system (e.g., wherein the enzyme system lacks enzyme or wherein the enzyme has been de-activated). In some embodiments, wherein the "enzyme system lacks enzyme," a layer may be applied, similar to an active enzyme layer, but without the actual enzyme included therein. In some embodiments, wherein "the enzyme has been de-activated" the enzyme can be inactivated (e.g., by heat or solvent) prior to addition to the enzyme system solution or the enzyme can be inactivated after application to the window.

[0302] In one exemplary embodiment, an enzyme is applied to both windows **904a** and **904b** followed by deactivation of the enzyme in one window. For example, one window can be masked (e.g., to protect the enzyme under the mask) and the sensor then irradiated (to deactivate the enzyme in the unmasked window). Alternatively, one of the enzyme-coated windows (e.g., the first window but not the second window) can be sprayed or dipped in an enzyme-deactivating solvent (e.g., treated with a protic acid solution such a hydrochloric acid or sulfuric acid). For example, a window coated with GOx can be dipped in dimethyl acetamide (DMAC), ethanol, or tetrahydrofuran (THF) to deactivate the GOx. In another example, the enzyme-coated window can be dipped into a hot liquid (e.g., water or saline) to deactivate the enzyme with heat.

[0303] In these embodiments, the design of the active and inactive enzyme window is at least partially dependent upon the sensor's intended use. In some embodiments, it is preferred to deactivate the enzyme coated on window **904a**. In other embodiments, it is preferred to deactivate the enzyme coated on window **904b**. For example, in the case of a sensor to be used in a host's blood stream, the choice depends upon whether the sensor will be inserted pointing upstream (e.g., against the blood flow) or pointing downstream (e.g., with the blood flow).

[0304] In one exemplary embodiment, an intravascular sensor is inserted into the host's vein pointing upstream (against the blood flow), an enzyme coating on electrode **E1** (window **904a**) is inactivated (e.g., by dipping in THF and rinsing) and an enzyme coating on electrode **E2** (in window **904b**) is not inactivated (e.g., by not dipping in THF). Because the enzyme on the first electrode **E1** (e.g., in window **904a**) is inactive, electroactive species (e.g., H_2O_2) will not be substantially generated at window **904a** (e.g., the first electrode **E1** generates

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substantially no H_2O_2 to effect the second electrode **E2**). In contrast, the active enzyme on the second electrode **E2** (in window **904b**) generates H_2O_2 which at least partially diffuses down stream (away from the windows) and thus has no effect on the first electrode **E1**, other features and advantages of spatial diffusion barriers are described in more detail elsewhere herein.

[0305] In another exemplary embodiment, an intravascular sensor is inserted into the host's vein pointing downstream (with the blood flow), the enzyme coating on electrode **E1** (window **904a**) is active and the enzyme coating on electrode **E2** (in window **904b**) is inactive. Because window **904a** is located farther downstream than window **904b**, the H_2O_2 produced by the enzyme in **904a** diffuses downstream (away from window **904b**), and therefore does not affect substantially electrode **E2**. In a preferred embodiment, the enzyme is GOx, and the sensor is configured to detect glucose. Accordingly, H_2O_2 produced by the GOx in window **904a** does not affect electrode **E2**, because the sensor is pointing downstream and the blood flow carries away the H_2O_2 produced on electrode **E1**.

[0306] **Figs. 9A** and **9B** illustrate two embodiments of a sensor having a stepped second end (e.g., the back end, distal end or *ex vivo* end, described with reference to **Fig. 8B**) that connects the sensor to the sensor electronics. Namely, each electrode terminates within an electrical connector **804** such as but not limited to an elastomeric electrical connector. Additionally, each electrode is of a different length, such that each electrode terminates within one of a plurality of sequential electrical connectors. For example, with reference to **Fig. 9A**, the reference electrode **R** is the shortest in length and terminates within the first electrical connector **804**. The first working electrode **E1** is longer than the reference electrode **R**, and terminates within the second electrical connector **804**. Finally, the second working electrode **E2** is the longest electrode and terminates within the third electrical connector **804**. One skilled in the art appreciates that other configurations are possible. For example, the first working electrode **E1** can be longer than the second working electrode **E2**. Accordingly, the second working electrode **E2** would terminate within the second (e.g., middle) electrical connector **804** and the first working electrode **E1** would terminate within the third (e.g., last) electrical connector **804**. With reference to Fig. 9B, additional stepped second end configurations are possible. In alternative embodiments, the second ends of the sensor may be separated from each other to connect to non-parallel, non-sequential electrical connectors.

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[0307] **Fig. 11** is a schematic view of a sensor in yet another embodiment. In preferred embodiments, the sensor is integrally formed, coaxial, and has a stepped *ex vivo* end (e.g., back or second end). Electrodes **E1**, **E2** and **E3** are twisted to form a helix, such as a triple helix. Additionally, at the back end of the sensor, the electrodes are stepped and each electrode is individually connected to the sensor electronics by an electrical connector **804**. At each electrode's second end, the electrode engages an electrical connector **804** that joins the electrode to the sensor electronics. For example, the second end of electrode **E1** electrically connects electrical connector **1106**. Similarly, the second end of electrode **E2** electrically connects electrical connector **1108** and the second end of electrode **E3** electrically connects electrical connector **1110**. As described elsewhere herein, each sensor component is difunctional, and provides electrical conductance, structural support, a diffusion barrier, or insulation (see description elsewhere herein). Although this exemplary embodiment illustrates an integrally formed, coaxial sensor having a stepped back end, one skilled in the art appreciates a variety of alternative configurations. For example, one of the electrodes **E1**, **E2** or **E3** can be a reference electrode, or the reference electrode can be disposed remotely from the sensor, such as but not limited to on the host's skin. In another example, the sensor can have only two electrodes or more than three electrodes.

[0308] One skilled in the art recognizes a variety of alternative configurations for the embodiments described herein. For example, in any embodiment of an analyte sensor, the reference electrode (and optionally a counter electrode) can be disposed remotely from the working electrodes. For example, in **Figures 7A1** through **9B** and **Fig. 11**, the reference electrode R can be replaced with a non-conductive material, such as an insulator **I**. Depending upon the sensor's configuration and location of use, the reference electrode **R** can then be inserted into the host in a location near to the sensor, applied to the host's skin, be disposed within a fluid connector, be disposed on the ex-vivo portion of the sensor or even disposed on the exterior of the sensor electronics.

[0309] **Fig. 7L** illustrates an embodiment in which the reference and/or counter electrode is located remotely from the first and second working electrodes **E1** and **E2**, respectively. In one exemplary embodiment, the sensor is a needle-type sensor such as described with reference to **Fig. 1B**, and the working electrodes **E1**, **E2** are integrally formed together with

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a substantially X-shaped insulator **I** and the reference electrode (and/or counter electrode) is placed on the host's skin (e.g., a button, plate, foil or wire, such as under the housing) or implanted transcutaneously in a location separate from the working electrodes.

[0310] As another example, in one embodiment of a sensor configured to measure a host's blood, such as described in co-pending U.S. Patent Application 11/543,396, entitled "ANALYTE SENSOR" and filed on even date herewith, and which is incorporated herein by reference in its entirety; one or more working electrodes can be inserted into the host's blood *via* a catheter and the reference and/or counter electrode can be placed within the a fluid connector (on the sensor) configured to be in fluid communication with the catheter; in such an example, the reference and/or counter electrode is in contact with fluid flowing through the fluid connector but not in direct contact with the host's blood. In still other embodiments, the reference and/or counter electrodes can be placed exterior to the sensor, in bodily contact for example.

[0311] With reference to the analyte sensor embodiments disclosed herein, the surface area of the electroactive portion of the reference (and/or counter) electrode is at least six times the surface area of one or more working electrodes. In other embodiments, the reference (and/or counter) electrode surface is 1, 2, 3, 4, 5, 7, 8, 9 or 10 times the surface area of the working electrodes. In other embodiments, the reference (and/or counter) electrode surface area is 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 times the surface area of the working electrodes. For example, in a needle-type glucose sensor, similar to the embodiment shown in **Fig. 1B**, the surface area of the reference electrode (e.g., **18** or **20**) includes the exposed surface of the reference electrode, such as but not limited to the electrode surface facing away from the working electrode **16**.

[0312] In various embodiments, the electrodes can be stacked or grouped similar to that of a leaf spring configuration, wherein layers of electrode and insulator (or individual insulated electrodes) are stacked in offset layers. The offset layers can be held together with bindings of non-conductive material, foil, or wire. As is appreciated by one skilled in the art, the strength, flexibility, and/or other material property of the leaf spring-configured or stacked sensor can be either modified (e.g., increased or decreased), by varying the amount of offset, the amount of binding, thickness of the layers, and/or materials selected and their thicknesses, for example.

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[0313] In some embodiments, the sensor (e.g., a glucose sensor) is configured for implantation into the host. For example, the sensor may be wholly implanted into the host, such as but not limited to in the host's subcutaneous tissue (e.g., the embodiment shown in **Fig. 1A**). In other embodiments, the sensor is configured for transcutaneous implantation in the host's tissue. For example, the sensor can have a portion that is inserted through the host's skin and into the underlying tissue, and another portion that remains outside the host's body (e.g., such as described in more detail with reference to **Fig. 1B**). In still other embodiments, the sensor is configured for indwelling in the host's blood stream. For example, a needle-type sensor can be configured for insertion into a catheter dwelling in a host's vein or artery. In another example, the sensor can be integrally formed on the exterior surface of the catheter, which is configured to dwell within a host's vein or artery. Examples of indwelling sensors can be found in co-pending U.S. patent application 11/543,396 filed on even date herewith and entitled "ANALYTE SENSOR." In various embodiments, the *in vivo* portion of the sensor can take alternative configurations, such as but not limited to those described in more detail with reference to **Figs. 7A-9B** and **11**.

[0314] In preferred embodiments, the analyte sensor substantially continuously measures the host's analyte concentration. In some embodiments, for example, the sensor can measure the analyte concentration every fraction of a second, about every fraction of a minute or every minute. In other exemplary embodiments, the sensor measures the analyte concentration about every 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes. In still other embodiments, the sensor measures the analyte concentration every fraction of an hour, such as but not limited to every 15, 30 or 45 minutes. Yet in other embodiments, the sensor measures the analyte concentration about every hour or longer. In some exemplary embodiments, the sensor measures the analyte concentration intermittently or periodically. In one preferred embodiment, the analyte sensor is a glucose sensor and measures the host's glucose concentration about every 4-6 minutes. In a further embodiment, the sensor measures the host's glucose concentration every 5 minutes.

[0315] In one exemplary embodiment, the analyte sensor is a glucose sensor having a first working electrode configured to generate a first signal associated with both glucose and non-glucose related electroactive compounds that have a first oxidation potential. Non-glucose related electroactive compounds can be any compound, in the sensor's local environment that has

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an oxidation potential substantially overlapping with the oxidation potential of H_2O_2, for example. While not wishing to be bound by theory, it is believed that the glucose-measuring electrode can measure both the signal directly related to the reaction of glucose with GOx (produces H_2O_2 that is oxidized at the working electrode) and signals from unknown compounds that are in the extracellular milieu surrounding the sensor. These unknown compounds can be constant or non-constant (e.g., intermittent or transient) in concentration and/or effect. In some circumstances, it is believed that some of these unknown compounds are related to the host's disease state. For example, it is know that blood chemistry changes dramatically during/after a heart attack (e.g., pH changes, changes in the concentration of various blood components/protein, and the like). Other compounds that can contribute to the non-glucose related signal are believed to be related to the wound healing process that is initiated by implantation/insertion of the sensor into the host, which is described in more detail with reference to co-pending U.S. Patent Application 11/503,367 filed August 10, 2006 and entitled "ANALYTE SENSOR," which is incorporated herein by reference in its entirety. For example, transcutaneously inserting a needle-type sensor initiates a cascade of events that includes the release of various reactive molecules by macrophages.

[0316] In some embodiments, the glucose sensor includes a second (e.g., auxiliary) working electrode that is configured to generate a second signal associated with non-glucose related electroactive compounds that have the same oxidation potential as the above-described first working electrode (e.g., *para supra*). In some embodiments, the non-glucose related electroactive species includes at least one of interfering species, non-reaction-related H_2O_2, and other electroactive species. For example, interfering species includes any compound that is not directly related to the electrochemical signal generated by the glucose-GOx reaction, such as but not limited to electroactive species in the local environment produces by other bodily processes (e.g., cellular metabolism, wound healing, a disease process, and the like). Non-reaction-related H_2O_2 includes H_2O_2 from sources other than the glucose-GOx reaction, such as but not limited to H_2O_2 released by nearby cells during the course of the cells' metabolism, H_2O_2 produced by other enzymatic reactions (e.g., extracellular enzymes around the sensor or such as can be released during the death of nearby cells or such as can be released by activated macrophages),

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and the like. Other electroactive species includes any compound that has an oxidation potential similar to or overlapping that of H_2O_2.

[0317] The non-analyte (e.g., non-glucose) signal produced by compounds other than the analyte (e.g., glucose) obscured the signal related to the analyte, contributes to sensor inaccuracy, and is considered background noise. As described in greater detail in the section entitled "Noise Reduction," background noise includes both constant and non-constant components and must be removed to accurately calculate the analyte concentration. While not wishing to be bound by theory, it is believed that the sensor of the preferred embodiments are designed (e.g., with symmetry, coaxial design and/or integral formation) such that the first and second electrodes are influenced by substantially the same external/environmental factors, which enables substantially equivalent measurement of both the constant and non-constant species/noise. This advantageously allows the substantial elimination of noise (including transient biologically related noise that has been previously seen to affect accuracy of sensor signal due to it's transient and unpredictable behavior) on the sensor signal (using electronics described elsewhere herein) to substantially reduce or eliminate signal effects due to noise, including non-constant noise (e.g., unpredictable biological, biochemical species or the like) known to effect the accuracy of conventional continuous sensor signals. Preferably, the sensor includes electronics operably connected to the first and second working electrodes. The electronics are configured to provide the first and second signals that are used to generate glucose concentration data substantially without signal contribution due to non-glucose-related noise. Preferably, the electronics include at least a potentiostat that provides a bias to the electrodes. In some embodiments, sensor electronics are configured to measure the current (or voltage) to provide the first and second signals. The first and second signals are used to determine the glucose concentration substantially without signal contribution due to non-glucose-related noise such as by but not limited to subtraction of the second signal from the first signal or alternative data analysis techniques. In some embodiments, the sensor electronics include a transmitter that transmits the first and second signals to a receiver, where additional data analysis and/or calibration of glucose concentration can be processed. U.S. Patent Publication No. US-2005-0027463-A1, US-2005-0203360-A1 and U.S. Patent Publication No. US-2006-0036142-A1

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describe systems and methods for processing sensor analyte data and are incorporated herein by reference in their entirety.

[0318] In preferred embodiments, the sensor electronics (e.g., electronic components) are operably connected to the first and second working electrodes. The electronics are configured to calculate at least one analyte sensor data point. For example, the electronics can include a potentiostat, A/D converter, RAM, ROM, transmitter, and the like. In some embodiments, the potentiostat converts the raw data (e.g., raw counts) collected from the sensor to a value familiar to the host and/or medical personnel. For example, the raw counts from a glucose sensor can be converted to milligrams of glucose per deciliter of glucose (e.g., mg/dl). In some embodiments, the electronics are operably connected to the first and second working electrodes and are configured to process the first and second signals to generate a glucose concentration substantially without signal contribution due to non-glucose noise artifacts. The sensor electronics determine the signals from glucose and non-glucose related signal with an overlapping measuring potential (e.g., from a first working electrode) and then non-glucose related signal with an overlapping measuring potential (e.g., from a second electrode). The sensor electronics then use these data to determine a substantially glucose-only concentration, such as but not limited to subtracting the second electrode's signal from the first electrode's signal, to give a signal (e.g., data) representative of substantially glucose-only concentration, for example. In general, the sensor electronics may perform additional operations, such as but not limited to data smoothing and noise analysis.

Bifunctionality

[0319] In some embodiments, the components of at least a portion (e.g., the *in vivo* portion or the sensing portion) of the sensor possess bifunctional properties (e.g., provide at least two functions to the sensor). These properties can include electrical conductance, insulative properties, structural support, and diffusion barrier properties.

[0320] In one exemplary embodiment, the analyte sensor is designed with two working electrodes, a membrane system and an insulating material disposed between the working electrodes. An active enzymatic membrane is disposed above the first working electrode, while an inactive- or non-enzymatic membrane is disposed above the second working electrode. Additionally, the working electrodes and the insulating material are configured provide at least

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two functions to the sensor, including but not limited to electrical conductance, insulative properties, structural support, and diffusion barrier. For example, in one embodiment of a glucose sensor, the two working electrodes support the sensor's structure and provide electrical conductance; the insulating material provides insulation between the two electrodes and provides additional structural support and/or a diffusional barrier.

[0321] In some embodiments, a component of the sensor is configured to provide both electrical conductance and structural support. In an exemplary embodiment, the working electrode(s) and reference electrode are generally manufactured of electrically conductive materials, such as but not limited silver or silver/silver chloride, copper, gold, platinum, iridium, platinum-iridium, palladium, graphite, carbon, conductive polymers, alloys, and the like. Accordingly, the electrodes are both conductive and they give the sensor its shape (e.g., are supportive).

[0322] Referring to **Fig. 1B**, all three electrodes **16**, **18**, and **20** are manufactured from plated insulator, a plated wire, or electrically conductive material, such as but not limited to a metal wire. Accordingly, the three electrodes provide both electrical conductance (to measure glucose concentration) and structural support. Due to the configuration of the electrodes (e.g., the wires are about 0.001 inches in diameter or less, to about 0.01 inches or more), the sensor is needle-like and only about 0.003 inches or less to about 0.015 inches or more.

[0323] Similarly, the electrodes of **Fig. 7A** through **Fig. 9** provide electrical conductance, to detect the analyte of interest, as well as structural support for the sensor. For example, the sensors depicted in **Figs. 7A** through **7L** embodiments that are substantially needle-like. Additionally, these sensors are substantially resilient, and therefore able to flex in response to mechanical pressure and then to regain their original shapes. **Fig. 7M** depicts a cross-section of another sensor embodiment, which can be a composite (e.g., built up of layers of working and reference electrode materials) needle-like sensor or the composite "wire" can be cut to produce pancake-shaped sensors [describe its bifunctionality without unnecessary characterizations (e.g., not "pancake-shaped"). **Fig. 7N** through **Fig. 9** illustrate additional sensor embodiments, wherein the electrodes provide electrical conductance and support the sensor's needle-like shape.

[0324] In some embodiments, the first and second working electrodes are configured to provide both electrical conductance and structural support. For example, in a needle-type

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sensor, the working electrodes are often manufactured of bulk metal wires (e.g., copper, gold, platinum, iridium, platinum-iridium, palladium, graphite, carbon, conductive polymers, alloys, and the like). The reference electrode, which can function as a reference electrode alone, or as a dual reference and counter electrode, are formed from silver or silver/silver chloride, or the like. The metal wires are conductive (e.g., can conduct electricity) and give the sensor its shape and/or structural support. For example, one electrode metal wire may be coiled around the other electrode metal wire (e.g., **Fig. 1B** or **Fig. 7B**). In a further embodiment, the sensor includes a reference electrode that is also configured to provide electrical conductance and structural support (e.g., **Fig. 1B**, **Figs. 7C** to **7E**). In general, reference electrodes are made of metal, such as bulk silver or silver/silver chloride wires. Like the two working electrodes, the reference electrode both conducts electricity and supports the structure of the sensor.

[0325] In some embodiments, the first and second working electrode and the insulating material are configured provide at least two functions, such as but not limited to electrical conductance, insulative properties, structural support, and diffusion barrier. As described elsewhere herein, the working electrodes are electrical conductors and also provide support for the sensor. The insulating material (e.g., **I**) acts as an insulator, to prevent electrical communication between certain parts of the various electrodes. The insulating material also provides structural support or substantially prevents diffusion of electroactive species from one working electrode to the other, which is discussed in greater detail elsewhere herein.

[0326] In preferred embodiments, the sensor has a diffusion barrier disposed between the first and second working electrodes. The diffusion barrier is configured to substantially block diffusion of the analyte or a co-analyte (e.g., H_2O_2) between the first and second working electrodes. For example, a sheet of a polymer through which H_2O_2 cannot diffuse can be interposed between the two working electrodes. Diffusion barriers are discussed in greater detail elsewhere herein.

[0327] In some embodiments of the preferred embodiments, the analyte sensor includes a reference electrode that is configured to provide electrical conductance and a diffusion barrier. Electrical conductance is an inherent property of the metal used to manufacture the reference electrode. However, the reference electrode can be configured to prevent species (e.g., H_2O_2) from diffusing from the first working electrode to the second working electrode. For

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example, a sufficiently large reference electrode can be placed between the two working electrodes. In some embodiments, the reference electrode projects farther than the two working electrodes. In other embodiments, the reference electrode is so broad that a substantial portion of the H_2O_2 produced at the first working electrode cannot diffuse to the second working electrode, and thereby significantly affect the second working electrode's function.

[0328] In a further embodiment, the reference electrode is configured to provide a diffusion barrier and structural support. As described elsewhere herein, the reference electrode can be constructed of a sufficient size and/or shape that a substantial portion of the H_2O_2 produced at a first working electrode cannot diffuse to the second working electrode and affect the second working electrode's function. Additionally, metal wires are generally resilient and hold their shape, the reference electrode can also provide structural support to the sensor (e.g., help the sensor to hold its shape).

[0329] In some embodiments of the analyte sensor described elsewhere herein, the insulating material is configured to provide both electrical insulative properties and structural support. In one exemplary embodiment, portions of the electrodes are coated with a non-conductive polymer. Inherently, the non-conductive polymer electrically insulates the coated electrodes from each other, and thus substantially prevents passage of electricity from one coated wire to another coated wire. Additionally, the non-conductive material (e.g., a non-conductive polymer or insulating material) can stiffen the electrodes and make them resistant to changes in shape (e.g., structural changes).

[0330] In some embodiments, a sensor component is configured to provide electrical insulative properties and a diffusion barrier. In one exemplary embodiment, the electrodes are coated with the non-conductive material that substantially prevents direct contact between the electrodes, such that electricity cannot be conducted directly from one electrode to another. Due to the non-conductive coatings on the electrodes, electrical current must travel from one electrode to another through the surrounding aqueous medium (e.g., extracellular fluid, blood, wound fluid, or the like). Any non-conductive material (e.g., insulator) known in the art can be used to insulate the electrodes from each other. In exemplary embodiments, the electrodes can be coated with non-conductive polymer materials (e.g., parylene, PTFE, ETFE, polyurethane,

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polyethylene, polyimide, silicone and the like) by dipping, painting, spraying, spin coating, or the like.

[0331] Non-conductive material (e.g., insulator, as discussed elsewhere herein) applied to or separating the electrodes can be configured to prevent diffusion of electroactive species (e.g., H_2O_2) from one working electrode to another working electrode. Diffusion of electroactive species from one working electrode to another can cause a false analyte signal. For example, electroactive species (e.g., H_2O_2) that are created at a first working electrode having active enzyme (e.g., GOx) can diffuse to a nearby working electrode (e.g., without active GOx). When the electroactive species arrives at the second working electrode, the second electrode registers a signal (e.g., as if the second working electrode comprised active GOx). The signal registered at the second working electrode due to the diffusion of the H_2O_2 is aberrant and can cause improper data processing in the sensor electronics. For example, if the second electrode is configured to measure a substantially non-analyte related signal (e.g., background) the sensor will record a higher non-analyte related signal than is appropriate, possibly resulting in the sensor reporting a lower analyte concentration than actually is present in the host. This is discussed in greater detail elsewhere herein.

[0332] In preferred embodiments, the non-conductive material is configured to provide a diffusion barrier and structural support to the sensor. Diffusion barriers are described elsewhere herein. Non-conductive materials can be configured to support the sensor's structure. In some, non-conductive materials with relatively more or less rigidity can be selected. For example, if the electrodes themselves are relatively flexible, it may be preferred to select a relatively rigid non-conductive material, to make the sensor stiffer (e.g., less flexible or bendable). In another example, if the electrodes are sufficiently resilient or rigid, a very flexible non-conductive material may be coated on the electrodes to bind the electrodes together (e.g., keep the electrodes together and thereby hold the sensor's shape).

[0333] Referring now to **Figs. 7C** to **7J**, the non-conductive material can be coated on or wrapped around the grouped or bundled electrodes, to prevent the electrodes from separating and also to prevent the electrodes from directly touching each other. For example, with reference to **Fig. 7C**, each electrode can be individually coated by a first non-conductive material and then bundled together. Then the bundle of individually insulated electrodes can be coated with a

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second layer of the first non-conductive material or with a layer or a second non-conductive material. In an embodiment of a sensor having the structure shown in **Fig. 7K**, each electrode **E1**, **E2** is coated with a non-conductive material/insulator **I**, and then coated with a second non-conductive material **703** (e.g., instead of a biointerface membrane). Similarly, **in Fig. 7L**, the non-conductive material **I** prevents electrodes **E1** and **E2** from making direct contact with each other as well as giving the needle-like sensor its overall dimensions and shape.

[0334] **Fig. 7N** illustrates one method of configuring a sensor having a non-conductive material **I** that both provides electrical insulation between the electrodes **E1**, **E2**, **R** and provides structural support to the sensor. Namely, the electrodes are embedded in a non-conductive polymer **I**, which is subsequently vulcanized (**704** = before shaping). After vulcanization, the excess non-conductive polymer **I** is trimmed away (e.g., cutting or scraping, etc.) to produce a sensor having the final desired sensor shape **705** = after shaping).

[0335] In some embodiments, a component of the sensor is configured to provide both insulative properties and a diffusion barrier. Diffusion barriers are discussed elsewhere herein. In one exemplary embodiment, the working electrodes are separated by a non-conductive material/insulator that is configured such that electroactive species (e.g., H_2O_2) cannot diffuse around it (e.g., from a first electrode to a second electrode). For example, with reference to the embodiment shown in **Fig. 7H**, the electrodes **E1**, **E2** are placed in the groves carved into a cylinder of non-conductive material **I**. The distance ***D*** from **E1** to **E2** (e.g., around **I**) is sufficiently great that H_2O_2 produced at **E1** cannot diffuse to **E2** and thereby cause an aberrant signal at **E2**.

[0336] In some preferred embodiments, in addition to two working electrodes and a non-conductive material/insulator, the sensor includes at least a reference or a counter electrode. In preferred embodiments, the reference and/or counter electrode, together with the first and second working electrodes, integrally form at least a portion of the sensor. In some embodiments, the reference and/or counter electrode is located remote from the first and second working electrodes. For example, in some embodiments, such as in the case of a transcutaneous sensor, the reference and/or counter electrodes can be located on the *ex vivo* portion of the sensor or reside on the host's skin, such as a portion of an adhesive patch. In other embodiments, such as in the case of an intravascular sensor, the reference and/or counter electrode can be located on

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the host's skin, within or on the fluid connector (e.g., coiled within the *ex vivo* portion of the device and in contact with fluid within the device, such as but not limited to saline) or on the exterior of the *ex vivo* portion of the device. In preferred embodiments, the surface area of the reference and/or counter electrode is as least six times the surface area of at least one of the first and second working electrodes. In a further embodiment, the surface area of the reference and/or counter electrode is at least ten times the surface area of at least one of the first and second electrodes.

[0337] In preferred embodiments, the sensor is configured for implantation into the host. The sensor can be configured for subcutaneous implantation in the host's tissue (e.g., transcutaneous or wholly implantable). Alternatively, the sensor can be configured for indwelling in the host's blood stream (e.g., inserted through an intravascular catheter or integrally formed on the exterior surface of an intravascular catheter that is inserted into the host's blood stream).

[0338] In some embodiments, the sensor is a glucose sensor that has a first working electrode configured to generate a first signal associated with glucose (e.g., the analyte) and non-glucose related electroactive compounds (e.g., physiological baseline, interferents, and non-constant noise) having a first oxidation potential. For example, glucose has a first oxidation potential. The interferents have an oxidation potential that is substantially the same as the glucose oxidation potential (e.g., the first oxidation potential). In a further embodiment, the glucose sensor has a second working electrode that is configured to generate a second signal associated with noise of the glucose sensor. The noise of the glucose sensor is signal contribution due to non-glucose related electroactive compounds (e.g., interferents) that have an oxidation potential that substantially overlaps with the first oxidation potential (e.g., the oxidation potential of glucose, the analyte). In various embodiments, the non-glucose related electroactive species include an interfering species, non-reaction-related hydrogen peroxide, and/or other electroactive species.

[0339] In preferred embodiments, the glucose sensor has electronics that are operably connected to the first and second working electrodes and are configured to provide the first and second signals to generate glucose concentration data substantially without signal contribution due to non-glucose-related noise. For example, the sensor electronics analyze the signals from

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the first and second working electrodes and calculate the portion of the first electrode signal that is due to glucose concentration only. The portion of the first electrode signal that is not due to the glucose concentration can be considered to be background, such as but not limited to noise.

[0340] In preferred embodiments, the glucose sensor has a non-conductive material (e.g., insulative material) positioned between the first and second working electrodes. The non-conductive material substantially prevents cross talk between the first and second working electrodes. For example, the electrical signal cannot pass directly from a first insulated electrode to a second insulated electrode. Accordingly, the second insulated electrode cannot aberrantly record an electrical signal due to electrical signal transfer from the first insulated electrode.

[0341] In preferred embodiments, the first and second working electrodes and the non-conductive material integrally form at least a portion of the sensor (e.g., a glucose sensor). The first and second working electrodes integrally form a substantial portion of the sensor configured for insertion in the host (e.g., the *in vivo* portion of the sensor). In a further embodiment, the sensor (e.g., a glucose sensor) includes a reference electrode that, in addition to the first and second working electrodes, integrally forms a substantial portion of the sensor configured for insertion in the host (e.g., the *in vivo* portion of the sensor). In yet a further embodiment, the sensor (e.g., a glucose sensor) has an insulator (e.g., non-conductive material), wherein the first and second working electrodes and the insulator integrally form a substantial portion of the sensor configured for insertion in the host (e.g., the *in vivo* portion of the sensor).

[0342] In preferred embodiments, the sensor (e.g., a glucose sensor) includes a diffusion barrier configured to substantially block diffusion of the analyte (e.g., glucose) or a co-analyte (e.g., H_2O_2) between the first and second working electrodes. For example, as described with reference to **Fig. 10**, a diffusion barrier ***D*** (e.g., spatial, physical and/or temporal) blocks (e.g., attenuates) diffusion of a species (e.g., glucose and/or H_2O_2) from the first working electrode **E1** to the second working electrode **E2**. In some embodiments, the diffusion barrier ***D*** is a physical diffusion barrier, such as a structure between the working electrodes that blocks glucose and H_2O_2 from diffusing from the first working electrode **E1** to the second working electrode **E2**. In other embodiments, the diffusion barrier ***D*** is a spatial diffusion barrier, such as a distance between the working electrodes that blocks glucose and H_2O_2 from diffusing from the first working electrode **E1** to the second working electrode **E2**. . In still other embodiments, the

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diffusion barrier ***D*** is a temporal diffusion barrier, such as a period of time between the activity of the working electrodes such that if glucose or H_2O_2 diffuses from the first working electrode **E1** to the second working electrode **E2**, the second working electrode **E2** will not substantially be influenced by the H_2O_2 from the first working electrode **E1.**.

[0343] With reference to **Fig. 7H**, if the diffusion barrier is spatial, a distance **D** separates the working electrodes, such that the analyte or co-analyte substantially cannot diffuse from a first electrode **E1** to a second electrode **E2**. In some embodiments, the diffusion barrier is physical and configured from a material that substantially prevents diffusion of the analyte or co-analyte there through. Again referring to **Fig. 7H**, the insulator **I** and/or reference electrode **R** is configured from a material that the analyte or co-analyte cannot substantially pass through. For example, H_2O_2 cannot substantially pass through a silver/silver chloride reference electrode. In another example, a parylene insulator can prevent H_2O_2 diffusion between electrodes. In some embodiments, wherein the diffusion barrier is temporal, the two electrodes are activated at separate, non-overlapping times (e.g., pulsed). For example, the first electrode **E1** can be activated for a period of one second, followed by activating the second electrode **E2** three seconds later (e.g., after **E1** has been inactivated) for a period of one second.

[0344] In additional embodiments, a component of the sensor is configured to provide both a diffusional barrier and a structural support, as discussed elsewhere herein. Namely, the diffusion barrier can be configured of a material that is sufficiently rigid to support the sensor's shape. In some embodiments, the diffusion barrier is an electrode, such as but not limited to the reference and counter electrodes (e.g., **Fig. 7G** to **7J** and **Fig. 8A**). In other embodiments, the diffusion barrier is an insulating coating (e.g., parylene) on an electrode (e.g., **Fig. 7K** to **7L**) or an insulating structure separating the electrodes (e.g., **Fig. 8A** and **Fig. 10**).

[0345] One preferred embodiment provides a glucose sensor configured for insertion into a host for measuring a glucose concentration in the host. The sensor includes a first working electrode configured to generate a first signal associated with glucose and non-glucose related electroactive compounds having a first oxidation potential. The sensor also includes a second working electrode configured to generate a second signal associated with noise of the glucose sensor comprising signal contribution due to non-glucose related electroactive compounds that have an oxidation potential that substantially overlaps with the first oxidation potential (e.g., the

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oxidation potential of H_2O_2). Additionally, the glucose sensor includes a non-conductive material located between the first and second working electrodes. Each of the first working electrode, the second working electrode, and the non-conductive material are configured to provide at least two functions selected from the group consisting of: electrical conductance, insulative properties, structural support, and diffusion barrier.

[0346] In some embodiments of the glucose sensor, each of the first working electrode and the second working electrode are configured to provide electrical conductance and structural support. For example, the metal plated wire of electrodes conducts electricity and helps maintain the sensor's shape. In a further embodiment, the glucose sensor includes a reference electrode that is configured to provide electrical conductance and structural support. For example, the silver/silver chloride reference electrode is both electrically conductive and supports the sensor's shape. In some embodiments of the glucose sensor includes a reference electrode that is configured to provide electrical conductance and a diffusion barrier. For example, the silver/silver chloride reference electrode can be configured as a large structure or protruding structure, which separates the working electrodes by the distance ***D*** (e.g., **Fig. 7G**). Distance "***D***" is sufficiently large that glucose and/or H_2O_2 cannot substantially diffuse around the reference electrode. Accordingly, H_2O_2 produced at a first working electrode does not substantially contribute to signal at a second working electrode. In some embodiments of the glucose sensor includes a reference electrode that is configured to provide a diffusion barrier and structural support. In some embodiments of the glucose sensor, the non-conductive material is configured to provide electrical insulative properties and structural support. For example, non-conductive dielectric materials can insulate an electrode and can be sufficiently rigid to stiffen the sensor. In still other embodiments, the non-conductive material is configured to provide electrical insulative properties and a diffusion barrier. For example, a substantially rigid, non-conductive dielectric can coat the electrodes and provide support, as shown in **Fig. 7L**. In other embodiments, the non-conductive material is configured to provide diffusion barrier and structural support. For example, a dielectric material can protrude between the electrodes, to act as a diffusion barrier and provide support to the sensor's shape, as shown in **Fig. 10**.

Noise Reduction

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[0347] In another aspect, the sensor is configured to reduce noise, including non-constant non-analyte related noise with an overlapping measuring potential with the analyte. A variety of noise can occur when a sensor has been implanted in a host. Generally, implantable sensors measure a signal (e.g., counts) that generally comprises at least two components, the background signal (e.g., background noise) and the analyte signal. The background signal is composed substantially of signal contribution due to factors other than glucose (e.g., interfering species, non-reaction-related hydrogen peroxide, or other electroactive species with an oxidation potential that overlaps with the analyte or co-analyte). The analyte signal (e.g., glucose) is composed substantially of signal contribution due to the analyte. Consequently, because the signal includes these two components, a calibration is performed in order to determine the analyte (e.g., glucose) concentration by solving for the equation y=mx+b, where the value of b represents the background of the signal.

[0348] In some circumstances, the background is comprised of both constant (e.g., baseline) and non-constant (e.g., noise) factors. Generally, it is desirable to remove the background signal, to provide a more accurate analyte concentration to the host or health care professional.

[0349] The term "baseline" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a substantially constant signal derived from certain electroactive compounds found in the human body that are relatively constant (e.g., baseline of the host's physiology, non-analyte related). Therefore, baseline does not significantly adversely affect the accuracy of the calibration of the analyte concentration (e.g., baseline can be relatively constantly eliminated using the equation $y=mx+b$).

[0350] In contrast, "noise" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a substantially intermittent signal caused by relatively non-constant factors (e.g., the presence of intermittent noise-causing compounds that have an oxidation potential that substantially overlaps the oxidation potential of the analyte or co-analyte and arise due to the host's ingestion, metabolism, wound healing, and other mechanical, chemical and/or biochemical factors, also non-analyte related). Noise can be

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difficult to remove from the sensor signal by calibration using standard calibration equations (e.g., because the background of the signal does not remain constant). Noise can significantly adversely affect the accuracy of the calibration of the analyte signal. Additionally noise, as described herein, can occur in the signal of conventional sensors with electrode configurations that are not particularly designed to measure noise substantially equally at both active and in-active electrodes (e.g., wherein the electrodes are spaced and/or non symmetrical, noise may not be equally measured and therefore not easily removed using conventional dual electrode designs).

[0351] There are a variety of ways noise can be recognized and/or analyzed. In preferred embodiments, the sensor data stream is monitored, signal artifacts are detected, and data processing is based at least in part on whether or not a signal artifact has been detected, such as described in U.S. Patent Publication No. US-2005-0043598-A1 and co-pending U.S. Application No. 11/503,367 filed August 10, 2006 and entitled "ANALYTE SENSOR," herein incorporated by reference in its entirety.

[0352] Accordingly, if a sensor is designed such that the signal contribution due to baseline and noise can be removed, then more accurate analyte concentration data can be provided to the host or a healthcare professional.

[0353] One embodiment provides an analyte sensor (e.g., glucose sensor) configured for insertion into a host for measuring an analyte (e.g., glucose) in the host. The sensor includes a first working electrode disposed beneath an active enzymatic portion of a membrane on the sensor; a second working electrode disposed beneath an inactive- or non-enzymatic portion of the membrane on the sensor; and electronics operably connected to the first and second working electrode and configured to process the first and second signals to generate an analyte (e.g., glucose) concentration substantially without signal contribution due to non-glucose related noise artifacts.

[0354] Referring now to **Fig. 9B**, in another embodiment, the sensor has a first working electrode **E1** and a second working electrode **E2**. The sensor includes a membrane system (not shown) covering the electrodes, as described elsewhere herein. A portion of the membrane system on the first electrode contains active enzyme, which is depicted schematically as oval **904a** (e.g., active GOx). A portion of the membrane system on the second electrode is

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non-enzymatic or contains inactivated enzyme, which is depicted schematically as oval **904b** (e.g., heat- or chemically-inactivated GOx or optionally no GOx). A portion of the sensor includes electrical connectors **804**. In some embodiments, the connectors **804** are located on an *ex vivo* portion of the sensor. Each electrode (e.g., **E1**, **E2**, etc.) is connected to sensor electronics (not shown) by a connector **804**. Since the first electrode **E1** includes active GOx, it produces a first signal that is related to the concentration of the analyte (in this case glucose) in the host as well as other species that have an oxidation potential that overlaps with the oxidation potential of the analyte or co-analyte (e.g., non-glucose related noise artifacts, noise-causing compounds, background). Since the second electrode **E2** includes inactive GOx, it produces a second signal that is not substantially related to the analyte or co-analyte. Instead, the second signal is substantially related to noise-causing compounds and other background noise. The sensor electronics process the first and second signals to generate an analyte concentration that is substantially free of the non-analyte related noise artifacts. Elimination or reduction of noise (e.g., non-constant background) is attributed at least in part to the configuration of the electrodes in the preferred embodiments, e.g., the locality of first and second working electrode, the symmetrical or opposing design of the first and second working electrodes, and/or the overall sizing and configuration of the exposed electroactive portions. Accordingly, the host is provided with improved analyte concentration data, upon which he can make medical treatment decisions (e.g., if he should eat, if he should take medication or the amount of medication he should take). Advantageously, in the case of glucose sensors, since the sensor can provide improved quality of data, the host can be maintained under tighter glucose control (e.g., about 80 mg/dl to about 120 mg/dl) with a reduced risk of hypoglycemia and hypoglycemia's immediate complications (e.g., coma or death). Additionally, the reduced risk of hypoglycemia makes it possible to avoid the long-term complications of hyperglycemia (e.g., kidney and heart disease, neuropathy, poor healing, loss of eye sight) by consistently maintaining tight glucose control (e.g., about 80 mg/dl to about 120 mg/dl).

[0355] In one embodiment, the sensor is configured to substantially eliminate (e.g., subtract out) noise due to mechanical factors. Mechanical factors include macro-motion of the sensor, micro-motion of the sensor, pressure on the sensor, local tissue stress, and the like. Since both working electrodes are constructed substantially symmetrically and identically, and due to

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the sensor's small size, the working electrodes are substantially equally affected by mechanical factors impinging upon the sensor. For example, if a build-up of noise-causing compounds occurs (e.g., due to the host pressing upon and manipulating (e.g., fiddling with) the sensor, for example) both working electrodes will measure the resulting noise to substantially the same extend, while only one working electrode (the first working electrode, for example) will also measure signal due to the analyte concentration in the host's body. The sensor then calculates the analyte signal (e.g., glucose-only signal) by removing the noise that was measured by the second working electrode from the total signal that was measured by the first working electrode.

[0356] Non-analyte related noise can also be caused by biochemical and/or chemical factors (e.g., compounds with electroactive acidic, amine or sulfhydryl groups, urea, lactic acid, phosphates, citrates, peroxides, amino acids (e.g., L-arginine), amino acid precursors or break-down products, nitric oxide (NO), NO-donors, NO-precursors or other electroactive species or metabolites produced during cell metabolism and/or wound healing). As with noise due to mechanical factors, noise due to biochemical/chemical factors will impinge upon the two working electrodes of the preferred embodiments (e.g., with and without active GOx) about the same extent, because of the sensor's small size and symmetrical configuration. Accordingly, the sensor electronics can use these data to calculate the glucose-only signal, as described elsewhere herein.

[0357] In one exemplary embodiment, the analyte sensor is a glucose sensor that measures a first signal associated with both glucose and non-glucose related electroactive compounds having a first oxidation potential. For example, the oxidation potential of the non-glucose related electroactive compounds substantially overlaps with the oxidation potential of H_2O_2, which is produced according to the reaction of glucose with GOx and subsequently transfers electrons to the first working electrode (e.g., **E1**; **Fig. 10**). The glucose sensor also measures a second signal, which is associated with background noise of the glucose sensor. The background noise is composed of signal contribution due to noise-causing compounds (e.g., interferents), non-reaction-related hydrogen peroxide, or other electroactive species with an oxidation potential that substantially overlaps with the oxidation potential of H_2O_2 (the co-analyte). The first and second working electrodes integrally form at least a portion of the sensor, such as but not limited to the *in vivo* portion of the sensor, as discussed elsewhere herein.

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Additionally, each of the first working electrode, the second working electrode, and a non-conductive material/insulator are configured provide at least two functions (to the sensor), such as but not limited to electrical conductance, insulative properties, structural support, and diffusion barrier (described elsewhere herein). Furthermore, the sensor has a diffusion barrier that substantially blocks (e.g., attenuates) diffusion of glucose or H_2O_2 between the first and second working electrodes.

Diffusion Barrier

[0358] Another aspect of the sensor is a diffusion barrier, to prevent an undesired species, such as H_2O_2 or the analyte, from diffusing between active (with active enzyme) and inactive (without active enzyme) electrodes. In various embodiments, the sensor includes a diffusion barrier configured to be physical, spatial, and/or temporal.

[0359] **Fig. 10** is a schematic illustrating one embodiment of a sensor (e.g., a portion of the *in vivo* portion of the sensor, such as but not limited to the sensor electroactive surfaces) having one or more components that act as a diffusion barrier (e.g., prevent diffusion of electroactive species from one electrode to another). The first working electrode **E1** is coated with an enzyme layer **1000** comprising active enzyme. For example, in a glucose sensor, the first working electrode **E1** is coated with glucose oxidase enzyme (GOx). A second working electrode **E2** is separated from the first working electrode **E1** by a diffusion barrier ***D***, such as but not limited to a physical diffusion barrier (e.g., either a reference electrode or a layer of non-conductive material/insulator). The diffusion barrier can also be spatial or temporal, as discussed elsewhere herein.

[0360] Glucose and oxygen diffuse into the enzyme layer **1000**, where they react with GOx, to produce gluconate and H_2O_2. At least a portion of the H_2O_2 diffuses to the first working electrode **E1**, where it is electrochemically oxidized to oxygen and transfers two electrons (e.g., $2e^-$) to the first working electrode **E1**, which results in a glucose signal that is recorded by the sensor electronics (not shown). The remaining H_2O_2 can diffuse to other locations in the enzyme layer or out of the enzyme layer (illustrated by the wavy arrows). Without a diffusion barrier ***D***, a portion of the H_2O_2 can diffuse to the second working electrode **E2**, which results in an aberrant signal that can be recorded by the sensor electronics as a non-glucose related signal (e.g., background).

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[0361] Preferred embodiments provide for a substantial diffusion barrier ***D*** between the first and second working electrodes (**E1**, **E2**) such that the H_2O_2 cannot substantially diffuse from the first working electrode **E1** to the second working electrode **E2**. Accordingly, the possibility of an aberrant signal produced by H_2O_2 from the first working electrode **E1** (at the second working electrode **E2**) is reduced or avoided.

[0362] In some alternative embodiments, the sensor is provided with a spatial diffusion barrier between electrodes (e.g., the working electrodes). For example, a spatial diffusion barrier can be created by separating the first and second working electrodes by a distance that is too great for the H_2O_2 to substantially diffuse between the working electrodes. In some embodiments, the spatial diffusion barrier is about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, or 0.08 inches to about 0.09, 0.10, 0.11, or 0.120 inches. In other embodiments, the spatial diffusion barrier is about 0.020 inches to about 0.050 inches. Still in other embodiments, the spatial diffusion barrier is about 0.055 inches to about 0.095 inches. A reference electrode **R** (e.g., a silver or silver/silver chloride electrode) or a non-conductive material **I** (e.g., a polymer structure or coating such as Parylene) can be configured to act as a spatial diffusion barrier.

[0363] **Figs. 9A** and **9B** illustrate two exemplary embodiments of sensors with spatial diffusion barriers. In each embodiment, the sensor has two working electrodes **E1** and **E2**. Each working electrode includes an electroactive surface, represented schematically as windows **904a** and **904b**, respectively. The sensor includes a membrane system (not shown). Over one electroactive surface (e.g., **904a**) the membrane includes active enzyme (e.g., GOx). Over the second electroactive surface (e.g., **904b**) the membrane does not include active enzyme. In some embodiments, the portion of the membrane covering the second electroactive surface contains inactivated enzyme (e.g., heat- or chemically-inactivated GOx) while in other embodiments, this portion of the membrane does not contain any enzyme (e.g., non-enzymatic). The electroactive surfaces **904a** and **904b** are separated by a spatial diffusion barrier that is substantially wide such that H_2O_2 produced at the first electroactive surface **904a** cannot substantially affect the second electroactive surface **904b**. In some alternative embodiments, the diffusion barrier can be physical (e.g., a structure separating the electroactive surfaces) or temporal (e.g., oscillating activity between the electroactive surfaces).

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[0364] In another embodiment, the sensor is an indwelling sensor, such as configured for insertion into the host's circulatory system *via* a vein or an artery. In some exemplary embodiments, an indwelling sensor includes at least two working electrodes that are inserted into the host's blood stream through a catheter. The sensor includes at least a reference electrode that can be disposed either with the working electrodes or remotely from the working electrodes. The sensor includes a spatial, a physical, or a temporal diffusion barrier. A spatial diffusion barrier can be configured as described elsewhere herein, with reference to **Fig. 7A** through **Fig. 8A**.

[0365] **Fig. 9B** provides one exemplary embodiment of an indwelling analyte sensor, such as but not limited to an intravascular glucose sensor to be used from a few hours to ten days or longer. Namely, the sensor includes two working electrodes. One working electrode detects the glucose-related signal (due to active GOx applied to the electroactive surface) as well as non-glucose related signal. The other working electrode detects only the non-glucose related signal (because no active GOx is applied to its electroactive surface). H_2O_2 is produced on the working electrode with active GOx. If the H_2O_2 diffuses to the other working electrode (the no GOx electrode) an aberrant signal will be detected at this electrode, resulting in reduced sensor activity. Accordingly, it is desirable to separate the electroactive surfaces with a diffusion barrier, such as but not limited to a spatial diffusion barrier. Indwelling sensors are described in more detail in copending U.S. patent application 11/543,396 filed on even date herewith and entitled "ANALYTE SENSOR," herein incorporated in its entirety by reference.

[0366] To configure a spatial diffusion barrier between the working electrodes, the location of the active enzyme (e.g., GOx) is dependent upon the orientation of the sensor after insertion into the host's artery or vein. For example, in an embodiment configured for insertion upstream in the host's blood flow (e.g., against the blood flow), active GOx would be applied to electroactive surface **904b** and inactive GOX (or no GOx) would be applied to electroactive surface **904a** (e.g., upstream from **904b**, relative to the direction of blood flow). Due to this configuration, H_2O_2 produced at electroactive surface **904b** would be carrier down stream (e.g., away from electroactive surface **904a**) and thus not affect electrode **E1**.

[0367] Alternatively, the indwelling electrode can also be configured for insertion of the sensor into the host's vein or artery in the direction of the blood flow (e.g., pointing downstream). In this configuration, referred to as a spatial diffusion barrier, or as a flow path

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diffusion barrier, the active GOx can be advantageously applied to electroactive surface **904a** on the first working electrode **E1**. The electroactive surface **904b** on the second working electrode **E2** has no active GOx. Accordingly, H_2O_2 produced at electroactive surface **904a** is carried away by the blood flow, and has no substantial effect on the second working electrode **E2**.

[0368] In another embodiment of an indwelling analyte sensor, the reference electrode, which is generally configured of silver/silver chloride, can extend beyond the working electrodes, to provide a physical barrier around which the H_2O_2 generated at the electrode comprising active GOx cannot pass the other working electrode (that has active GOx). In some embodiments, the reference electrode has a surface area that is at least six times larger than the surface area of the working electrodes. In other embodiments, a 2-working electrode analyte sensor includes a counter electrode in addition to the reference electrode. As is generally know in the art, the inclusion of the counter electrode allows for a reduction in the reference electrode's surface area, and thereby allows for further miniaturization of the sensor (e.g., reduction in the sensor's diameter and/or length, etc.).

[0369] **Fig. 7H** provides one exemplary embodiment of a spatial diffusion barrier, wherein the reference electrode/non-conductive insulating material **R/I** is sized and shaped such that H_2O_2 produced at the first working electrode **E1** (e.g., with enzyme) does not substantially diffuse around the reference electrode/non-conductive material **R/I** to the second working electrode **E2** (e.g., without enzyme). In another example, shown in **Fig. 7J**, the X-shaped the reference electrode/non-conductive material **R/I** substantially prevents diffusion of electroactive species from the first working electrode **E1** (e.g., with enzyme) to the second working electrode **E2** (e.g., without enzyme). In another embodiment, such as the sensor shown in **Fig. 7A**, the layer of non-conductive material **I** (between the electrodes) is of a sufficient length that the H_2O_2 produced at one electrode cannot substantially diffuse to another electrode. (e.g., from **E1** to either **E2** or **E3**; or from **E2** to either **E1** or **E3**, etc.).

[0370] In some embodiments, a physical diffusion barrier is provided by a physical structure, such as an electrode, insulator, and/or membrane. For example, in the embodiments shown in Figs. 7G to 7J, the insulator (I) or reference electrode (R) act as a diffusion barrier. As another example, the diffusion barrier can be a bioprotective membrane (e.g., a membrane that substantially resists, attenuates or blocks the transport of a species (e.g., hydrogen peroxide),

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such as a polyurethane. As yet another example, the diffusion barrier can be a resistance domain, as described in more detail elsewhere herein; namely, a semipermeable membrane that controls the flux of oxygen and an analyte (e.g., glucose) to the underlying enzyme domain. Numerous other structures and membranes can function as a physical diffusion barrier as is appreciated by one skilled in the art.

[0371] In other embodiments, a temporal diffusion barrier is provided (e.g., between the working electrodes). By temporal diffusion barrier is meant a period of time that substantially prevents an electroactive species (e.g., H_2O_2) from diffusing from a first working electrode to a second working electrode. For example, in some embodiments, the differential measurement can be obtained by switching the bias potential of each electrode between the measurement potential and a non-measurement potential. The bias potentials can be held at each respective setting (e.g., high and low bias settings) for as short as milliseconds to as long as minutes or hours. Pulsed amperometric detection (PED) is one method of quickly switching voltages, such as described in Bisenberger, M.; Brauchle, C.; Hampp, N. A triple-step potential waveform at enzyme multisensors with thick-film gold electrodes for detection of glucose and sucrose. *Sensors and Actuators* 1995, *B*, 181-189, which is incorporated herein by reference in its entirety. In some embodiments, bias potential settings are held long enough to allow equilibration.

[0372] One preferred embodiment provides a glucose sensor configured for insertion into a host for measuring glucose in the host. The sensor includes first and second working electrodes and an insulator located between the first and second working electrodes. The first working electrode is disposed beneath an active enzymatic portion of a membrane on the sensor and the second working electrode is disposed beneath an inactive- or non-enzymatic portion of the membrane on the sensor. The sensor also includes a diffusion barrier configured to substantially block (e.g., attenuate, restrict, suppress) diffusion of glucose or hydrogen peroxide between the first and second working electrodes.

[0373] In a further embodiment, the glucose sensor includes a reference electrode configured integrally with the first and second working electrodes. In some embodiments, the reference electrode can be located remotely from the sensor, as described elsewhere herein. In some embodiments, the surface area of the reference electrode is at least six times the surface

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area of the working electrodes. In some embodiments, the sensor includes a counter electrode that is integral to the sensor or is located remote from the sensor, as described elsewhere herein.

[0374] In a further embodiment, the glucose sensor detects a first signal associated with glucose and non-glucose related electroactive compounds having a first oxidation potential (e.g., the oxidation potential of H_2O_2). In some embodiments, the glucose sensor also detects a second signal is associated with background noise of the glucose sensor comprising signal contribution due to interfering species, non-reaction-related hydrogen peroxide, or other electroactive species with an oxidation potential that substantially overlaps with the oxidation potential of hydrogen peroxide; the first and second working electrodes integrally form at least a portion of the sensor; and each of the first working electrode, the second working electrode and the non-conductive material/insulator are configured provide at least two functions such as but not limited to electrical conductance, insulation, structural support, and a diffusion barrier

[0375] In further embodiments, the glucose sensor includes electronics operably connected to the first and second working electrodes. The electronics are configured to calculate at least one analyte sensor data point using the first and second signals described above. In still another further embodiment, the electronics are operably connected to the first and second working electrode and are configured to process the first and second signals to generate a glucose concentration substantially without signal contribution due to non-glucose noise artifacts.

Membrane Configurations

[0376] **Figs. 3A** to **3B** are cross-sectional exploded schematic views of the sensing region of a glucose sensor **10**, which show architectures of the membrane system **22** disposed over electroactive surfaces of glucose sensors in some embodiments. In the illustrated embodiments of Figs. 3A and 3B, the membrane system **22** is positioned at least over the glucose-measuring working electrode **16** and the optional auxiliary working electrode **18**; however the membrane system may be positioned over the reference and/or counter electrodes **20**, **22** in some embodiments.

[0377] Reference is now made to **Fig. 3A**, which is a cross-sectional exploded schematic view of the sensing region in one embodiment wherein an active enzyme **32** of the enzyme domain is positioned only over the glucose-measuring working electrode **16**. In this embodiment, the membrane system is formed such that the glucose oxidase **32** only exists above

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the glucose-measuring working electrode **16**. In one embodiment, during the preparation of the membrane system **22**, the enzyme domain coating solution can be applied as a circular region similar to the diameter of the glucose-measuring working electrode **16**. This fabrication can be accomplished in a variety of ways such as screen-printing or pad printing. Preferably, the enzyme domain is pad printed during the enzyme domain fabrication with equipment as available from Pad Print Machinery of Vermont (Manchester, VT). This embodiment provides the active enzyme **32** above the glucose-measuring working electrode **16** only, so that the glucose-measuring working electrode **16** (and not the auxiliary working electrode **18**) measures glucose concentration. Additionally, this embodiment provides an added advantage of eliminating the consumption of O_2 above the counter electrode (if applicable) by the oxidation of glucose with glucose oxidase.

[0378] **Fig. 3B** is a cross-sectional exploded schematic view of a sensing region of the preferred embodiments, and wherein the portion of the active enzyme within the membrane system **22** positioned over the auxiliary working electrode **18** has been deactivated **34**. In one alternative embodiment, the enzyme of the membrane system **22** may be deactivated **34** everywhere except for the area covering the glucose-measuring working electrode **16** or may be selectively deactivated only over certain areas (for example, auxiliary working electrode 18, counter electrode **22**, and/or reference electrode **20**) by irradiation, heat, proteolysis, solvent, or the like. In such a case, a mask (for example, such as those used for photolithography) can be placed above the membrane that covers the glucose-measuring working electrode **16**. In this way, exposure of the masked membrane to ultraviolet light deactivates the glucose oxidase in all regions except that covered by the mask.

[0379] In some alternative embodiments, the membrane system is disposed on the surface of the electrode(s) using known deposition techniques. The electrode-exposed surfaces can be inset within the sensor body, planar with the sensor body, or extending from the sensor body. Although some examples of membrane systems have been provided above, the concepts described herein can be applied to numerous known architectures not described herein.

Sensor Configurations for Equivalent Measurement of Noise Signals at the Two Working Electrodes

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[0380] In dual electrode biosensors (e.g., an analyte sensor having two working electrodes **E1**, **E2**), noise can be caused by a variety of sources, for example, located outside (e.g., by noise-causing species produced metabolically and/or consumed by the host) or within (e.g., crosstalk) the sensor. In some circumstances, biological and/or metabolic processes occurring in the host's body, such as in the locale of the implanted sensor, can cause noise. These metabolic processes, such as but not limited to wound healing, the body's response to illness and even daily cellular metabolic processes, can generate noise-causing metabolic species (e.g., compounds, substances) that impinge upon the sensor and cause noise on the signal. For example, some noise-causing species, the levels of which are relatively stable due to production during daily cellular metabolism, generally cause constant noise. In another example, some noise-causing species, the levels of which fluctuate due to production by intermittent metabolic process (e.g., wound healing or response to infection), generally cause non-constant noise. Noise-causing metabolic species include but are not limited to externally generated H_2O_2 (e.g., produced outside the sensor), compounds having electroactive acidic, amine or sulfhydryl groups, urea, lactic acid, phosphates, citrates, peroxides, amino acids (*e.g.*, L-arginine), amino acid precursors or break-down products, nitric oxide (NO), NO-donors, NO-precursors, reactive oxygen species or other electroactive species or metabolites produced during cell metabolism and/or wound healing, for example. Noise-causing species, such as drugs, vitamins and the like, can also be consumed by the host. These noise causing species include but are not limited to acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide and triglycerides. Further discussion of noise and its sources can be found in U.S. Patent Publication No. US-2007-0027370-A1 and co-pending U.S. Patent Application 11/750,907, filed on May 18, 2007 and entitled "ANALYTE SENSORS HAVING AN OPTIMIZED SIGNAL-TO-NOISE RATIO", both of which are incorporated herein by reference in their entirety.

[0381] In dual-electrode sensors, noise can also be generated within the sensor, namely due to diffusion of a measured species (e.g., H_2O_2) from a first working electrode (e.g., the H_2O_2 is generated in an active enzymatic portion of the sensor membrane associated with the first working electrode) to a second working electrode and detection thereby (e.g., which is associated with a non-enzymatic portion of the sensor membrane). This type of noise is

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commonly referred to as "crosstalk." Crosstalk is undesirable as it causes sensor error, which can result in inaccurate reporting of sensor data. In conventional sensors, a common solution to the problem of crosstalk is to space the two working electrodes far enough apart that a measured species diffusing from one working electrode cannot reach the other working electrode; unfortunately, such spacing does not enable substantially equivalent measurement of noise-cause species, as discussed in more detail elsewhere herein. Unlike conventional sensors, the sensors of the preferred embodiments ensure accurate subtraction of noise signal by ensuring substantially equivalent measurement of the noise (e.g., noise component, constant and/or non-constant noise components) detected by the two working electrodes.

[0382] Depending upon the scale (e.g., point) of reference, noise has a dual nature. On a larger scale, with respect to the *in vivo* portion of the sensor and the surrounding tissue, noise occurs randomly (e.g., is scattered, intermittent, dispersed, unevenly distributed) in the local of an implanted sensor. Yet, on a smaller scale, such as that of a few cells (e.g., 100-300 microns), noise is a localized phenomenon because it creates hot spots of noise-causing species generation whose effects extend about a thousandths of an inch (e.g., localized nature, character). A "hot spot" of noise generation is referred to herein as a "point source." A point source (e.g., a localized hot spot for noise generation) can be a cell or a group of cells adjacent to the sensor membrane, or a noise-causing species (e.g., compound, substance, molecule) that diffused to the location of sensor implantation, such as by diffusion between cells (e.g., to the sensor). For example, in the circumstance of a single point source in contact with the sensor membrane's surface, noise is a local phenomenon, because the noise-causing species' ability to affect adjacent structures is limited by the maximum distance it can diffuse (e.g., through the membrane), which is generally very short (e.g., a few microns, such as between about 1-μm to about 500-μm). Due to the random yet localized nature of noise, the configuration of the electroactive surfaces (of the working electrodes) can substantially affect noise measurement. With respect to the configuration and arrangement (e.g., surface area) of the dual-electrode sensor's electroactive surfaces, the random yet localized nature of noise is discussed in greater detail below.

[0383] **Fig. 16** is a two-dimensional schematic illustrating, on the scale of a sensor and the surrounding tissue (e.g., a generally larger scale), the random nature of noise relative to a dual-electrode sensor, in one exemplary embodiment. This figure is for illustrative purposes

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only, and should not be considered as a to-scale representation of a particular sensor configuration or of the events discussed herein. In the embodiment shown in **Fig. 16**, the dual electrode analyte sensor includes two electroactive surfaces **1004a**, **1004b** disposed beneath the sensor's membrane. While **Fig. 16** illustrates only one dimension of the electroactive surfaces, in some embodiments, the electroactive surfaces (e.g., the surface area of each electroactive surface) can include both a length and a width. In some embodiments, the area can include additional dimensions, such as a circumference and/or a height. In some embodiments, the sensor can have a planar configuration. In some embodiments, the sensor can have a cylindrical, pyramidal, polygonal configuration. It should also be understood that the electroactive surfaces **1004a**, **1004b** are shown as boxes as a matter of illustrative convenience; however, electroactive surfaces can be thinner or thicker than illustrated in **Fig. 16** or elsewhere herein. The membrane has a thickness ***D1*** and a surface **1002**. Depending upon the membrane configuration, fabrication methods and/or materials, ***D1*** can vary in size, from less than about 0.001, 0.002, 0.003, 0.004, 0.005, 0.006, 0.007, 0.008, 0.009, or 0.010 inches to more than about 0.011, 0.012, 0.013, 0.014, 0.015, 0.015, 0.016, 0.017, 0.018, 0.019, 0.020, 0.025, 0.03, 0.035, or 0.050 inches. In some embodiments, a preferred membrane thickness is between about 0.001, 0.0012, 0.0014, 0.0016, or 0.0018 inches to about 0.002, 0.0022, 0.0024, 0.0026, 0.0028, or 0.003 inches. Noise-causing species (represented by squiggly arrows **1006**) can be generated by and/or at point sources **1000** (e.g., noise hot spots) unevenly distributed relative the *in vivo* portion of the sensor. For example, some of the point sources **1000** (shown in **Fig. 16**) are concentrated at one end of electroactive surface **1004a**, while some are distributed more evenly across electroactive surface **1004b**. In some circumstances, the point source may be one or more cells (e.g., in contact with the membrane surface **1002**) that release the noise-causing species during wound healing or another metabolic process, such as when a sensor is implanted *in vivo*. In some circumstances, the implanted sensor can be located within the diffusion distance of one or more noise-causing species produced during a nearby metabolic process. In some circumstances, the noise-causing species (e.g., a compound consumed by the host) can be carried to the local of the sensor *via* the circulatory and/or lymph system and diffuse to the sensor (e.g., between cells).

[0384] Random and/or unequally distributed noise can be generated in a variety of circumstances. For example, a peroxide-generating immune cell could be located adjacent to one

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electroactive surface but not the other. In general, a noise-causing species must be generated and/or occur close enough to the sensor membrane such that it can diffuse to (and through) the membrane, to the electroactive surfaces, and affect the sensor signal. If the noise-causing species is generated farther away from the membrane than the diffusion distance of the noise-causing species, then the noise-causing species may be unable to reach the electroactive surfaces, and therefore may have little effect on sensor signal. For example, H_2O_2 (produced by metabolic process when the sensor is implanted in a host) must be generated sufficiently close to the membrane for it to diffuse to the membrane and affect sensor function. The maximum distance that the noise-causing species can diffuse (e.g., from the cell to the membrane, from one working electrode to another working electrode) and still substantially affect sensor function is referred to herein as a "diffusion distance."

[0385] The sensor electronics are configured to mathematically correct for noise on the sensor signal (e.g., such as by subtraction of the noise signal, applying a filter, averaging, or other calculations), such that a substantially analyte-only signal can be presented to the user. The inventors have discovered that successful mathematical correction of noise on the sensor signal can be substantially affected by the equivalence (e.g., similarity) of the noise signals detected by the two working electrodes. If the detected noise signals are substantially equivalent (e.g., similar amounts, amplitudes, levels, relatively equal), then the calculations will be produce a more accurate resultant analyte signal. If, on the other hand, the detected noise signals are not substantially equal (e.g., have very different amplitudes and/or wave forms), then the calculations will have a greater degree of error. While not wishing to be bound by theory, it is believed that presentation of more accurate sensor data (e.g., to the host) will improve the host's management of his diabetes, which will prevent the immediate risks of hypoglycemia (e.g., loss of consciousness and death) and postpone and/or prevent long term diabetes complications (blindness, loss of limb, kidney dysfunction, and the like). Additionally, the increased accuracy afforded by the sensors of the preferred embodiment increases the feasibility of insulin dosing and/or an artificial pancreas system based on a continuous glucose sensor.

[0386] In order to compensate for the unevenly distributed nature of noise (e.g., the point sources are randomly and/or non-equally and/or non-equivalently distributed relative to the *in vivo* portion of the sensor) and thereby render the noise components equivalent, a continuous

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dual electrode glucose sensor having sufficiently large electroactive surfaces, such that the noise components can be substantially equalized (e.g., made and/or become equivalent) by integration there across, is provided in one embodiment. The first working electrode includes a first electroactive surface (**1004a**, **Fig. 16**) disposed beneath an active enzymatic portion (e.g., plus-GOx) of the sensor's membrane, as described elsewhere herein. The first electroactive surface includes a first area (e.g., first electroactive surface area) configured to detect a first signal (e.g., including an analyte-related component and a noise component) having a first noise component related to a noise-causing species. The sensor also includes a second working electrode having a second electroactive surface (**1004b**, **Fig. 16**) disposed beneath an inactive-enzymatic or a non-enzymatic portion of the sensor membrane, as described elsewhere herein. For example, an inactive-enzymatic portion of the membrane can include inactivated GOx or no GOx. The second electroactive surface includes a second area (e.g., second electroactive surface area) configured to generate a second signal having a second noise component related to the noise-causing species. In preferred embodiments, the first and second areas are dimensioned (e.g., sized) to be sufficiently large such that the first and second noise components integrated there across, such that the first and second integrated noise signals (e.g., from the first and second electroactive surfaces, respectively) are substantially equivalent. In some embodiments, the first and second integrated noise signals (e.g., noise components) are within 20% of each other (e.g., plus or minus 10%). In some embodiments, the first and second electroactive surfaces are dimensioned to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

[0387] Due to the random nature of noise, the configuration and/or arrangement of the first and second electroactive surfaces **1004a**, **1004b** can substantially affect the equivalence of the noise measured. , the areas of the electroactive surfaces are dimensioned (e.g., sized, shaped) to be sufficiently large such that the noise detected at (e.g., across, along, and the like) each electroactive surface can be integrated. While not wishing to be bound by theory, it is believed that integration of noise across a sufficiently large area (e.g., surface area of an electroactive surface) ensures that, even though noise-causing species **1006** affect each electroactive surface unevenly (e.g., local hot spots **1000** for noise-causing species generation are intermittently distributed across the area of each electroactive surface), a sufficient amount of

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signal is detected at each electroactive surface, such that the first and second noise components caused by noise-causing species are substantially equivalent. Accordingly, in some embodiments, the first and second areas are each configured and arranged to integrate the signal caused by a plurality of local point sources **1000** that produce noise-causing species **1006**, when the sensor is implanted in a host. In other words, each electroactive surface includes a sufficiently large area (e.g., in at least one dimension, such as but not limited to ***D2***), such that the detected noise signals (e.g., noise components) can be integrated (e.g., averaged), such that the amount of the two noise components are substantially equivalent. In some embodiments, the areas are dimensioned such that noise signals integrated there across are equivalent by at least 40% (e.g., within plus or minus 20% of each other). In more preferred embodiment, the integrated signals are equivalent by at least 20% (e.g., within plus or minus 10% of each other). In a more preferred embodiment, the integrated signals are equivalent by at least 10% (e.g., within plus or minus 5% of each other).

[0388] In preferred embodiments, at least one dimension of each of the first and second areas is greater than the sum of the diameters of from about 10 to about 500 (or more) average human cells (e.g., the sum of the diameters of the cells). The diameter of an average human cell is about 20μm to about 160μm. Thus, in some embodiments, the at least one dimension (e.g., ***D2***) of each of the first and second electroactive surface areas is greater than between about 200μm to about 10,000μm. In some embodiments, if an average human cell has a diameter of about 20μm, the at least one dimension is greater than the sum of the diameters (e.g., total diameter) of about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95 average human cells, such as greater than about 300-μm, 400-μm, 500-μm, 600-μm, 700-μm, 800-μm, 900-μm, 1000-μm, 1200-μm, 1300-μm, 1400-μm, 1500-μm, 1600-μm, 1700-μm, 1800-μm, or 1900-μm in at least one dimension. In some embodiments, if an average human cell has a diameter of about 160μm, the at least one dimension is greater than the sum of the diameters (e.g., total diameter) of about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95 average human cells, such as greater than about 2400-μm, 3200-μm, 4000-μm, 4800-μm, 5600-μm, 6400-μm, 7200-μm, 8000-μm, 8800-μm, 9600-μm, 10400-μm, 11200-μm, 12000-μm, 12800-μm, 13600-μm, or 14400-μm in at least one dimension. In some embodiments, the

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dimension is greater than the sum of the diameters of about 110 to 500 average human cells, or more.

[0389] In some embodiments, the first and second areas (e.g., of the electroactive surfaces) are also configured and arranged to integrate signals detected about a circumference of the sensor. For example, in some embodiments, the dual electrode sensor is fabricated of cylindrical wires, each of which includes a circumference. Accordingly, the electroactive surfaces can be disposed about a wire's circumference. In one exemplary embodiment, the two working electrodes can be twisted to share a common axis. As a result, in addition to extending along the sensor's length and/or width and/or about each wire's circumference, the electroactive surfaces extend around at least a portion of the sensor's circumference, and noise (e.g., from one or more point sources producing noise-causing species) can impinge upon the sensor about that circumference. Thus, noise impinging upon the sensor about a circumference can be integrated.

[0390] **Fig. 17** is a two-dimensional schematic illustrating the localized character of noise species (represented by squiggly arrows **1006**) generated by a point source **1000**, when examined from a cellular scale, as discussed elsewhere herein. **Fig. 17** depicts a cross-section of a sensor, in one embodiment, wherein the sensor includes two working electrodes having electroactive surfaces **1004a** and **1004b**, and a membrane having surface **1002** and thickness ***D1***. Distance ***D3*** separates the electroactive surfaces; the distance between their outer edges is denoted by ***D4***. Note that dimension ***D2***, described above, is not shown in this figure. The sensor of this exemplary embodiment can have a variety of configurations, such as but not limited to planar, cylindrical or polygonal. Accordingly, the dimensions of an electroactive surface's surface area (referred to as "area" herein) can include but is not limited to length, width, height, and/or circumference. For example, in some embodiments, the area of each electroactive surface is defined by a length and a width. In some embodiments, the area includes a length or width and a circumference. In some embodiments, the area includes length, width and height. Additionally, it is know to one skilled in the art that, in some circumstances, differences in signal amplitude and/or sensitivity (e.g., from the two working electrodes), due to differences in electrode sizes (or some differences in compositions of membranes) can be corrected (adjusted, compensated for, calibrated out) mathematically. For example, if a first electroactive surface is

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two times as large as the second electroactive surface, then the signal from the second electroactive surface can be multiplied by two, such that the sensitivities are substantially similar.

[0391] Referring now to **Fig. 17**, in this exemplary circumstance the point source (e.g., noise hot spot) is an individual cell **1000** disposed adjacent to the membrane surface **1002** and generally above and/or over the sensor's electroactive surfaces **1004a**, **1004b**. The cell can produce noise-causing substances (e.g., **1006**) that can diffuse to and affect its local environment. In general, the ability of a noise-causing substance to affect the local environment is limited by the maximum distance the substance can diffuse (e.g., the substance's diffusion distance). In some circumstances, some of the noise-causing substances can diffuse through the sensor membrane and affect the sensor's electroactive surfaces. While not wishing to be bound by theory, the inventors have found that in order for the two electroactive surfaces to be substantially equivalently affected by the noise **1006** from a point source, such as a cell, the electroactive surfaces must be affected by substantially the same microenvironment. In various circumstances, the electroactive surfaces will be affected by substantially the same microenvironment, if the electroactive surfaces are configured and arranged such that the electroactive surfaces are sufficiently close together and/or their external edges are sufficiently close together.

[0392] **Fig. 17** shows that the sensor's electroactive surfaces **1004a**, **1004b** are separated by a distance ***D3*** and their outer edges are spaced a distance ***D4*** (e.g., in at least one dimension), in one exemplary embodiment. In this example, a point source **1000** (e.g., a cell) of noise-causing species **1006** is adjacent to the membrane's surface **1002**. If the electroactive surfaces are configured and arranged such that ***D3*** is sufficiently small, then the noise-causing species diffusing from the point source can impinge equivalently on both of the electroactive surfaces. Additionally or alternatively, if ***D4*** is sufficiently small (e.g., the electroactive surfaces are sufficiently narrow in at least one dimension), then the noise-causing species diffusing from the point source can impinge equivalently on both of the electroactive surfaces. Accordingly, in preferred embodiments, the electroactive surfaces are spaced a distance (e.g., relative to each other, ***D3***) such that the electroactive surfaces (e.g., at least a portion of each electroactive surface) detect substantially equivalent noise from a point source. In some embodiments, the electroactive surfaces are sufficiently close together (e.g., such that the noise components

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measured are substantially equal) when the distance between the electroactive surfaces (***D3***) is between about 0.5-times to about 10-times (or more) the membrane thickness (***D1***). In some preferred embodiments, the electroactive surfaces are sufficiently close together when ***D3***is about 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-times the membrane thickness. In some embodiments, ***D3*** is between about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 microns or less to about 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 microns or more. In preferred embodiments, ***D3*** is between about 20 to about 40 microns. In some embodiments, ***D4*** is between about 25 microns or less to about 500 microns or more.

[0393] Depending upon the sensor's configuration, in some embodiments, ***D4*** can be the distance between the outer edges of the electroactive surfaces, or ***D4*** can be a distance equivalent to the maximum diameter of the bundles and/or twisted pair of working electrodes. For example, **Fig. 17** illustrates a cross-section of a sensor (e.g., width and height), but doesn't illustrate any additional dimensions (e.g., length). The cross-section could be that of a planar sensor configuration, wherein the sensor also includes an additional dimension that has not been shown, such as but not limited to ***D2***. In some circumstances, the sensor can have a non-planar configuration. For example, in the embodiment shown in **Fig. 18**, the working electrodes **E1**, **E2** are fabricated from two wires. Since the wires are cylindrical, the electroactive surfaces do not include outer edges. In this exemplary circumstance, ***D4*** is the total diameter of the bundled and/or twisted working electrodes. In both types of sensor configurations (e.g., planar and non-planar), if ***D4*** is sufficiently small, then the two working electrodes can be equivalently affected by noise-causing species **1006** derived from a point source **1000**.

[0394] As described above, dual electrode sensors can be affected by internally generated noise (e.g., generated by the sensor). The inventors have found that, in general, when ***D3*** is sized to be sufficiently small such that the electroactive surfaces are equivalently affect by noise from an adjacent point source, the electroactive surfaces are also close enough together that crosstalk (an internally generated noise) can occur. In general, crosstalk is detection of an analyte signal generated at the plus-GOx working electrode (wherein the electrode includes the membrane portion thereon) by the minus-GOx working electrode (including the No GOx membrane portion thereon). For example, when the measured species is H_2O_2, crosstalk occurs when the H_2O_2 diffuses from the plus-GOx enzyme domain to the No GOx working electrode

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and is detected (e.g., a signal is generated on the No GOx electrode). In general, crosstalk is undesirable as it causes sensor error. However, in order for the two working electrodes to measure equivalent noise signals from a point source **1000**, the electroactive surfaces must be spaced very close together. Accordingly, in preferred embodiments, this distance (***D3***) is less than a crosstalk diffusion distance of the measured species. In other words, ***D3*** is shorter than the diffusion distance of H_2O_2 (e.g., the maximum distance H_2O_2 can diffuse from a first electrode to a second and still cause a signal on the second electrode).

[0395] In conventional dual-electrode sensors, spacing the electroactive surfaces within the crosstalk diffusion distance of the measured species is generally undesirable due to increased sensor error. However, in preferred embodiments, the sensor includes a physical diffusion barrier configured to attenuate crosstalk by physically blocking (e.g., suppressing, blocking, restricting) some of the crosstalk from the active enzymatic portion of the sensor membrane to the second electroactive surface. More preferably, the physical diffusion barrier is configured and arranged to attenuate and/or physically block a substantial amount of the measurable species (e.g., H_2O_2) diffusing from the active enzymatic portion of the membrane to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

[0396] **Fig. 18** is a schematic illustrating a perspective view of a cross-section of a dual electrode sensor that includes a physical diffusion barrier **1010**, in one exemplary embodiment. In this embodiment, wires form the working electrodes **E1**, **E2**. The working electrodes each include a membrane, including an electrode domain **24**, an enzyme domain **26** and a resistance domain **28**. For example, **E1** includes a first electrode domain, a first enzyme domain (Plus GOx) and a first resistance domain, and **E2** includes a second electrode domain, a second enzyme domain (No GOx) and a second resistance domain. In this particular exemplary embodiment, the electrodes are placed together and coated with an additional resistance domain **28A** (e.g., a third resistance domain). Depending upon the circumstances, the electrodes can be placed and/or held together using a variety of methods, such as bundling, twisting, wrapping, and the like, either alone or in combination. The distances shown are as follows; a thickness of the membrane ***D1***, at least one dimension of the electroactive surface ***D2***, a distance between the electroactive surfaces ***D3***, and a distance between the outer edges of the electroactive surfaces

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D4. In the illustrated exemplary embodiment, the first and second electroactive surfaces extend about the circumferences of **E1** and **E2** (or portions thereof), respectively.

[0397] In preferred embodiments, the physical diffusion barrier **1010** is disposed between the electroactive surfaces of working electrodes **E1** and **E2**. In some embodiments, the physical diffusion barrier is formed of one or more membrane materials, such as those used in formation of an interference domain and/or a resistance domain. Such materials include but are not limited to silicones, polyurethanes, cellulose derivatives (cellulose butyrates and cellulose acetates, and the like) and combinations thereof, as described elsewhere herein. In some embodiments, the physical diffusion barrier includes one or more membrane domains. For example, in the exemplary embodiment of **Fig. 18**, the physical diffusion barrier is a discontinuous portion of the membrane (e.g., separate, distinct or discontinuous membrane structures) disposed between the first and second electroactive surfaces, and can include one or more membrane portion(s) within distance ***D3*** (e.g., interference and/or resistance domains). For example, in some embodiments, H_2O_2 diffusing from the Plus GOX working electrode to the No GOx working electrode must pass through two "sensor membranes" such as the first and second resistance domains disposed on **E1** and **E2** respectively, and optionally electrode, interference and/or enzyme domains disposed on **E2**. In some embodiments, the physical diffusion barrier includes first and second barrier layers formed independently on the first and second electrodes. In some embodiments the barrier layer is the resistance domain **28**. In still other embodiments, the physical diffusion barrier can be a continuous membrane (and/or membrane domain(s)) disposed between the electroactive surfaces. In some embodiments, the physical diffusion barrier attenuates (e.g., suppresses, blocks, prevents) diffusion of the H_2O_2 (e.g., crosstalk) by at least 2-fold. In preferred embodiments, crosstalk is attenuated at least 5-fold. In a more preferred embodiment, crosstalk is attenuated at least 10-fold. In some embodiments, the physical diffusion barrier attenuates crosstalk at least about 50%. In a further embodiment, the physical diffusion barrier is configured and arranged to physically block an amount of the measured species diffusing from the active enzymatic portion of the membrane to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

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[0398] In some embodiments, a dual electrode sensor having a physical barrier layer can be fabricated by initially preparing (e.g., fabricating, building) the first and second working electrodes **E1**, **E2** independently (e.g., separately from each other), followed by joining and/or grouping and/or bundling the working electrodes and optionally applying one or more additional membrane domains fabrication. In this exemplary embodiment, to the first working electrode **E1**, an optional electrode domain **24**, an enzyme domain **26** (e.g., plus-GOx), and at least one layer of the resistance domain material **28** (e.g., first resistance domain) are sequentially applied. Similarly, to the second working electrode **E2**, an optional electrode domain **24**, an enzyme domain **26** (e.g., no-GOx), and at least one layer of the resistance domain material **28** (e.g., second resistance domain) are sequentially applied. The working electrodes are then held together, such as but not limited to by bundling and/or twisting them together, wrapping a material around them, or by any other method known in the art. In this embodiment, the physical diffusion barrier includes a discontinuous portion of a membrane (e.g., the initial layers of the resistance domain material applied independently to the two working electrodes) disposed between the first and second electroactive surfaces.

[0399] In an alternative exemplary sensor embodiment, the sensor includes working electrodes (including electroactive surfaces) disposed on a planar substrate and/or surface. The electroactive surfaces can be spaced a distance ***D3*** that is sufficiently close together that the electroactive surfaces are equivalently affected by an adjacent noise hot spot (e.g., point source). In this configuration, ***D3*** is also sufficiently small that crosstalk can occur between the Plus GOx working electrode (wherein the term "electrode" includes the membrane disposed thereon, for the purposes of this example) and the No GOx working electrode. However, in preferred embodiments, crosstalk is substantially attenuated by a physical diffusion barrier disposed between the working electrodes. Namely, the electrode domains (if present) and enzyme domains can be separately applied to the working electrodes and/or electroactive surfaces; followed by application of a continuous resistance domain applied thereon, such that a portion the resistance domain is deposited between the working electrodes. For example, a portion of resistance domain deposited on a planar substrate and between working electrodes can attenuate diffusion of the measured species (e.g., H_2O_2) from **E1** to **E2**, such that the noise measured on **E1** and **E2** is equivalent.

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[0400] In the context of glucose sensors, one skilled in the art recognizes that equivalent noise signals can have different amplitudes, but equivalent signal patterns (e.g., rises, falls, trends and the like) such that a noise component can be subtracted out (as described elsewhere herein) while compensating for any difference in signal amplitude (i.e., sensitivity of the first and second working electrodes), as described elsewhere herein. In some circumstances, the membrane portions associated with the working electrodes (e.g., of a dual electrode sensor) can possess different sensitivities (e.g., signal sensitivities), such that the amplitudes of the noise components measured by the working electrodes are not equivalent. In some circumstances, the areas of the electroactive surfaces may be different sizes, which can also result in non-equivalent signal amplitudes and/or sensitivities. While such differences in signal sensitivity can be corrected mathematically (e.g., by mathematical filters), mathematical correction of noise, in general, is improved when the signal sensitivities of the first and second working electrodes are closer. Accordingly, in a preferred embodiment, an additional resistance domain **28A** (e.g., applied continuously over the discontinuous resistance domains **28** described elsewhere herein) is provided, such that the signal sensitivities are equivalent. In the exemplary embodiment shown in **Fig. 18**, the signal sensitivities are substantially equalized on a sensor including the combination of discontinuous resistance domains (e.g., resistance domains **28**, applied independently to **E1** and **E2**) and a continuous resistance domain **28A** (e.g., applied over and/or adjacent to the discontinuous resistance domains). In other words, the noise signals detected on both **E1** and **E2** will have substantially the same amplitude (e.g., intensity, amount), as described with reference to **Example 7**, below. In a preferred embodiment, the sensitivities (of the working electrodes) are within 40% of each other (e.g., plus or minus 20%). In a preferred embodiment, the sensitivities (of the working electrodes) are within 20% of each other (e.g., plus or minus 10%). In a more preferred embodiment, the sensitivities (of the working electrodes) are within 10% of each other (e.g., plus or minus 5%).

[0401] In an alternative embodiment, the sensor electrodes can be disposed on a planar, cylindrical, pyramidal or otherwise shaped support. For example, the sensor's first and second working electrodes can be conductive traces deposited, such as by screen printing, sputtering or other thin film techniques known in the art, on a planar substrate. In this alternative embodiment, a physical diffusion barrier can be formed by layers of resistance domain material

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deposited separately (e.g., discontinuously) on each working electrode and/or between the electrodes, for example.

[0402] In the exemplary embodiments described above, diffusion of the H_2O_2 from the first working electrode **E1** to the electroactive surface of the second working electrode **E2** is first attenuated by the resistance domain **28** disposed over the first working electrode **E1** (an independently formed first barrier layer), and then again by the resistance domain **28** disposed over the second working electrode **E2** (an independently formed second barrier layer), such that only insubstantial amounts of H_2O_2 can reach the electroactive surface of the second working electrode. In preferred embodiments, the first and second resistance domains are configured and arranged to reduce diffusion of the measurable species (e.g., H_2O_2) from the first electroactive surface to the second electroactive surface by at least 2-fold. In more preferred embodiments, the physical diffusion barrier is configured and arranged to reduce diffusion of the measurable species by at least 10-fold. In some embodiments, the physical diffusion barrier is configured and arranged to reduce diffusion of the measurable species by at least 3-, 4-, 5-, 6-, 7-, 8-, or 9-fold. In some embodiments, the physical diffusion barrier is configured and arranged to reduce diffusion of the measurable species by at least 20-, 30-, 40- or 50- fold, or more. In some embodiments, the sensor's working electrodes E1, E2 are by an insulator **I**, which insulates the working electrodes from each other. In some embodiments, the insulator **I** is at least a portion of the sensor membrane.

[0403] In another exemplary embodiment, the membrane can be configured to function as an insulator **I**, and therefore block and/or attenuate crosstalk between the first and second working electrodes **E1**, **E2**. For example, as described herein in the section entitled "Exemplary Sensor Configurations," a physical diffusion barrier can be formed by integrally forming the first and second working electrodes **E1**, **E2** either on a reference electrode **R** or an insulator **I**, such that the reference electrode **R** and/or insulator **I** physically blocks diffusion from one working electrode to the other, such that substantially no crosstalk affects the sensor signal. For example, if the insulator **I** is a planar polymer sheet or support, the working electrodes **E1**, **E2** can be integrally formed on opposite sides to the polymer sheet and/or support, such H_2O_2 produced in the active enzymatic portion of the sensor membrane (e.g., disposed over **E1**) cannot diffuse around the sheet and/or support (e.g., and impinge upon **E2**).

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[0404] In yet another exemplary embodiment, if the working electrodes are integrally formed on a substrate (planar, cylindrical, pyramidal, and the like) an insulative material can be deposited between the working electrodes (e.g., onto the substrate) to form a physical diffusion barrier. For example, the physical diffusion barrier can project a sufficient distance away from the substrate (e.g., similar to a wall-like structure) such that the measurable species cannot diffuse around it. Such a physical diffusion barrier can be formed from a variety of insulative materials (e.g., materials through which only insubstantial amounts of the measurable species can diffuse) can be integrally formed and/or deposited on the substrate. Additionally, any thin film deposition technique known to one skilled in the art (e.g., printing, sputtering, spin coating, and the like) can be employed to form the physical diffusion barrier on the substrate.

[0405] In some embodiments, a continuous glucose sensor configured for insertion into a host and detecting glucose in the host is provided. In general, the sensor includes first and second working electrodes, wherein each working electrode includes an electroactive surface (each including an area) disposed beneath a sensor membrane. The first electroactive surface (e.g., of the first working electrode) is disposed beneath an active enzymatic portion (plus-GOx) of the membrane while the second electroactive surface (of the second working electrode) is disposed beneath a non-enzymatic (no-GOx) portion of the membrane. The non-enzymatic portion of the membrane can include inactivated enzyme and/or no enzyme. Additionally, each working electrode is configured to generate a signal having a noise component related to a noise-causing species. In some circumstances, the noise-causing species is non-constant and related to a biological process. Preferably, the first and second areas are sufficiently large such that the noise components (e.g., first and second noise components detected by the first and second working electrodes) are substantially equivalent. In some embodiments, the first and second areas are each greater than the sum of the diameters of about 10 average human cells, in at least one dimension. In some embodiments, the first and second areas are each greater than about 500μm, in at least one dimension. Preferably, the first and second areas (e.g., of the electroactive surfaces) are configured and arranged such that the signals caused by a plurality of local point sources (that produce noise-causing species when implanted in a host) can be integrated along each area (e.g., each area independently from the other). In some further embodiments, the first and second areas are configured and arranged to integrate signals detected about a circumference

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of the sensor. Preferably, the first and second electroactive surfaces are spaced a distance that is less than a crosstalk diffusion distance of a measured species, such as H_2O_2 produced in the active enzymatic portion of the membrane. In some embodiments, the sensor includes a physical diffusion barrier configured and arranged to physically block some crosstalk from the active enzymatic portion of the membrane to the second electroactive surface. In some further embodiments, the physical diffusion barrier is configured and arranged to physically block a substantial amount of the measurable species diffusing from the active enzymatic portion of the membrane to the second electroactive surface (e.g., crosstalk), such that there is substantially no signal associated with crosstalk measured at the second working electrode. In some embodiments, the physical diffusion barrier is a discontinuous portion of the membrane disposed between the first and second electroactive surfaces. In some further embodiments, the physical diffusion barrier includes a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein the first and second barrier layers are independently formed (e.g., formed separately on the two electroactive surfaces). In some further embodiments, the physical diffusion barrier includes a first resistance domain formed on the first working electrode and a second resistance domain formed on the second working electrode, and wherein the first and second resistance domains are configured and arranged to reduce diffusion of the measurable species (e.g., crosstalk) from the active enzymatic portion of the sensor to the second electroactive surface by at least 2-fold. In a preferred embodiment, the physical diffusion barrier can reduce the diffusion of the measurable species (e.g., crosstalk) by at least 10-fold.

[0406] In some embodiments, the continuous glucose sensor includes first and second working electrodes, each working electrode including an electroactive surface (each including an area) disposed beneath a sensor membrane. As described elsewhere herein, the first electroactive surface is disposed beneath an active enzymatic portion of the membrane and the second electroactive surface is disposed beneath a non-enzymatic portion of the membrane. Preferably, the sensor includes a physical diffusion barrier, and the first and second electroactive surfaces are disposed sufficiently close together that the first and second noise components (detected by the first and second working electrodes) are substantially equivalent. In some embodiments, the distance between the first and second electroactive surfaces is less than about twice the thickness

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of the membrane. In some embodiments, the first and second electroactive surfaces are spaced a distance that is less than or equal to about a crosstalk diffusion distance of a measurable species, such as the H_2O_2 produced in the active enzymatic portion of the sensor membrane. In some embodiments, the physical diffusion barrier is configured and arranged to physically block some diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface (e.g., crosstalk). In preferred embodiments, the physical diffusion barrier blocks a substantial amount of the measurable species, such that there is substantially no signal associated with crosstalk measured at the second working electrode. In some embodiments, the physical diffusion barrier is a discontinuous portion of the membrane disposed between the first and second electroactive surfaces. In some embodiments, the physical diffusion barrier is a first barrier layer formed on the first electrode and a second barrier layer formed on the second electrode, wherein the first and second barrier layers are independently formed. In some embodiments, the physical diffusion barrier includes a first resistance domain formed on the first electrode and a second resistance domain formed on the second electrode. Preferably, the first and second resistance domains reduce diffusion of the measurable species (e.g., crosstalk) by at least 2-fold. In more preferred embodiments, the diffusion of the measurable species is reduced by at least 10-fold. In some embodiments, the membrane is an insulator that insulates the first working electrode from the second working electrodes. In some further embodiments, the first and second areas are sufficiently large that the first and second noise components are substantially equivalent.

Sensor Electronics

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[0407] In some embodiments, the sensing region may include reference and/or electrodes associated with the glucose-measuring working electrode and separate reference and/or counter electrodes associated with the optional auxiliary working electrode(s). In yet another embodiment, the sensing region may include a glucose-measuring working electrode, an auxiliary working electrode, two counter electrodes (one for each working electrode), and one shared reference electrode. In yet another embodiment, the sensing region may include a glucose-measuring working electrode, an auxiliary working electrode, two reference electrodes, and one shared counter electrode. However, a variety of electrode materials and configurations can be used with the implantable analyte sensor of the preferred embodiments.

[0408] In some alternative embodiments, the working electrodes are interdigitated. In some alternative embodiments, the working electrodes each comprise multiple exposed electrode surfaces; one advantage of these architectures is to distribute the measurements across a greater surface area to overcome localized problems that may occur *in vivo*, for example, with the host's immune response at the biointerface. Preferably, the glucose-measuring and auxiliary working electrodes are provided within the same local environment, such as described in more detail elsewhere herein.

[0409] **Fig. 4** is a block diagram that illustrates the continuous glucose sensor electronics in one embodiment. In this embodiment, a first potentiostat **36** is provided that is operatively associated with the glucose-measuring working electrode **16**. The first potentiostat **36** measures a current value at the glucose-measuring working electrode and preferably includes a resistor (not shown) that translates the current into voltage. An optional second potentiostat **37** is provided that is operatively associated with the optional auxiliary working electrode **18**. The second potentiostat **37** measures a current value at the auxiliary working electrode **18** and preferably includes a resistor (not shown) that translates the current into voltage. It is noted that in some embodiments, the optional auxiliary electrode can be configured to share the first potentiostat with the glucose-measuring working electrode. An A/D converter **38** digitizes the analog signals from the potentiostats **36**, **37** into counts for processing. Accordingly, resulting raw data streams (in counts) can be provided that are directly related to the current measured by each of the potentiostats **36** and **37**.

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[0410] A microprocessor **40**, also referred to as the processor module, is the central control unit that houses EEPROM **42** and SRAM **44**, and controls the processing of the sensor electronics. It is noted that certain alternative embodiments can utilize a computer system other than a microprocessor to process data as described herein. In other alternative embodiments, an application-specific integrated circuit (ASIC) can be used for some or all the sensor's central processing. The EEPROM **42** provides semi-permanent storage of data, for example, storing data such as sensor identifier (ID) and programming to process data streams (for example, such as described in U.S. Patent Publication No. US-2005-0027463-A1, which is incorporated by reference herein in its entirety. The SRAM **44** can be used for the system's cache memory, for example for temporarily storing recent sensor data. In some alternative embodiments, memory storage components comparable to EEPROM and SRAM may be used instead of or in addition to the preferred hardware, such as dynamic RAM, non-static RAM, rewritable ROMs, flash memory, or the like.

[0411] A battery **46** is operably connected to the microprocessor **40** and provides the necessary power for the sensor **10a**. In one embodiment, the battery is a Lithium Manganese Dioxide battery, however any appropriately sized and powered battery can be used (for example, AAA, Nickel-cadmium, Zinc-carbon, Alkaline, Lithium, Nickel-metal hydride, Lithium-ion, Zinc-air, Zinc-mercury oxide, Silver-zinc, and/or hermetically-sealed). In some embodiments the battery is rechargeable. In some embodiments, a plurality of batteries can be used to power the system. In some embodiments, one or more capacitors can be used to power the system. A Quartz Crystal 48 may be operably connected to the microprocessor **40** to maintain system time for the computer system as a whole.

[0412] An RF Transceiver **50** may be operably connected to the microprocessor **40** to transmit the sensor data from the sensor **10** to a receiver (see Figs. 4 and 5) within a wireless transmission **52** *via* antenna **54**. Although an RF transceiver is shown here, some other embodiments can include a wired rather than wireless connection to the receiver. In yet other embodiments, the receiver can be transcutaneously powered via an inductive coupling, for example. A second quartz crystal **56** can provide the system time for synchronizing the data transmissions from the RF transceiver. It is noted that the transceiver **50** can be substituted with

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a transmitter in other embodiments. In some alternative embodiments other mechanisms such as optical, infrared radiation (IR), ultrasonic, or the like may be used to transmit and/or receive data.

Receiver

[0413] **Fig. 5** is a schematic drawing of a receiver for the continuous glucose sensor in one embodiment. The receiver **58** comprises systems necessary to receive, process, and display sensor data from the analyte sensor, such as described in more detail elsewhere herein. Particularly, the receiver **58** may be a pager-sized device, for example, and house a user interface that has a plurality of buttons and/or keypad and a liquid crystal display (LCD) screen, and which may include a backlight. In some embodiments the user interface may also include a speaker, and a vibrator such as described with reference to **Fig. 6**.

[0414] **Fig. 6** is a block diagram of the receiver electronics in one embodiment. In some embodiments, the receiver comprises a configuration such as described with reference to **Fig. 5**, above. However, the receiver may comprise any reasonable configuration, including a desktop computer, laptop computer, a personal digital assistant (PDA), a server (local or remote to the receiver), or the like. In some embodiments, a receiver may be adapted to connect (via wired or wireless connection) to a desktop computer, laptop computer, a PDA, a server (local or remote to the receiver), or the like in order to download data from the receiver. In some alternative embodiments, the receiver may be housed within or directly connected to the sensor in a manner that allows sensor and receiver electronics to work directly together and/or share data processing resources. Accordingly, the receiver, including its electronics, may be generally described as a "computer system."

[0415] A quartz crystal **60** may be operably connected to an RF transceiver **62** that together function to receive and synchronize data streams via an antenna **64** (for example, transmission **52** from the RF transceiver **50** shown in **Fig. 4**). Once received, a microprocessor **66** can process the signals, such as described below.

[0416] The microprocessor **66**, also referred to as the processor module, is the central control unit that provides the processing, such as storing data, calibrating sensor data, downloading data, controlling the user interface by providing prompts, messages, warnings and alarms, or the like. The EEPROM **68** may be operably connected to the microprocessor **66** and provides semi-permanent storage of data, storing data such as receiver ID and programming to

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process data streams (for example, programming for performing calibration and other algorithms described elsewhere herein). SRAM **70** may be used for the system's cache memory and is helpful in data processing. For example, the SRAM stores information from the continuous glucose sensor for later recall by the patient or a doctor; a patient or doctor can transcribe the stored information at a later time to determine compliance with the medical regimen or a comparison of glucose concentration to medication administration (for example, this can be accomplished by downloading the information through the pc com port **76**). In addition, the SRAM **70** can also store updated program instructions and/or patient specific information. In some alternative embodiments, memory storage components comparable to EEPROM and SRAM can be used instead of or in addition to the preferred hardware, such as dynamic RAM, non-static RAM, rewritable ROMs, flash memory, or the like.

[0417] A battery **72** may be operably connected to the microprocessor 66 and provides power for the receiver. In one embodiment, the battery is a standard AAA alkaline battery, however any appropriately sized and powered battery can be used. In some embodiments, a plurality of batteries can be used to power the system. In some embodiments, a power port (not shown) is provided permit recharging of rechargeable batteries. A quartz crystal 84 may be operably connected to the microprocessor **66** and maintains system time for the system as a whole.

[0418] A PC communication (com) port **76** can be provided to enable communication with systems, for example, a serial communications port, allows for communicating with another computer system (for example, PC, PDA, server, or the like). In one exemplary embodiment, the receiver is able to download historical data to a physician's PC for retrospective analysis by the physician. The PC communication port **76** can also be used to interface with other medical devices, for example pacemakers, implanted analyte sensor patches, infusion devices, telemetry devices, or the like.

[0419] A user interface **78** comprises a keypad **80**, speaker **82**, vibrator **84**, backlight **86**, liquid crystal display (LCD) **88**, and one or more buttons **90**. The components that comprise the user interface **78** provide controls to interact with the user. The keypad **80** can allow, for example, input of user information about himself/herself, such as mealtime, exercise, insulin administration, and reference glucose values. The speaker **82** can provide, for example, audible

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signals or alerts for conditions such as present and/or predicted hyper- and hypoglycemic conditions. The vibrator **84** can provide, for example, tactile signals or alerts for reasons such as described with reference to the speaker, above. The backlight **94** can be provided, for example, to aid the user in reading the LCD in low light conditions. The LCD 88 can be provided, for example, to provide the user with visual data output. In some embodiments, the LCD is a touch-activated screen. The buttons **90** can provide for toggle, menu selection, option selection, mode selection, and reset, for example. In some alternative embodiments, a microphone can be provided to allow for voice-activated control.

[0420] The user interface **78**, which is operably connected to the microprocessor **70,** serves to provide data input and output for the continuous analyte sensor. In some embodiments, prompts can be displayed to inform the user about necessary maintenance procedures, such as "Calibrate Sensor" or "Replace Battery." In some embodiments, prompts or messages can be displayed on the user interface to convey information to the user, such as malfunction, outlier values, missed data transmissions, or the like. Additionally, prompts can be displayed to guide the user through calibration of the continuous glucose sensor, for example when to obtain a reference glucose value.

[0421] Keypad, buttons, touch-screen, and microphone are all examples of mechanisms by which a user can input data directly into the receiver. A server, personal computer, personal digital assistant, insulin pump, and insulin pen are examples of external devices that can be connected to the receiver via PC com port **76** to provide useful information to the receiver. Other devices internal or external to the sensor that measure other aspects of a patient's body (for example, temperature sensor, accelerometer, heart rate monitor, oxygen monitor, or the like) can be used to provide input helpful in data processing. In one embodiment, the user interface can prompt the patient to select an activity most closely related to their present activity, which can be helpful in linking to an individual's physiological patterns, or other data processing. In another embodiment, a temperature sensor and/or heart rate monitor can provide information helpful in linking activity, metabolism, and glucose excursions of an individual. While a few examples of data input have been provided here, a variety of information can be input and can be helpful in data processing as will be understood by one skilled in the art.

Calibration Systems and Methods

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[0422] As described above in the Overview Section, continuous analyte sensors define a relationship between sensor-generated measurements and a reference measurement that is meaningful to a user (for example, blood glucose in mg/dL). This defined relationship must be monitored to ensure that the continuous analyte sensor maintains a substantially accurate calibration and thereby continually provides meaningful values to a user. Unfortunately, both sensitivity *m* and baseline *b* of the calibration are subject to changes that occur *in vivo* over time (for example, hours to months), requiring updates to the calibration. Generally, any physical property that influences diffusion or transport of molecules through the membrane can alter the sensitivity (and/or baseline) of the calibration. Physical properties that can alter the transport of molecules include, but are not limited to, blockage of surface area due to foreign body giant cells and other barrier cells at the biointerface, distance of capillaries from the membrane, foreign body response/capsule, disease, tissue ingrowth, thickness of membrane system, or the like.

[0423] In one example of a change in transport of molecules, an implantable glucose sensor is implanted in the subcutaneous space of a human, which is at least partially covered with a biointerface membrane, such as described in U.S. Patent Publication No. US-2005-0112169-A1, which is incorporated by reference herein in its entirety. Although the body's natural response to a foreign object is to encapsulate the sensor, the architecture of this biointerface membrane encourages tissue ingrowth and neo-vascularization over time, providing transport of solutes (for example, glucose and oxygen) close to the membrane that covers the electrodes. While not wishing to be bound by theory, it is believed that ingrowth of vascularized tissue matures (changes) over time, beginning with a short period of high solute transport during the first few days after implantation, continuing through a time period of significant tissue ingrowth a few days to a week or more after implantation during which low solute transport to the membrane has been observed, and into a mature state of vascularized tissue during which the bed of vascularized tissue provides moderate to high solute transport, which can last for months and even longer after implantation. In some embodiments, this maturation process accounts for a substantial portion of the change in sensitivity and/or baseline of the calibration over time due to changes in solute transport to the membrane.

[0424] Accordingly, in one aspect of the preferred embodiments, systems and methods are provided for measuring changes in sensitivity, also referred to as changes in solute

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transport or biointerface changes, of an analyte sensor **10** implanted in a host over a time period. Preferably, the sensitivity measurement is a signal obtained by measuring a constant analyte other than the analyte being measured by the analyte sensor. For example, in a glucose sensor, a non-glucose constant analyte is measured, wherein the signal is measured beneath the membrane system **22** on the glucose sensor **10**. While not wishing to be bound by theory, it is believed that by monitoring the sensitivity over a time period, a change associated with solute transport through the membrane system **22** can be measured and used as an indication of a sensitivity change in the analyte measurement. In other words, a biointerface monitor is provided, which is capable of monitoring changes in the biointerface surrounding an implantable device, thereby enabling the measurement of sensitivity changes of an analyte sensor over time.

[0425] In some embodiments, the analyte sensor **10** is provided with an auxiliary electrode **18** configured as a transport-measuring electrode disposed beneath the membrane system **22**. The transport-measuring electrode can be configured to measure any of a number of substantially constant analytes or factors, such that a change measured by the transport-measuring electrode can be used to indicate a change in solute (for example, glucose) transport to the membrane system **22**. Some examples of substantially constant analytes or factors that can be measured include, but are not limited to, oxygen, carboxylic acids (such as urea), amino acids, hydrogen, pH, chloride, baseline, or the like. Thus, the transport-measuring electrode provides an independent measure of changes in solute transport to the membrane, and thus sensitivity changes over time.

[0426] In some embodiments, the transport-measuring electrode measures analytes similar to the analyte being measured by the analyte sensor. For example, in some embodiments of a glucose sensor, water soluble analytes are believed to better represent the changes in sensitivity to glucose over time than non-water soluble analytes (due to the water-solubility of glucose), however relevant information may be ascertained from a variety of molecules. Although some specific examples are described herein, one skilled in the art appreciates a variety of implementations of sensitivity measurements that can be used as to qualify or quantify solute transport through the biointerface of the analyte sensor.

[0427] In one embodiment of a glucose sensor, the transport-measuring electrode is configured to measure urea, which is a water-soluble constant analyte that is known to react

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directly or indirectly at a hydrogen peroxide sensing electrode (similar to the working electrode of the glucose sensor example described in more detail above). In one exemplary implementation wherein urea is directly measured by the transport-measuring electrode, the glucose sensor comprises a membrane system as described in more detail above, however, does not include an active interference domain or active enzyme directly above the transport-measuring electrode, thereby allowing the urea to pass through the membrane system to the electroactive surface for measurement thereon. In one alternative exemplary implementation wherein urea is indirectly measured by the transport-measuring electrode, the glucose sensor comprises a membrane system as described in more detail above, and further includes an active uricase oxidase domain located directly above the transport-measuring electrode, thereby allowing the urea to react at the enzyme and produce hydrogen peroxide, which can be measured at the electroactive surface thereon.

[0428] In some embodiments, the change in sensitivity is measured by measuring a change in oxygen concentration, which can be used to provide an independent measurement of the maturation of the biointerface, and to indicate when recalibration of the system may be advantageous. In one alternative embodiment, oxygen is measured using pulsed amperometric detection on the glucose-measuring working electrode **16** (eliminating the need for a separate auxiliary electrode). In another embodiment, the auxiliary electrode is configured as an oxygen-measuring electrode. In another embodiment, an oxygen sensor (not shown) is added to the glucose sensor, as is appreciated by one skilled in the art, eliminating the need for an auxiliary electrode.

[0429] In some embodiments, a stability module is provided; wherein the sensitivity measurement changes can be quantified such that a co-analyte concentration threshold is determined. A co-analyte threshold is generally defined as a minimum amount of co-analyte required to fully react with the analyte in an enzyme-based analyte sensor in a non-limiting manner. The minimum co-analyte threshold is preferably expressed as a ratio (for example, a glucose-to-oxygen ratio) that defines a concentration of co-analyte required based on a concentration of analyte available to ensure that the enzyme reaction is limited only by the analyte. While not wishing to be bound by theory, it is believed that by determining a stability of the analyte sensor based on a co-analyte threshold, the processor module can be configured to

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compensate for instabilities in the glucose sensor accordingly, for example by filtering the unstable data, suspending calibration or display, or the like.

[0430] In one such embodiment, a data stream from an analyte signal is monitored and a co-analyte threshold set, whereby the co-analyte threshold is determined based on a signal-to-noise ratio exceeding a predetermined threshold. In one embodiment, the signal-to-noise threshold is based on measurements of variability and the sensor signal over a time period, however one skilled in the art appreciates the variety of systems and methods available for measuring signal-to-noise ratios. Accordingly, the stability module can be configured to set determine the stability of the analyte sensor based on the co-analyte threshold, or the like.

[0431] In some embodiments, the stability module is configured to prohibit calibration of the sensor responsive to the stability (or instability) of the sensor. In some embodiments, the stability module can be configured to trigger filtering of the glucose signal responsive to a stability (or instability) of the sensor.

[0432] In some embodiments, sensitivity changes can be used to trigger a request for one or more new reference glucose values from the host, which can be used to recalibrate the sensor. In some embodiments, the sensor is re-calibrated responsive to a sensitivity change exceeding a preselected threshold value. In some embodiments, the sensor is calibrated repeatedly at a frequency responsive to the measured sensitivity change. Using these techniques, patient inconvenience can be minimized because reference glucose values are generally only requested when timely and appropriate (namely, when a sensitivity or baseline shift is diagnosed).

[0433] In some alternative embodiments, sensitivity changes can be used to update calibration. For example, the measured change in transport can be used to update the sensitivity m in the calibration equation. While not wishing to be bound by theory, it is believed that in some embodiments, the sensitivity m of the calibration of the glucose sensor is substantially proportional to the change in solute transport measured by the transport-measuring electrode.

[0434] It should be appreciated by one skilled in the art that in some embodiments, the implementation of sensitivity measurements of the preferred embodiments typically necessitate an addition to, or modification of, the existing electronics (for example, potentiostat configuration or settings) of the glucose sensor and/or receiver.

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[0435] In some embodiments, the signal from the oxygen measuring electrode may be digitally low-pass filtered (for example, with a passband of 0-10^{-5} Hz, dc-24 hour cycle lengths) to remove transient fluctuations in oxygen, due to local ischemia, postural effects, periods of apnea, or the like. Since oxygen delivery to tissues is held in tight homeostatic control, this filtered oxygen signal should oscillate about a relatively constant. In the interstitial fluid, it is thought that the levels are about equivalent with venous blood (40 mmHg). Once implanted, changes in the mean of the oxygen signal (for example, > 5%) may be indicative of change in transport through the biointerface (change in sensor sensitivity and/or baseline due to changes in solute transport) and the need for system recalibration.

[0436] The oxygen signal may also be used in its unfiltered or a minimally filtered form to detect or predict oxygen deprivation-induced artifact in the glucose signal, and to control display of data to the user, or the method of smoothing, digital filtering, or otherwise replacement of glucose signal artifact. In some embodiments, the oxygen sensor may be implemented in conjunction with any signal artifact detection or prediction that may be performed on the counter electrode or working electrode voltage signals of the electrode system. U.S. Patent Publication No. US-2005-0043598-A1, which is incorporated by reference in its entirety herein, describes some methods of signal artifact detection and replacement that may be useful such as described herein.

[0437] Preferably, the transport-measuring electrode is located within the same local environment as the electrode system associated with the measurement of glucose, such that the transport properties at the transport-measuring electrode are substantially similar to the transport properties at the glucose-measuring electrode.

[0438] In a second aspect the preferred embodiments, systems and methods are provided for measuring changes baseline, namely non-glucose related electroactive compounds in the host. Preferably the auxiliary working electrode is configured to measure the baseline of the analyte sensor over time. In some embodiments, the glucose-measuring working electrode **16** is a hydrogen peroxide sensor coupled to a membrane system **22** containing an active enzyme **32** located above the electrode (such as described in more detail with reference to Figs. 1 to 4, above). In some embodiments, the auxiliary working electrode **18** is another hydrogen peroxide sensor that is configured similar to the glucose-measuring working electrode however a portion

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34 of the membrane system **22** above the base-measuring electrode does not have active enzyme therein, such as described in more detail with reference to Figs. 3A and 3B. The auxiliary working electrode 18 provides a signal substantially comprising the baseline signal, *b*, which can be (for example, electronically or digitally) subtracted from the glucose signal obtained from the glucose-measuring working electrode to obtain the signal contribution due to glucose only according to the following equation:

$$\text{Signal}_{\text{glucose only}} = \text{Signal}_{\text{glucose-measuring working electrode}} - \text{Signal}_{\text{baseline-measuring working electrode}}$$

[0439] In some embodiments, electronic subtraction of the baseline signal from the glucose signal can be performed in the hardware of the sensor, for example using a differential amplifier. In some alternative embodiments, digital subtraction of the baseline signal from the glucose signal can be performed in the software or hardware of the sensor or an associated receiver, for example in the microprocessor.

[0440] One aspect the preferred embodiments provides for a simplified calibration technique, wherein the variability of the baseline has been eliminated (namely, subtracted). Namely, calibration of the resultant differential signal ($\text{Signal}_{\text{glucose only}}$) can be performed with a single matched data pair by solving the following equation:

$$y = mx$$

[0441] While not wishing to be bound by theory, it is believed that by calibrating using this simplified technique, the sensor is made less dependent on the range of values of the matched data pairs, which can be sensitive to human error in manual blood glucose measurements, for example. Additionally, by subtracting the baseline at the sensor (rather than solving for the baseline *b* as in conventional calibration schemes), accuracy of the sensor may increase by altering control of this variable (baseline *b*) from the user to the sensor. It is additionally believed that variability introduced by sensor calibration may be reduced.

[0442] In some embodiments, the glucose-measuring working electrode **16** is a hydrogen peroxide sensor coupled to a membrane system **22** containing an active enzyme **32** located above the electrode, such as described in more detail above; however the baseline signal is not subtracted from the glucose signal for calibration of the sensor. Rather, multiple matched data pairs are obtained in order to calibrate the sensor (for example using $y = mx + b$) in a conventional manner, and the auxiliary working electrode 18 is used as an indicator of baseline

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shifts in the sensor signal. Namely, the auxiliary working electrode 18 is monitored for changes above a certain threshold. When a significant change is detected, the system can trigger a request (for example, from the patient or caregiver) for a new reference glucose value (for example, SMBG), which can be used to recalibrate the sensor. By using the auxiliary working electrode signal as an indicator of baseline shifts, recalibration requiring user interaction (namely, new reference glucose values) can be minimized due to timeliness and appropriateness of the requests. In some embodiments, the sensor is re-calibrated responsive to a baseline shifts exceeding a preselected threshold value. In some embodiments, the sensor is calibrated repeatedly at a frequency responsive to the rate-of-change of the baseline.

[0443] In yet another alternative embodiment, the electrode system of the preferred embodiments is employed as described above, including determining the differential signal of glucose less baseline current in order to calibrate using the simplified equation ($y = mx$), and the auxiliary working electrode **18** is further utilized as an indicator of baseline shifts in the sensor signal. While not wishing to be bound by theory, it is believed that shifts in baseline may also correlate and/or be related to changes in the sensitivity m of the glucose signal. Consequently, a shift in baseline may be indicative of a change in sensitivity m. Therefore, the auxiliary working electrode **18** is monitored for changes above a certain threshold. When a significant change is detected, the system can trigger a request (for example, from the patient or caregiver) for a new reference glucose value (for example, SMBG), which can be used to recalibrate the sensor. By using the auxiliary signal as an indicator of possible sensitivity changes, recalibration requiring user interaction (new reference glucose values) can be minimized due to timeliness and appropriateness of the requests.

[0444] It is noted that infrequent new matching data pairs may be useful over time to recalibrate the sensor because the sensitivity m of the sensor may change over time (for example, due to maturation of the biointerface that may increase or decrease the glucose and/or oxygen availability to the sensor). However, the baseline shifts that have conventionally required numerous and/or regular blood glucose reference measurements for updating calibration (for example, due to interfering species, metabolism changes, or the like) can be consistently and accurately eliminated using the systems and methods of the preferred embodiments, allowing

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reduced interaction from the patient (for example, requesting less frequent reference glucose values such as daily or even as infrequently as monthly).

[0445] An additional advantage of the sensor of the preferred embodiments includes providing a method of eliminating signal effects of interfering species, which have conventionally been problematic in electrochemical glucose sensors. Namely, electrochemical sensors are subject to electrochemical reaction not only with the hydrogen peroxide (or other analyte to be measured), but additionally may react with other electroactive species that are not intentionally being measured (for example, interfering species), which cause an increase in signal strength due to this interference. In other words, interfering species are compounds with an oxidation potential that overlap with the analyte being measured. Interfering species such as acetaminophen, ascorbate, and urate, are notorious in the art of glucose sensors for producing inaccurate signal strength when they are not properly controlled. Some glucose sensors utilize a membrane system that blocks at least some interfering species, such as ascorbate and urate. Unfortunately, it is difficult to find membranes that are satisfactory or reliable in use, especially *in vivo,* which effectively block all interferants and/or interfering species (for example, see U.S. Patent No. 4,776,944, U.S. Patent No. 5,356,786, U.S. Patent No. 5,593,852, U.S Patent No. 5776324B1, and U.S. Patent No. 6,356,776).

[0446] The preferred embodiments are particularly advantageous in their inherent ability to eliminate the erroneous transient and non-transient signal effects normally caused by interfering species. For example, if an interferant such as acetaminophen is ingested by a host implanted with a conventional implantable electrochemical glucose sensor (namely, one without means for eliminating acetaminophen), a transient non-glucose related increase in signal output would occur. However, by utilizing the electrode system of the preferred embodiments, both working electrodes respond with substantially equivalent increased current generation due to oxidation of the acetaminophen, which would be eliminated by subtraction of the auxiliary electrode signal from the glucose-measuring electrode signal.

[0447] In summary, the system and methods of the preferred embodiments simplify the computation processes of calibration, decreases the susceptibility introduced by user error in calibration, and eliminates the effects of interfering species. Accordingly, the sensor requires less interaction by the patient (for example, less frequent calibration), increases patient

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convenience (for example, few reference glucose values), and improves accuracy (via simple and reliable calibration).

[0448] In another aspect of the preferred embodiments, the analyte sensor is configured to measure any combination of changes in baseline and/or in sensitivity, simultaneously and/or iteratively, using any of the above-described systems and methods. While not wishing to be bound by theory, the preferred embodiments provide for improved calibration of the sensor, increased patient convenience through less frequent patient interaction with the sensor, less dependence on the values/range of the paired measurements, less sensitivity to error normally found in manual reference glucose measurements, adaptation to the maturation of the biointerface over time, elimination of erroneous signal due to non-constant analyte-related signal so interfering species, and/or self-diagnosis of the calibration for more intelligent recalibration of the sensor.

Examples

Example 1: Dual- Electrode Sensor with Coiled Reference Electrode

[0449] Dual-electrode sensors (having a configuration similar to the embodiment shown in **Fig. 9B**) were constructed from two platinum wires, each coated with non-conductive material/insulator. Exposed electroactive windows were cut into the wires by removing a portion thereof. The platinum wires were laid next to each other such that the windows are offset (e.g., separated by a diffusion barrier). The bundle was then placed into a winding machine & silver wire was wrapped around the platinum electrodes. The silver wire was then chloridized to produce a silver/silver chloride reference electrode. The sensor was trimmed to length, and a glucose oxidase enzyme solution applied to both windows (e.g., enzyme applied to both sensors). To deactivate the enzyme in one window (e.g., window **904a**, **Fig. 9B**) the window was dipped into dimethylacetamide (DMAC) and rinsed. After the sensor was dried, a resistance layer was sprayed onto the sensor and dried.

[0450] **Fig. 12** shows the results from one experiment, comparing the signals from the two electrodes of the dual-electrode sensor having a coiled silver/silver chloride wire reference electrode described above. The "Plus GOx" electrode included active GOx in its window. The "No GOx" electrode included DMAC-inactivated GOx in its window. To test, the sensor was incubated in room temperature phosphate buffered saline (PBS) for 30 minutes. During this

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time, the signals from the two electrodes were substantially equivalent. Then the sensor was moved to a 40-mg/dl solution of glucose in PBS. This increase in glucose concentration resulting in an expected rise in signal from the "Plus GOx" electrode but no significant increase in signal from the "No GOx" electrode. The sensor was then moved to a 200-mg/dl solution of glucose in PBS. Again, the "Plus GOx" electrode responded with a characteristic signal increase while no increase in signal was observed for the "No GOx" electrode. The sensor was then moved to a 400-mg/dl solution of glucose in PBS. The "Plus GOx" electrode signal increased to about 5000 counts while no increase in signal was observed for the "No GOx" electrode. As a final test, the sensor was moved to a solution of 400 mg/dl glucose plus 0.22mM acetaminophen (a known interferant) in PBS. Both electrodes recorded similarly dramatic increases in signal (raw counts). These data indicate that the "No GOx" electrode is measuring sensor background (e.g., noise) that is substantially related to non-glucose factors.

Example 2: Dual-Electrode Sensor with X-Shaped Reference Electrode

[0451] This sensor was constructed similarly to the sensor of Example 1, except that the configuration was similar to the embodiment shown in **Fig. 7J**. Two platinum electrode wires were dipped into non-conductive material and then electroactive windows formed by removing portions of the nonconductive material. The two wires were then bundled with an X-shaped silver reference electrode therebetween. An additional layer of non-conductive material held the bundle together.

[0452] **Fig. 13** shows the results from one experiment, comparing the signals from the two electrodes of a dual-electrode sensor having an X-shaped reference electrode. The "Plus GOx" electrode has active GOx in its window. The "No GOx" electrode has DMAC-inactivated GOx in its window. The sensor was tested as was described for Experiment 1, above. Signal from the two electrodes were substantially equivalent until the sensor was transferred to the 40-mg/dl glucose solution. As this point, the "Plus GOx" electrode signal increased but the "No GOx" electrode signal did not. Similar increases were observed in the "Plus GOx" signal when the sensor was moved consecutively to 200-mg/dl and 400-mg/dl glucose solution, but still not increase in the "No GOx" signal was observed. When sensor was moved to a 400-mg/dl glucose solution containing 0.22 mM acetaminophen, both electrodes recorded a similar increase in

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signal (raw counts). These data indicate that the "No GOx" electrode measures sensor background (e.g., noise) signal that is substantially related to non-glucose factors.

Example 3: Dual-Electrode Challenge with Hydrogen Peroxide, Glucose, and Acetaminophen

[0453] A dual-electrode sensor was assembled similarly to the sensor of Example 1, with a bundled configuration similar to that shown in **Fig. 7C** (two platinum working electrodes and one silver/silver chloride reference electrode, not twisted). The electroactive windows were staggered by 0.085 inches, to create a diffusion barrier.

[0454] **Fig. 14** shows the experimental results. The Y-axis shows the glucose signal (volts) and the X-axis shows time. The "Enzyme" electrode included active GOx. The "No Enzyme" electrode did not include active GOx. The "Enzyme minus No Enzyme" represents a simple subtraction of the "Enzyme" minus the "NO Enzyme." The "Enzyme" electrode measures the glucose-related signal and the non-glucose-related signal. The "No Enzyme" electrode measures only the non-glucose-related signal. The "Enzyme minus No Enzyme" graph illustrates the portion of the "Enzyme" signal related to only the glucose-related signal.

[0455] The sensor was challenged with increasing concentrations of hydrogen peroxide in PBS. As expected, both the "Enzyme" and "No Enzyme" electrodes responded substantially the same with increases in signal corresponding increased in H_2O_2 concentration (~50 μM, 100 μM and 250 μM H_2O_2). When the "No Enzyme" signal was subtracted from the "Enzyme" signal, the graph indicated that the signal was not related to glucose concentration.

[0456] The sensor was challenged with increasing concentrations of glucose (~20 mg/dl, 200 mg/dl, 400 mg/dl) in PBS. As glucose concentration increased, the "Enzyme" electrode registered a corresponding increase in signal. In contrast, the "No Enzyme" electrode did not record an increase in signal. Subtracting the "No Enzyme" signal from the "Enzyme" signal shows a step-wise increase in signal related to only glucose concentration.

[0457] The sensor was challenged with the addition of acetaminophen (~.22 mM) to the highest glucose concentration. Acetaminophen is known to be an interferent (e.g., produces non-constant noise) of the sensors built as described above, e.g., due to a lack of acetaminophen-blocking membrane and/or mechanism formed thereon or provided therewith. Both the "Enzyme" and "No Enzyme" electrodes showed a substantial increase in signal. The "Enzyme

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minus No Enzyme" graph substantially shows the portion of the signal that was related to glucose concentration.

[0458] From these data, it is believed that a dual-electrode system can be used to determine the analyte-only portion of the signal.

Example 4: IV Dual-Electrode Sensor in Dogs

[0459] An intravascular dual-electrode sensor was built substantially as described in co-pending U.S. Patent application 11/543,396 filed on even date herewith and entitled "ANALYTE SENSOR." Namely, the sensor was built by providing two platinum wires (e.g., dual working electrodes) and vapor-depositing the platinum wires with Parylene to form an insulating coating. A portion of the insulation on each wire was removed to expose the electroactive surfaces (e.g., **904a** and **904b**). The wires were bundled such that the windows were offset to provide a diffusion barrier, as described herein, cut to the desired length, to form an "assembly." A silver/silver chloride reference electrode was disposed remotely from the working electrodes (e.g., coiled inside the sensor's fluid connector).

[0460] An electrode domain was formed over the electroactive surface areas of the working electrodes by dip coating the assembly in an electrode solution (comprising BAYHYDROL® 123 with PVP and added EDC)) and drying.

[0461] An enzyme domain was formed over the electrode domain by subsequently dip coating the assembly in an enzyme domain solution (BAYHYDROL 140AQ mixed with glucose oxidase and glutaraldehyde) and drying. This dip coating process was repeated once more to form an enzyme domain having two layers and subsequently drying. Next an enzyme solution containing active GOx was applied to one window; and an enzyme solution without enzyme (e.g., No GOx) was applied to the other window.

[0462] A resistance domain was formed over the enzyme domain by subsequently spray coating the assembly with a resistance domain solution (Chronothane H and Chronothane 1020) and drying.

[0463] After the sensor was constructed, it was placed in a protective sheath and then threaded through and attached to a fluid coupler, as described in co-pending U.S. Patent application 11/543,396 filed on even date herewith and entitled "ANALYTE SENSOR." Prior to use, the sensors were sterilized using electron beam radiation.

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[0464] The forelimb of an anesthetized dog (2 years old, ~40 pounds) was cut down to the femoral artery and vein. An arterio-venous shunt was placed from the femoral artery to the femoral vein using 14 gauge catheters and 1/8-inch IV tubing. A pressurized arterial fluid line was connected to the sensor systems at all times. The test sensor system included a 20 gauge x 1.25-inch catheter and took measurements every 30 seconds. The catheter was aseptically inserted into the shunt, followed by insertion of the sensor into the catheter. As controls, the dog's glucose was checked with an SMBG, as well as removing blood samples and measuring the glucose concentration with a Hemocue.

[0465] **Fig. 15** shows the experimental results. Glucose test data (counts) is shown on the left-hand Y-axis, glucose concentration for the controls (SMBG and Hemocue) are shown on the right-hand y-axis and time is shown on the X-axis. Each time interval on the X-axis represents 29-minutes (e.g., 12:11 to 12:40 equals 29 minutes). An acetaminophen challenge is shown as a vertical line on the graph.

[0466] The term "Plus GOx" refers to the signal from the electrode coated with active GOx., which represents signal due to both the glucose concentration and non-glucose-related electroactive compounds as described elsewhere herein (e.g., glucose signal and background signal, which includes both constant and non-constant noise). "No GOx" is signal from the electrode lacking GOx, which represents non-glucose related signal (e.g., background signal, which includes both constant and non-constant noise). The "Glucose Only" signal (e.g., related only to glucose concentration) is determined during data analysis (e.g., by sensor electronics). In this experiment, the "Glucose Only" signal was determined by a subtraction of the "No GOx" signal from the "Plus GOx" signal.

[0467] During the experiment, the "No GOx" signal (thin line) substantially paralleled the "Plus GOx" signal (medium line). The "Glucose Only" signal substantially paralleled the control tests (SMBG/Hemocue).

[0468] Acetaminophen is known to be an interferent (e.g., produces non-constant noise) of the sensors built as described above, e.g., due to a lack of acetaminophen-blocking membrane and/or mechanism formed thereon or provided therewith. The SMBG or Hemocue devices utilized in this experiment, however, do include mechanisms that substantially block acetaminophen from the signal (see **Fig. 15**). When the dog was challenged with acetaminophen,

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the signals from both working electrodes ("Plus GOx" and "No GOx") increased in a substantially similar manner. When the "Glucose Only" signal was determined, it substantially paralleled the signals of the control devices and was of a substantially similar magnitude.

[0469] From these experimental results, the inventors believe that an indwelling, dual-electrode glucose sensor system (as described herein) in contact with the circulatory system can provide substantially continuous glucose data that can be used to calculate a glucose concentration that is free from background components (e.g., constant and non-constant noise), in a clinical setting.

Example 5: Detection of Crosstalk *In Vitro*

[0470] In general, crosstalk in dual electrode sensors can be examined by recording the signal detected at each working electrode while placing them in a series of analyte solutions. This example describes one exemplary *in vitro* test for crosstalk on a dual electrode analyte sensor. A variety of dual electrode analyte sensors can be tested for crosstalk, using this method.

[0471] First, the sensor to be tested is placed in a phosphate buffered saline (PBS) for several minutes, such as until a stable signal is detected from both working electrodes. Next, the sensor is challenged with glucose solutions and optionally with one or more known noise-causing substances. For example, sensor can be placed sequentially in a series of glucose solutions (e.g., 40-mg/dl, 200-mg/dl and 400-mg/dl glucose in PBS) and the signals from the two working electrodes graphed.

[0472] If there is no crosstalk between the working electrodes, then, as the sensor is placed in solutions of increasingly higher glucose concentration, the graphed signal of the Plus GOx electrode should show corresponding signal increases, while the No GOx electrode signal should exhibit little or no change in signal. However, when the sensor is placed in a solution of a known noise-causing species (e.g., acetaminophen, ibuprofen, vitamin C, urea, and the like), both working electrodes (Plus GOx and No GOx) should exhibit an increase in signal. In some circumstances, this increase in signal is a dramatic spike in signal.

[0473] If there is crosstalk, then the signals from both electrodes should increase as the sensor is moved to solutions of increased glucose concentration. Similarly, when the sensor is placed in a solution of a known noise-causing species, both working electrodes should exhibit an increase in signal.

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Example 6: Effect of Electroactive Surface Size in Dual Electrodes *In Vivo*

[0474] The effect of size of the electroactive surfaces (of the working electrodes) on noise measurement was examined in non-diabetic human hosts. Sensors having electroactive surfaces of different sizes, and lacking GOx in the enzyme layer were constructed as follows. Clean, insulated Pt/Ir wires were separated into two groups. For **Group 1**, 0.029" of the insulation was removed from each wire (e.g., about its entire circumference), to expose electroactive surfaces. For **Group 2**, the same procedure was performed, except that two sequential 0.029" portions of the insulation were removed; effectively doubling the size of the **Group 2** electroactive surfaces relative to those of **Group 1**. After exposure of the electroactive surfaces, the two groups of wires were treated identically. On each wire, a portion of the sensor's membrane was fabricated by the sequential application (and curing thereof) of electrode domain, enzyme domain and resistance domain materials. The enzyme domain material contained no active GOx, so that the sensors would be able to detect only noise (no analyte). Next, pairs of wires (e.g., two **Group 1** wires or two **Group 2** wires) were aligned such that the electroactive surfaces were parallel to each other, and then twisted together. An Ag/AgCl ribbon was wrapped around a portion of the twisted wires (to form the reference electrode), and then additional resistance domain material was applied to the assembly. Each host consumed 1,000-mg of acetaminophen near the end of the trial, so that the affect of a known interferent could be examined.

[0475] **Fig. 19A** is a graph illustrating the *in vivo* experimental results from implantation of a **Group 1** sensor (one 0.029" electroactive surface area per electrode). The Y-axis represents raw counts and the X-axis represents time. The data collected from each electroactive surface is shown as a line (**E1, No GOx** and **E2, No GOx**). Please note that the data represents only the noise component of the signal. No analyte component was detected, due to the lack of GOx in the portions of the membrane adjacent to the electroactive surfaces. Referring now to **Fig. 19A**, the noise signal detected by each of the working electrodes (**E1**, **E2**) fluctuated widely throughout the implantation time. The amplitude of the noise component detected by **E2** was substantially greater than the noise component detected by **E1**. For example, referring to the data circled by oval **A**, the noise signal peaks detected by **E2** were substantially greater than those detected by **E1**. Additionally, the noise fluctuations between the two working

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electrodes were not always in the same direction. For example, referring to the data circled by oval **B**, the **E2** noise signal component increased while the **E1** noise signal component decreased. When the sensor was challenged with acetaminophen (drug consumption indicated by the arrow), both electrodes registered a substantial increase in noise signal, wherein the shapes of the curves were substantially similar. However, **E1** detected a substantially lower total amount of noise when compared with that detected by **E2**; this difference in signal amplitude (in response to a non-biologic interferent) indicates that the signals (e.g., on the two working electrodes) did not have substantially similar sensitivities.

[0476] **Fig. 19B** is a graph illustrating the *in vivo* experimental results from implantation of a **Group 2** sensor (two 0.029" electroactive surface areas per electrode). As described above, the **Group 2** electroactive surfaces are about two-times as large as those of the **Group 1** sensors. As before, the Y-axis represents raw counts and the X-axis represents time, and the data collected from each electroactive surface is shown as a line (**E1, No GOx** and **E2, No GOx**). As before, the data represents only the noise component of the signal. No analyte component was detected, due to the lack of GOx in the portions of the membrane adjacent to the electroactive surfaces. Referring now to **Fig. 19B**, the noise signal detected by each of the working electrodes (**E1**, **E2**). Throughout the course of the experiment (~20-hours), noise signals detected by **E1** and **E2** tracked very closely throughout the entire experiment. Namely, the noise signals detected by **E1** and **E2** were of substantially the same amplitude and followed substantially similar fluctuations, varying from about 7,000 counts (at 4:00 PM) to about 4500 counts (from about 6:30 AM to about 9:00 AM). Even when the **Group 2** sensor was challenged with acetaminophen (a known non-biological interferent that should cause a false signal on the sensor), the working electrodes recorded substantially equal signal amplitudes (~6,900 counts) and followed substantially similar wave forms having substantially equivalent amplitudes; these data indicate that the two working electrodes had substantially equal sensitivities.

[0477] From these data, the inventors concluded that the electroactive surfaces of a dual electrode glucose sensor must be sufficiently large in order for the two electrodes to detect substantially equal noise signal components. For example, in this experiment, the electroactive surfaces of the **Group 1** working electrodes, which did not measure noise equivalently, were 0.029" (e.g., along the electrode's length); while electroactive surfaces of the **Group 2** working

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electrodes, which did measure noise substantially equivalently, were two times as large (e.g., 2x0.029"=0.058" along the electrode's length) as those of the **Group 1** working electrodes.

Example 7: Effect of Electroactive Surface Spacing in Dual Electrodes *In Vivo*

[0478] The effect of the spacing of the electroactive surfaces (of the working electrodes) on noise measurement was examined in non-diabetic human hosts. Sensors having two different configurations were built and tested. Sensors of **Configuration 1** (**Config. 1**) included Plus GOx and No GOx working electrodes with non-aligned (e.g., miss-aligned, skewed) electroactive surfaces. In other words, the electroactive surfaces were spaced such that, in the completed sensor, one electroactive surface would be more proximal to the sensor's tip than then other. Sensors of **Configuration 2** (**Config. 2**) also included Plus GOx and No GOx working electrodes, except that the electroactive surfaces were closely aligned (e.g., parallel). In **Config. 2**, the membrane was the insulator between the two working electrodes, enabling the very close spacing (i.e., the thickness of the membrane determined the spacing between the two working electrodes, between about 0.001 inches to about 0.003 inches between the two working electrodes.)

[0479] **Config. 1** sensors were fabricated as follow. For each sensor, two clean, insulated Pt/Ir wires were wound together (and an Ag/AgCl ribbon twisted there around), followed by removal of a portion of the insulating material from each wire to create the electroactive surfaces. The electroactive surfaces were offset (e.g., not next to each other) relative to the sensor's tip. The twisted wire pairs were then dipped in enzyme domain solution (including GOx) just far enough such that only the electroactive surface closest to the tip of the sensor was coated with the enzyme domain material (e.g., **E1, Plus GOx**). The electroactive surface farthest from the sensor tip was not coated with the enzyme domain material (e.g., **E2, No GOx**). After curing, resistance domain material was applied to the twisted pairs of wires.

[0480] **Config. 2** sensors were fabricated as follow. Clean, insulated Pt/Ir wires were divided into two groups. Electrode and enzyme (Plus GOx) domain materials were sequentially applied to the **E1, Plus GOx** working electrode wires. Electrode and enzyme (No GOx) domain materials were sequentially applied to the **E2, No GOx** working electrode wires. Resistance domain material was applied to all wires individually (e.g., to form independent/discontinuous first and second resistance domains). After the resistance domain material was cured, one each

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of the **E1, Plus GOx** and **E2, No GOx** were placed together such that the wires' electroactive surfaces were aligned, and then twisted together to form a twisted pair. An Ag/AgCl ribbon was wrapped around each twisted pair (but not covering the electroactive surfaces), followed by application of a continuous resistance domain (e.g., a third resistance domain) over the sensor. The resulting sensors included a configuration similar to the example illustrated in **Fig. 18**.

[0481] **Fig. 20A** is a graph illustrating the *in vivo* experimental results from implantation of a **Config. 1** sensor (non-aligned electroactive surfaces). The Y-axis represents raw counts and the X-axis represents time. The **E1, Plus GOx** electrode detected both glucose and noise signal components while the **E2, No GOx** electrode detected only the noise signal component. Throughout most of the experiment's duration, the two working electrodes recorded signals having somewhat similar waveforms with the two lines being relatively flat with little fluctuation in amplitude (the volunteer was not diabetic, and thus would generally not have large fluctuations in glucose level). During the acetaminophen challenge, the **E1, Plus GOx** signal rapidly peaked at about 12,000 counts and then gradually declined, while the **E2, No GOx** signal peak was much lower in amplitude (~6,000 counts).

[0482] **Fig. 20B** is a graph illustrating the *in vivo* experimental results from implantation of a **Config. 2** sensor (aligned electroactive surfaces). The Y-axis represents raw counts and the X-axis represents time. In general, the **E1, Plus GOx** electrode detected both glucose and noise signal components while the **E2, No GOx** electrode detected only the noise signal component. Throughout most of the experiment's duration, the two electrodes recorded signals having substantially similar waveforms; though the **E1, Plus GOx** electrode signal was generally higher in amplitude than that of the **E2, No GOx** electrode. When the sensor was challenged with acetaminophen, the signals of both working electrodes rapidly peaked at about 11,000-12,000 counts (e.g., the amplitudes of the two peaks were substantially equivalent/similar) and then gradually declined.

[0483] From these data, the inventors concluded that the electroactive surfaces of a dual electrode glucose sensor must be sufficiently close together in order for the two electrodes to detect substantially equivalent noise signal components. Additionally, the inventors concluded that for a dual electrode sensor including the combination of a continuous resistance domain disposed over discontinuous resistance domains (e.g., applied independently to the two working

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electrodes) the detected signal amplitudes more closely correspond to each other. This improves mathematical noise correction by enabling better noise signal subtraction.

[0484] Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in U.S. Patent No. 4,994,167; U.S. Patent No. 4,757,022; U.S. Patent No. 6,001,067; U.S. Patent No. 6,741,877; U.S. Patent No. 6,702,857; U.S. Patent No. 6,558,321; U.S. Patent No. 6,931,327; U.S. Patent No. 6,862,465; U.S. Patent No. 7,074,307; U.S. Patent No. 7,081,195; U.S. Patent No. 7,108,778; U.S. Patent No. 7,110,803; U.S. Patent No. 7,192,450; U.S. Patent No. 7,226,978; U.S. Patent No. 7,236,890.

[0485] Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in U.S. Patent Publication No. US-2005-0176136-A1; U.S. Patent Publication No. US-2005-0251083-A1; U.S. Patent Publication No. US-2005-0143635-A1; U.S. Patent Publication No. US-2005-0181012-A1; U.S. Patent Publication No. US-2005-0177036-A1; U.S. Patent Publication No. US-2005-0124873-A1; U.S. Patent Publication No. US-2005-0115832-A1; U.S. Patent Publication No. US-2005-0245799-A1; U.S. Patent Publication No. US-2005-0245795-A1; U.S. Patent Publication No. US-2005-0242479-A1; U.S. Patent Publication No. US-2005-0182451-A1; U.S. Patent Publication No. US-2005-0056552-A1; U.S. Patent Publication No. US-2005-0192557-A1; U.S. Patent Publication No. US-2005-0154271-A1; U.S. Patent Publication No. US-2004-0199059-A1; U.S. Patent Publication No. US-2005-0054909-A1; U.S. Patent Publication No. US-2005-0051427-A1; U.S. Patent Publication No. US-2003-0032874-A1; U.S. Patent Publication No. US-2005-0103625-A1; U.S. Patent Publication No. US-2005-0203360-A1; U.S. Patent Publication No. US-2005-0090607-A1; U.S. Patent Publication No. US-2005-0187720-A1; U.S. Patent Publication No. US-2005-0161346-A1; U.S. Patent Publication No. US-2006-0015020-A1; U.S. Patent Publication No. US-2005-0043598-A1; U.S. Patent Publication No. US-2005-0033132-A1; U.S. Patent Publication No. US-2005-0031689-A1; U.S. Patent Publication No. US-2004-0186362-A1; U.S. Patent Publication No. US-2005-0027463-A1; U.S. Patent Publication No. US-2005-0027181-A1; U.S. Patent Publication No. US-2005-0027180-A1; U.S. Patent Publication No. US-2006-0020187-A1; U.S. Patent Publication No. US-2006-0036142-A1; U.S. Patent Publication No. US-2006-0020192-A1; U.S. Patent Publication No. US-2006-0036143-A1; U.S. Patent Publication No. US-2006-0036140-A1; U.S. Patent Publication No. US-2006-0019327-

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A1; U.S. Patent Publication No. US-2006-0020186-A1; U.S. Patent Publication No. US-2006-0020189-A1; U.S. Patent Publication No. US-2006-0036139-A1; U.S. Patent Publication No. US-2006-0020191-A1; U.S. Patent Publication No. US-2006-0020188-A1; U.S. Patent Publication No. US-2006-0036141-A1; U.S. Patent Publication No. US-2006-0020190-A1; U.S. Patent Publication No. US-2006-0036145-A1; U.S. Patent Publication No. US-2006-0036144-A1; U.S. Patent Publication No. US-2006-0016700-A1; U.S. Patent Publication No. US-2006-0142651-A1; U.S. Patent Publication No. US-2006-0086624-A1; U.S. Patent Publication No. US-2006-0068208-A1; U.S. Patent Publication No. US-2006-0040402-A1; U.S. Patent Publication No. US-2006-0036142-A1; U.S. Patent Publication No. US-2006-0036141-A1; U.S. Patent Publication No. US-2006-0036143-A1; U.S. Patent Publication No. US-2006-0036140-A1; U.S. Patent Publication No. US-2006-0036139-A1; U.S. Patent Publication No. US-2006-0142651-A1; U.S. Patent Publication No. US-2006-0036145-A1; U.S. Patent Publication No. US-2006-0036144-A1; U.S. Patent Publication No. US-2006-0200022-A1; U.S. Patent Publication No. US-2006-0198864-A1; U.S. Patent Publication No. US-2006-0200019-A1; U.S. Patent Publication No. US-2006-0189856-A1; U.S. Patent Publication No. US-2006-0200020-A1; U.S. Patent Publication No. US-2006-0200970-A1; U.S. Patent Publication No. US-2006-0183984-A1; U.S. Patent Publication No. US-2006-0183985-A1; U.S. Patent Publication No. US-2006-0195029-A1; U.S. Patent Publication No. US-2006-0229512-A1; U.S. Patent Publication No. US-2007-0032706-A1; U.S. Patent Publication No. US-2007-0016381-A1; U.S. Patent Publication No. US-2007-0027370-A1; U.S. Patent Publication No. US-2007-0027384-A1; U.S. Patent Publication No. US-2007-0032717-A1; U.S. Patent Publication No. US-2007-0032718 A1; U.S. Patent Publication No. US-2007-0059196-A1; U.S. Patent Publication No. US-2007-0066873-A1; U.S. Patent Publication No. US-2007-0093704-A1; U.S. Patent Publication No. US-2007-0197890-A1; U.S. Patent Publication No. US-2007-0173709-A1; U.S. Patent Publication No. US-2007-0173710-A1; U.S. Patent Publication No. US-2007-0197889-A1; U.S. Patent Publication No. US-2007-0163880-A1; U.S. Patent Publication No. US-2007-0203966-A1; U.S. Patent Publication No. US-2007-0208245-A1; U.S. Patent Publication No. US-2007-0208246-A1; U.S. Patent Publication No. US-2007-0208244-A1; and U.S. Patent Publication No. US-2007-0173708 A1.

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[0486] Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in U.S. Patent Application No. 09/447,227 filed November 22, 1999 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS"; U.S. Patent Application No. 11/675,063 filed February 14, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/543,396 filed October 4, 2006 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/543,490 filed October 4, 2006 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/543,404 filed October 4, 2006 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/691,426 filed March 26, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/691,432 filed March 26, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/691,424 filed March 26, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/691,466 filed March 26, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/692,154 filed March 27, 2007 and entitled "DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR"; U.S. Patent Application No. 11/797,520 filed May 3, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; U.S. Patent Application No. 11/797,521 filed May 3, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; and U.S. Patent Application No. 11/750,907 filed May 18, 2007 and entitled "ANALYTE SENSORS HAVING A SIGNAL-TO-NOISE RATIO SUBSTANTIALLY UNAFFECTED BY NON-CONSTANT NOISE"; U.S. Patent Application No. 11/762,638 filed June 13, 2007 and entitled "SYSTEMS AND METHODS FOR REPLACING SIGNAL DATA ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM"; U.S. Patent Application No. 11/763,215 filed June 14, 2007 and entitled "SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE"; U.S. Patent Application No. 11/842,148 filed August 21, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; U.S. Patent Application No. 11/842,142 filed August 21, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; U.S. Patent Application No. 11/842,154 filed August 21, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; U.S. Patent Application No. 11/842,146 filed August 21, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/842,151 filed August 21, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/842,156 filed August 21, 2007 and entitled "ANALYTE SENSORS HAVING A SIGNAL-TO-NOISE RATIO SUBSTANTIALLY

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UNAFFECTED BY NON-CONSTANT NOISE"; U.S. Patent Application No. 11/842,157 filed August 21, 2007 and entitled "ANALYTE SENSOR"; U.S. Patent Application No. 11/842,143 filed August 21, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; U.S. Patent Application No. 11/842,149 filed August 21, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; and U.S. Patent Application No. 11/855,101 filed September 13, 2007 and entitled "TRANSCUTANEOUS ANALYTE SENSOR".

[0487] All references cited herein, including but not limited to published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0488] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0489] The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

[0490] The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

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WHAT IS CLAIMED IS:

1. A continuous glucose sensor, the sensor comprising:

a first working electrode comprising a first electroactive surface disposed beneath an active enzymatic portion of a sensor membrane, wherein the first working electrode is configured to generate a first signal having a first noise component related to a noise-causing species; and

a second working electrode comprising a second electroactive surface disposed beneath an inactive-enzymatic or a non-enzymatic portion of the sensor membrane, wherein the second working electrode is configured to generate a second signal having a second noise component related to the noise-causing species;

wherein the first electroactive surface and the second electroactive surface are each dimensioned to integrate at least one signal generated by a plurality of local point sources that produce the noise-causing species, such that the first noise component and the second noise component are substantially equivalent.

2. The sensor of claim 1, wherein at least one dimension of each of the first electroactive surface and second electroactive surface is greater than a sum of diameters of about 10 average human cells.

3. The sensor of claim 1, wherein at least one dimension of each of the first electroactive surface and second electroactive surface is greater than about 500μm.

4. The sensor of claim 1, wherein each of the first electroactive surface and second electroactive surface is configured and arranged to integrate noise detected about a circumference of the sensor.

5. The sensor of claim 1, wherein the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

6. The sensor of claim 5, wherein the noise-causing species is non-constant.

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7. The sensor of claim 1, wherein the first electroactive surface and second electroactive surface are spaced at a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first electroactive surface and the second electroactive surface.

8. The sensor of claim 1, wherein the first electroactive surface and second electroactive surface are spaced at a distance less than a crosstalk diffusion distance of a measured species.

9. The sensor of claim 8, wherein the measured species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

10. The sensor of claim 8, further comprising a physical diffusion barrier configured and arranged to physically block crosstalk from the active enzymatic portion of the sensor membrane to the second electroactive surface by at least 50%.

11. The sensor of claim 10, wherein the physical diffusion barrier is configured and arranged to physically block an amount of the measured species diffusing from the active enzymatic portion of the membrane to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

12. The sensor of claim 1, further comprising a physical diffusion barrier comprising a discontinuous portion of a membrane disposed between the first electroactive surface and the second electroactive surface.

13. The sensor of claim 12, wherein the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein the first barrier layer and the second barrier layer are each independently formed.

14. The sensor of claim 12, wherein the physical diffusion barrier comprises a first resistance domain formed on the first working electrode and a second resistance domain formed on the second working electrode, and the sensor membrane further comprises a third resistance domain disposed continuously over the first and second resistance domains, wherein the first resistance domain and the second resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the sensor to the second

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electroactive surface by at least 2-fold, and the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

15. The sensor of claim 14, wherein the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measured species by at least 10-fold.

16. The sensor of claim 14, wherein the sensitivities of the first signal and the second signals are within 20% of each other.

17. A continuous glucose sensor configured for insertion into a host and for detecting glucose in the host, the sensor comprising:

a first working electrode comprising a first electroactive surface disposed beneath an active enzymatic portion of a sensor membrane, wherein the first working electrode is configured to generate a first signal having a first noise component related to a noise-causing species;

a second working electrode comprising a second electroactive surface disposed beneath an inactive-enzymatic or a non-enzymatic portion of the sensor membrane, wherein the second working electrode is configured to generate a second signal having a second noise component related to the noise-causing species; and

a physical diffusion barrier;

wherein the first electroactive surface and the second electroactive surface are spaced at a distance that allows noise caused by a local point source that produces noise-causing species to be measured substantially equivalently at the first electroactive surface and the second electroactive surface.

18. The sensor of claim 17, wherein the sensor membrane has a thickness, and wherein the distance between the first electroactive surface and the second electroactive surface is less than about twice the thickness of the sensor membrane.

19. The sensor of claim 18, wherein the thickness of the sensor membrane is less than about 80 microns.

20. The sensor of claim 17, wherein the distance between the first electroactive surface and the second electroactive surface is less than or equal to about a crosstalk diffusion distance of a measurable species.

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21. The sensor of claim 20, wherein the measurable species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

22. The sensor of claim 17, wherein the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

23. The sensor of claim 17, wherein the active enzymatic portion of the membrane is configured to produce a measurable species, and wherein the physical diffusion barrier is configured and arranged to physically block at least some diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface.

24. The sensor of claim 23, wherein the physical diffusion barrier is configured and arranged to physically block at least 50% of the measurable species diffusing from the active enzymatic portion of the membrane to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

25. The sensor of claim 23, wherein the measurable species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

26. The sensor of claim 17, wherein the physical diffusion barrier comprises a discontinuous portion of the membrane disposed between the first electroactive surface and the second electroactive surface.

27. The sensor of claim 17, wherein the physical diffusion barrier comprises a first barrier layer formed on the first electrode and a second barrier layer formed on the second electrode, wherein each of the first barrier layer and the second barrier layer is independently formed.

28. The sensor of claim 17, wherein the physical diffusion barrier comprises a first resistance domain formed on the first electrode and a second resistance domain formed on the second electrode, and wherein the first resistance domain and the second resistance domain are

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configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface by at least 2-fold.

29. The sensor of claim 28, wherein the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measurable species by at least 10-fold.

30. The sensor of claim 28, wherein the sensor membrane further comprises a third resistance domain disposed continuously over the first electroactive surface and the second electroactive surface, wherein the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

31. The sensor of claim 17, further comprising an insulator configured to insulate the first working electrode from the second working electrode, wherein the sensor membrane is the insulator.

32. The sensor of claim 17, wherein the first electroactive surface and the second electroactive surface are each dimensioned to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

33. The sensor of claim 32, wherein the first electroactive surface and the second electroactive surface are each sized in at least one dimension such that each of the first noise component and second noise component can be integrated across the dimension.

34. The sensor of claim 33, wherein the dimension is greater than a sum of diameters of about 10 average human cells.

35. The sensor of claim 17, wherein each of the first electroactive surface and the second electroactive surface is dimensioned such that each of the first noise component and the second noise component is substantially equivalent.

36. A sensor configured and arranged for insertion into a host and for continuously detecting glucose in the host, the sensor comprising:

a first working electrode configured to generate a first signal having a first noise component related to a noise-causing species, the first working electrode having a first electroactive surface having a first surface area; and

a second working electrode configured to generate a second signal having a second noise component related to the noise-causing species, the second working electrode having a second electroactive surface having a second surface area;

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wherein the first working electrode and the second working electrode are configured and arranged to integrate the first noise component and the second noise component about a circumference of the sensor.

37. The sensor of claim 36, wherein the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

38. The sensor of claim 36, wherein the noise-causing species is non-constant.

39. The sensor of claim 36, wherein the first surface area and the second surface area are each dimensioned to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

40. The sensor of claim 36, wherein the first surface area and the second surface area are each sized in at least one dimension such that each of the first noise component and the second noise component can be integrated across the dimension.

41. The sensor of claim 40, wherein the dimension is greater than a sum of diameters of about 10 average human cells.

42. The sensor of claim 40, wherein the dimension is greater than about 500μm.

43. The sensor of claim 36, wherein the first surface area and the second surface area are each dimensioned such that each of the first noise component and the second noise component is substantially equivalent.

44. The sensor of claim 40, wherein the first surface area and the second surface area are each dimensioned such that each of the first noise component and the second noise component is equivalent to ±10%.

45. The sensor of claim 36, wherein the first electroactive surface and the second electroactive surface are spaced a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first electroactive surface and the second electroactive surface.

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46. The sensor of claim 36, wherein the first electroactive surface is disposed beneath an active enzymatic portion of a sensor membrane and the second electroactive surface is disposed beneath at least one of an inactive enzymatic or a non-enzymatic portion of the sensor membrane, and wherein the first electroactive surface and the second electroactive surface are spaced a distance less than about a crosstalk distance of a measurable species produced in the active enzymatic portion of the sensor membrane.

47. The sensor of claim 46, wherein the measurable species comprises H_2O_2.

48. The sensor of claim 46, wherein the crosstalk distance comprises a maximum distance the measurable species can diffuse from the active enzymatic portion of the sensor membrane to the second electroactive surface, and thereby cause a measurable signal on the second working electrode.

49. The sensor of claim 46, further comprising a physical diffusion barrier.

50. The sensor of claim 49, wherein the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein each of the first barrier layer and the second barrier layer is independently formed.

51. The sensor of claim 49, wherein the physical diffusion barrier comprises a first resistance domain formed on the first working electrode and a second resistance domain formed on the second working electrode, and wherein the first resistance domain and the second resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface by at least 2-fold.

52. The sensor of claim 51, wherein the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measurable species by at least 10-fold.

53. The sensor of claim 51, wherein the sensor membrane further comprises a third resistance domain disposed continuously over the first resistance domain and the second resistance domain, wherein the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

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54. The sensor of claim 36, further comprising an insulator configured to insulate the first working electrode from the second working electrode, wherein the sensor membrane is the insulator.

55. A continuous glucose sensor configured and arranged for insertion into a host and for detecting glucose in the host, the sensor comprising:

a first working electrode comprising a first electroactive surface disposed beneath an active enzymatic portion of a sensor membrane, wherein the first electroactive surface is configured to measure a measurable species;

a second working electrode comprising a second electroactive surface disposed beneath at least one of an inactive enzymatic portion of the sensor membrane and a non-enzymatic portion of the sensor membrane, wherein the second electroactive surface is configured to measure said measurable species, and wherein the first electroactive surface and the second electroactive surface are spaced within a crosstalk distance of the measurable species; and

a physical diffusion barrier disposed between the first working electrode and the second working electrode, wherein the physical diffusion barrier is configured and arranged such that there is substantially no signal associated with crosstalk.

56. The sensor of claim 55, wherein the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

57. The sensor of claim 56, wherein the noise-causing species is non-constant.

58. The sensor of claim 56, wherein the measurable species is H_2O_2 produced in an active enzymatic portion of a sensor membrane.

59. The sensor of claim 56, wherein the crosstalk distance is a maximum distance the measurable species can diffuse between the active enzymatic portion of the membrane and the second working electrode, and be detected as crosstalk.

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60. The sensor of claim 56, wherein the first electroactive surface has a first area and the second electroactive surface has a second area; wherein the first area and the second area are dimensioned such that the first noise component and the second noise component are substantially equivalent.

61. The sensor of claim 60, wherein at least one dimension of each of the first area and the second area is greater than a sum of diameters of about 10 average human cells.

62. The sensor of claim 60, wherein at least one dimension of each of the first area and the second area is greater than about 500μm.

63. The sensor of claim 60, wherein the first area and the second area are each configured and arranged to integrate noise caused by a plurality of local point sources that produce noise-causing species *in vivo*.

64. The sensor of claim 60, wherein the first area and the second area are each configured and arranged to integrate noise detected about a circumference of the sensor.

65. The sensor of claim 55, wherein the physical diffusion barrier comprises a discontinuous portion of the membrane disposed between the first electroactive surface and the second electroactive surface.

66. The sensor of claim 55, wherein the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the second working electrode, wherein the first barrier layer and the second barrier layer are independently formed.

67. The sensor of claim 55, wherein the physical diffusion barrier comprises a first resistance domain formed on the first working electrode and a second resistance domain formed on the second working electrode, and wherein the first resistance domain and the second resistance domain are configured and arranged to attenuate diffusion of the measurable species from the active enzymatic portion of the membrane to the second electroactive surface by at least 2-fold.

68. The sensor of claim 67, wherein the physical diffusion barrier is configured and arranged to attenuate the diffusion of the measurable species by at least 10-fold.

69. The sensor of claim 67, wherein the sensor membrane further comprises a third resistance domain disposed continuously over the first resistance domain and the second

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resistance domain, wherein the third resistance domain is configured such that a sensitivity of each of the first signal and the second signal is substantially equivalent.

70. The sensor of claim 55, further comprising an insulator configured to insulate the first working electrode from the second working electrode, wherein the sensor membrane is the insulator.

71. The sensor of claim 55, wherein the first electroactive surface and the second electroactive surface are spaced a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first electroactive surface and the second electroactive surface.

72. A continuous glucose sensor configured and arranged for insertion into a host for and detecting glucose in the host, the sensor comprising:

a first working electrode comprising a first resistance domain, wherein the first working electrode is configured to generate a first signal having a first noise component related to a noise-causing species;

a second working electrode comprising a second resistance domain, wherein the second working electrode is configured to generate a second signal having a second noise component related to the noise-causing species; and

a third resistance domain disposed continuously over the first resistance domain and the second resistance domain.

73. The sensor of claim 72, wherein the noise-causing species comprises at least one member selected from the group consisting of externally produced H_2O_2, urea, lactic acid, phosphates, citrates, peroxides, amino acids, amino acid precursors, amino acid break-down products, nitric oxide, NO-donors, NO-precursors, reactive oxygen species, compounds having electroactive acidic, amine or sulfhydryl groups, acetaminophen, ascorbic acid, dopamine, ephedrine, ibuprofen, L-dopa, methyldopa, salicylate, tetracycline, tolazamide, tolbutamide, and triglycerides.

74. The sensor of claim 72, wherein the noise-causing species is non-constant.

75. The sensor of claim 72, wherein the first signal comprises a first sensitivity and the second signal comprises a second sensitivity, and wherein the third resistance domain is configured such that the first sensitivity and the second sensitivity are substantially equivalent.

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76. The sensor of claim 75, wherein the first sensitivity and the second sensitivity are equivalent to ±10%.

77. The sensor of claim 72, wherein each of the first resistance domain and the second resistance domain is independently formed on the first working electrode and the second working electrode, respectively.

78. The sensor of claim 72, wherein the first working electrode comprises a first electroactive surface and a first membrane portion disposed thereon, the first membrane portion comprising an active enzymatic enzyme domain and the first resistance domain, and wherein the second working electrode comprises a second electroactive surface and a second membrane portion disposed thereon, the second membrane portion comprising at least one of an inactive enzymatic portion or a non-enzymatic portion and the second resistance domain.

79. The sensor of claim 78, wherein the active enzymatic enzyme domain is configured to generate a measurable species.

80. The sensor of claim 79, wherein the measurable species comprises H_2O_2 produced in the active enzymatic portion of the sensor membrane.

81. The sensor of claim 78, further comprising a physical diffusion barrier, wherein physical diffusion barrier comprises the first resistance domain and the second resistance domain.

82. The sensor of claim 81, wherein the physical diffusion barrier is configured and arranged to attenuate diffusion of the measurable species from the active enzymatic enzyme domain to the second electroactive surface by at least 2-fold.

83. The sensor of claim 82, wherein the diffusion is attenuated by at least 10-fold.

84. The sensor of claim 81, wherein the physical diffusion barrier is configured and arranged to physically block some crosstalk from the active enzymatic enzyme domain to the second electroactive surface.

85. The sensor of claim 81, wherein the physical diffusion barrier is configured and arranged to physically block an amount of a measurable species diffusing from the active enzymatic enzyme domain to the second electroactive surface, such that there is substantially no signal associated with crosstalk measured at the second working electrode.

86. The sensor of claim 81, wherein the physical diffusion barrier comprises a first barrier layer formed on the first working electrode and a second barrier layer formed on the

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second working electrode, wherein each of the first barrier layer and the second barrier layer is independently formed.

87. The sensor of claim 79, wherein the first electroactive surface and the second electroactive surface are spaced closer together than a crosstalk distance.

88. The sensor of claim 87, wherein the crosstalk distance comprises a distance less than a maximum distance the measurable species can diffuse, and generate a signal associated with crosstalk.

89. The sensor of claim 79, wherein the first electroactive surface and the second electroactive surface are spaced a distance that allows noise caused by a local point source that produces noise-causing species to be measured equivalently at the first and second electroactive surfaces.

90. The sensor of claim 79, wherein each of the first electroactive surface and the second electroactive surface is configured and arranged to integrate the signal caused by a plurality of local point sources that produce noise-causing species *in vivo*, such that the first noise component and the second noise component are substantially equivalent.

91. The sensor of claim 79, wherein the first electroactive surface and the second electroactive surface are configured and arranged to integrate signals detected about a circumference of the sensor.

92. The sensor of claim 79, wherein the first electroactive surface and the second electroactive surface are each sized in at least one dimension such that the first noise component and the second noise component can be integrated across the dimension.

93. The sensor of claim 79, wherein the dimension of each of the first electroactive surface and the second electroactive surface is greater than a sum of diameters of about 10 average human cells.

94. The sensor of claim 93, wherein the dimension of each of the first electroactive surface and the second electroactive surface is greater than about 500μm.

Abbott Ex. 1002 - 1141/1438

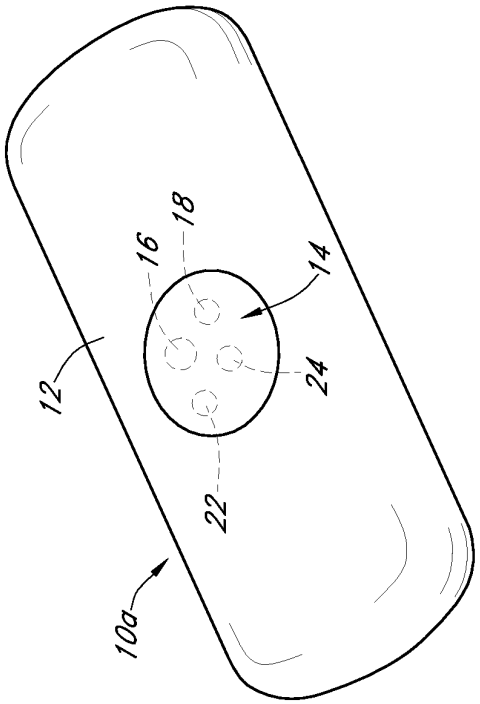


FIG. 1A

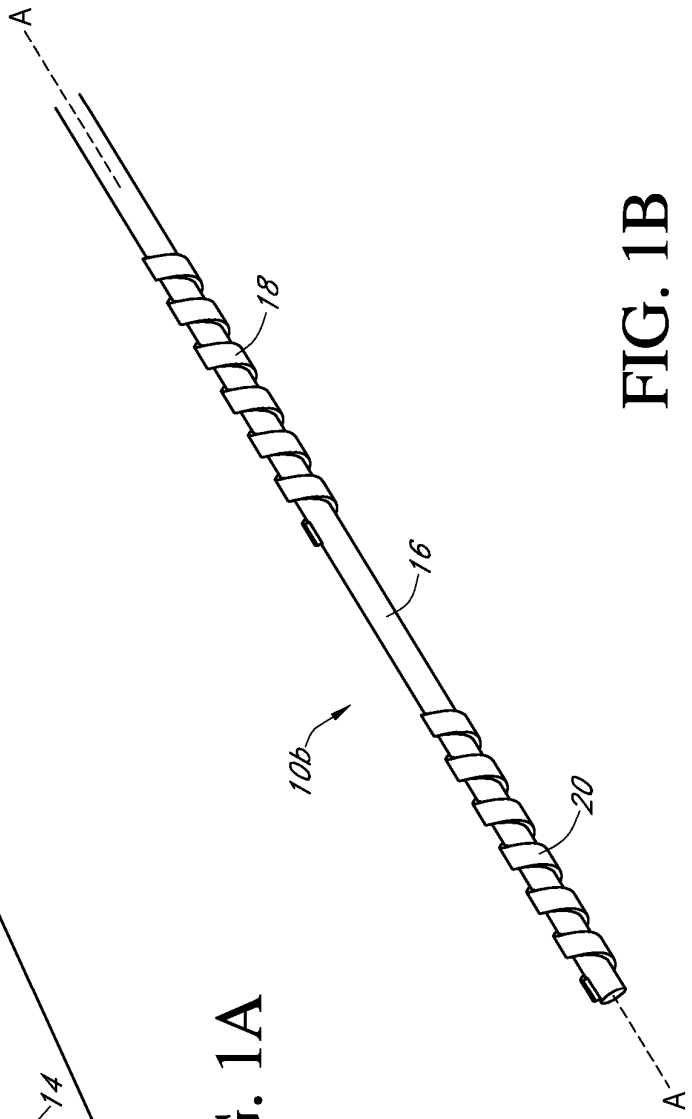


FIG. 1B

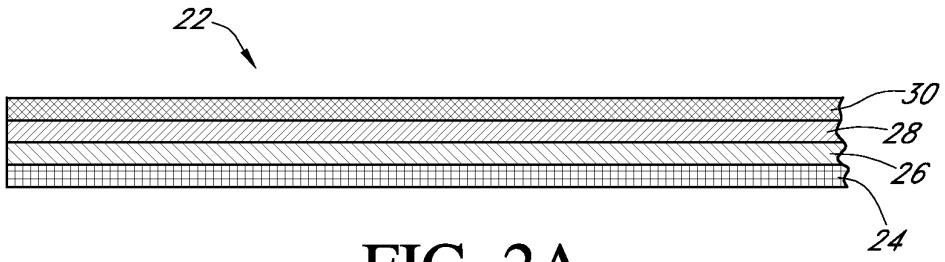


FIG. 2A

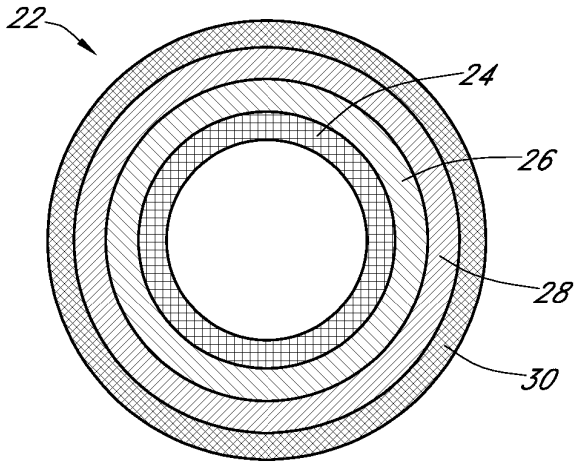


FIG. 2B

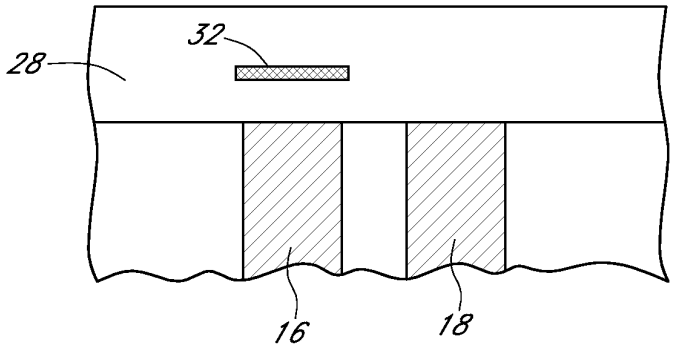


FIG. 3A

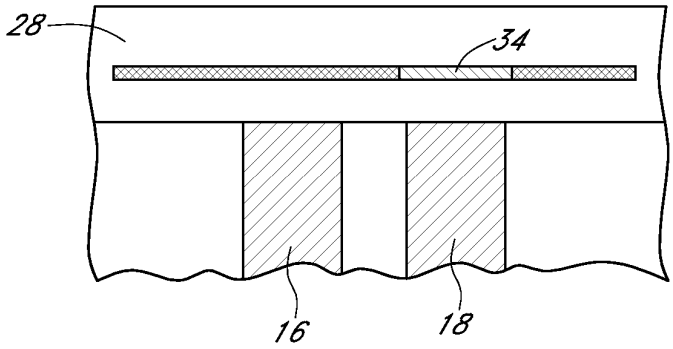


FIG. 3B

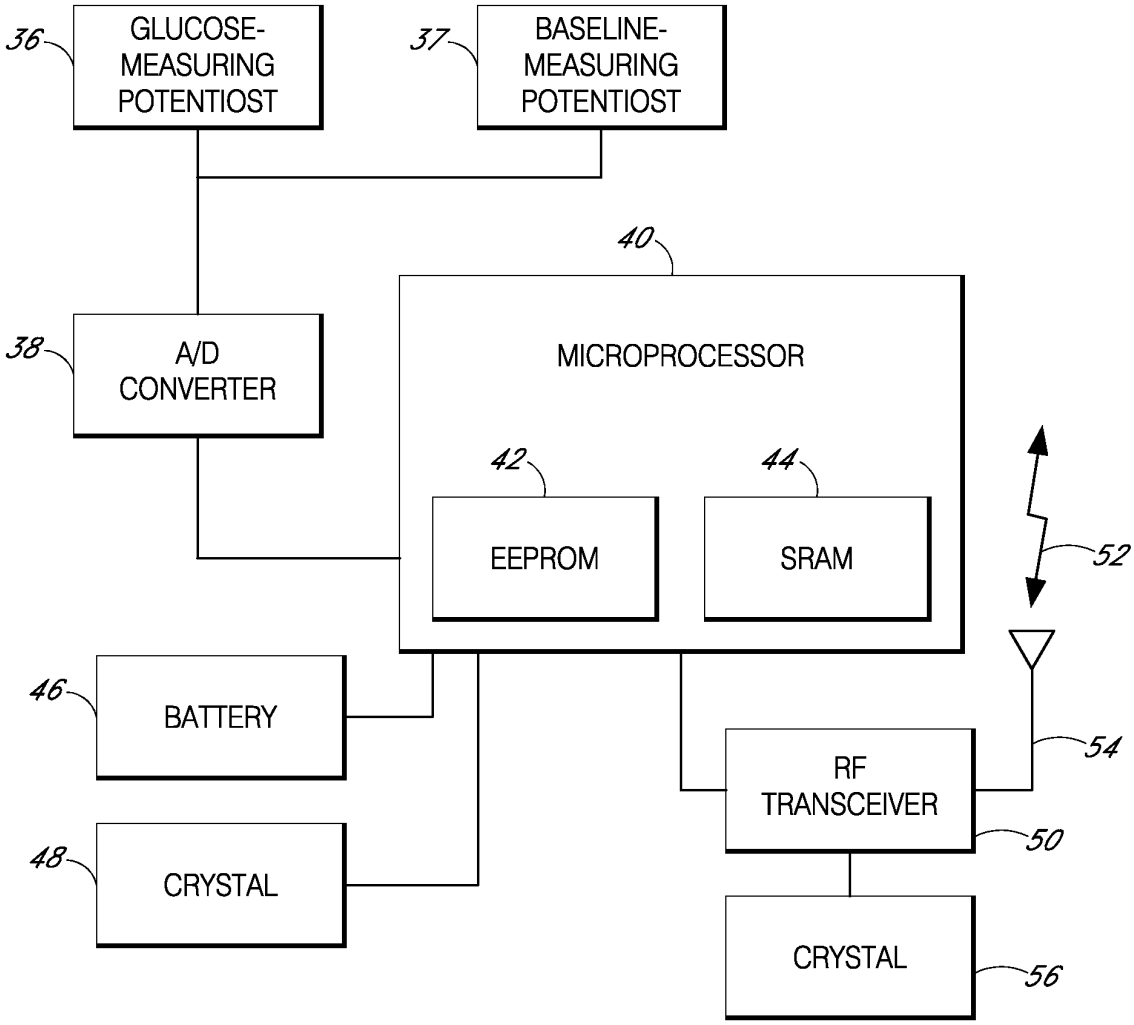

36
GLUCOSE-MEASURING POTENTIOST
37
BASELINE-MEASURING POTENTIOST
40
MICROPROCESSOR
38
A/D CONVERTER
42
EEPROM
44
SRAM
52
46
BATTERY
54
RF TRANSCEIVER
48
CRYSTAL
50
CRYSTAL
56

FIG. 4

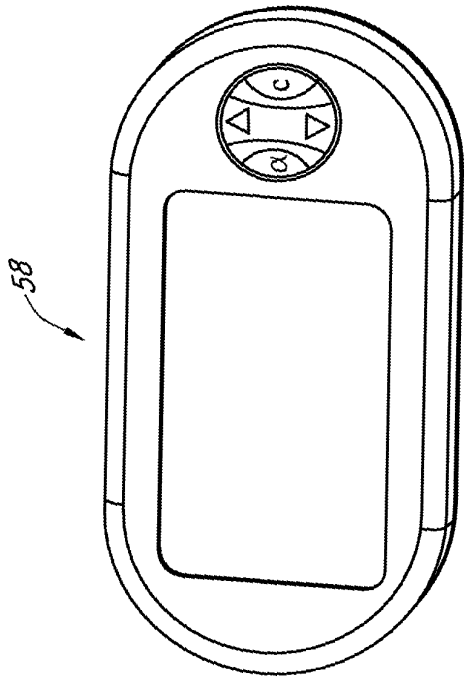


FIG. 5

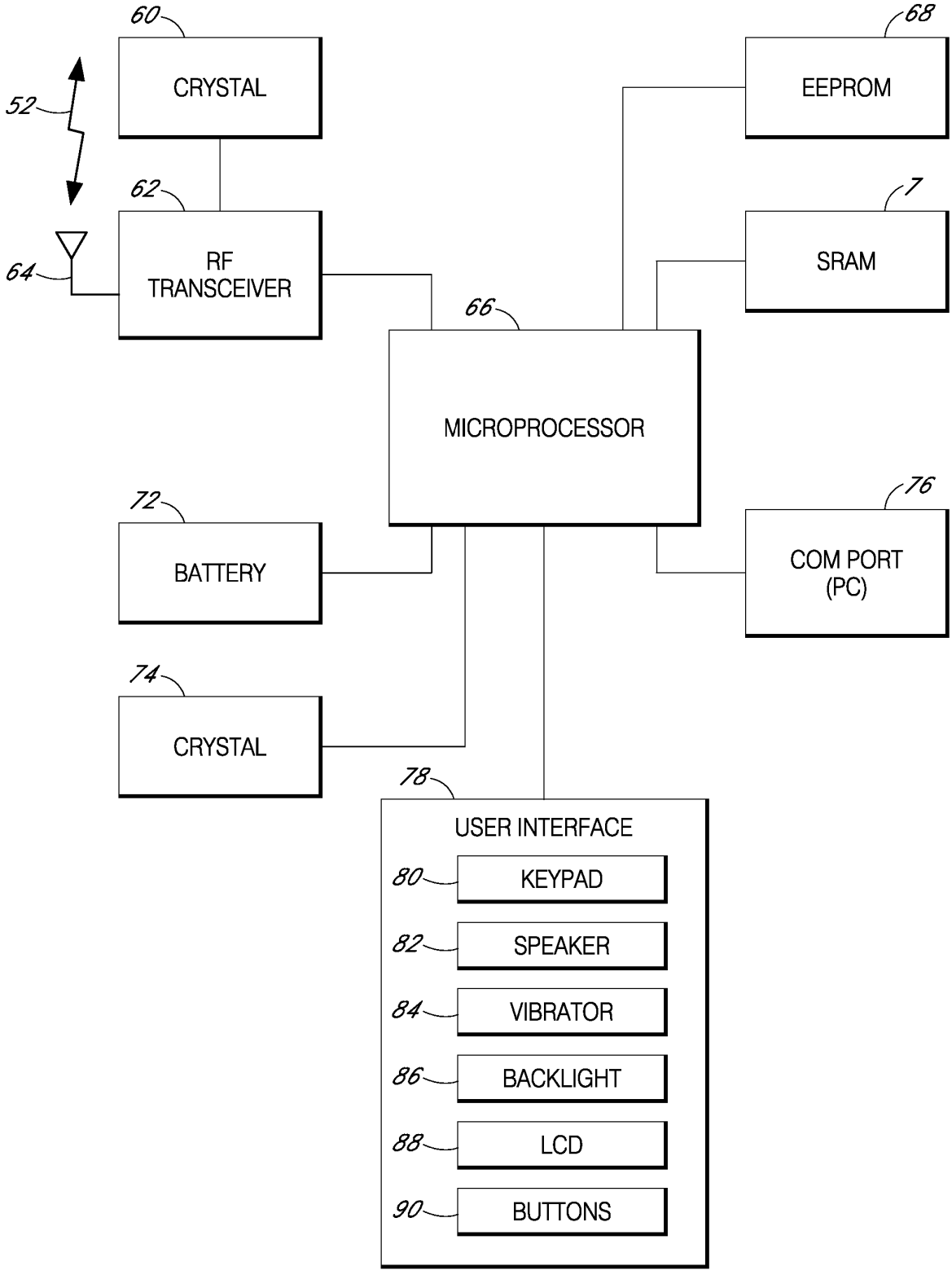

60
CRYSTAL
52
62
RF TRANSCEIVER
64
68
EEPROM
7
SRAM
66
MICROPROCESSOR
72
BATTERY
76
COM PORT (PC)
74
CRYSTAL
78
USER INTERFACE
80
KEYPAD
82
SPEAKER
84
VIBRATOR
86
BACKLIGHT
88
LCD
90
BUTTONS

FIG. 6

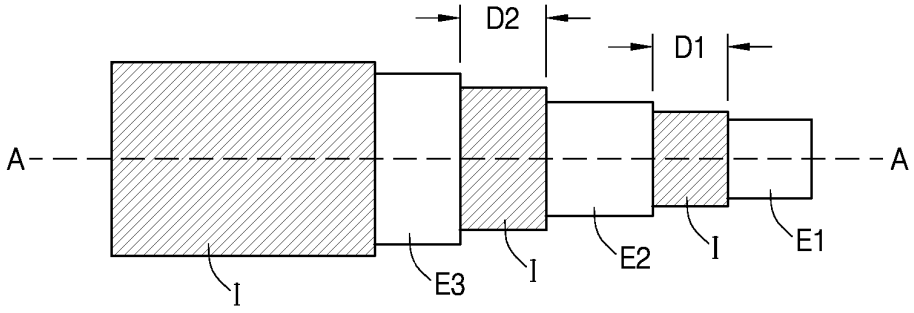


FIG. $7A_1$

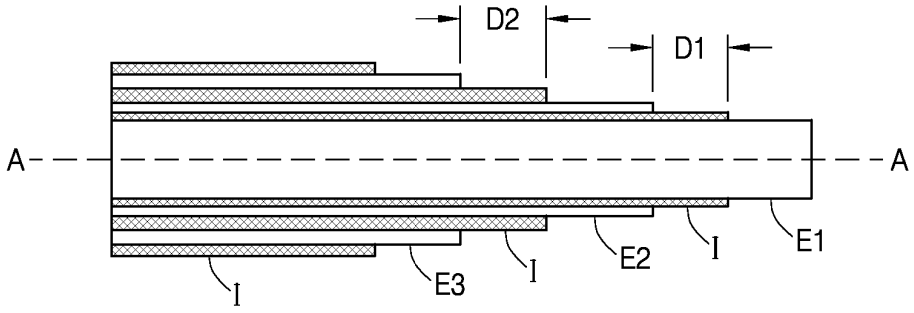


FIG. $7A_2$

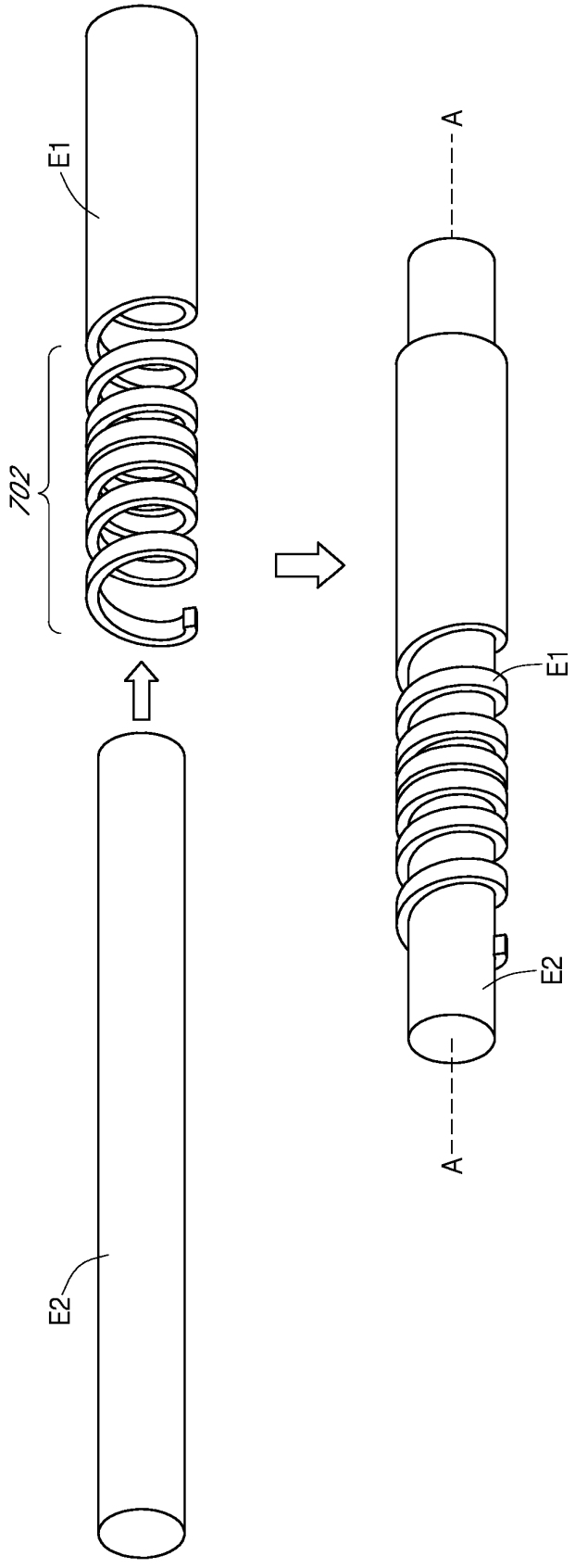


FIG. 7B

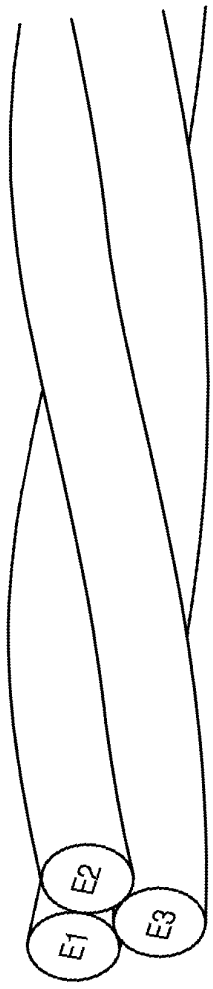


FIG. 7C

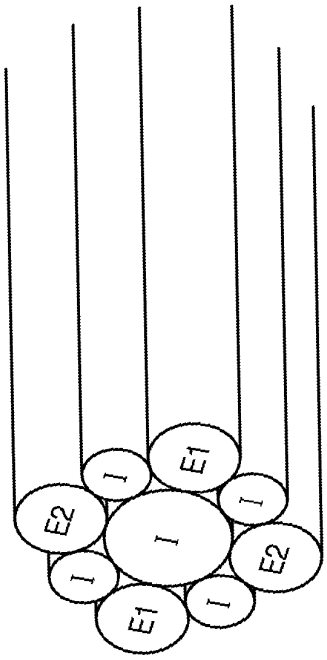


FIG. 7E

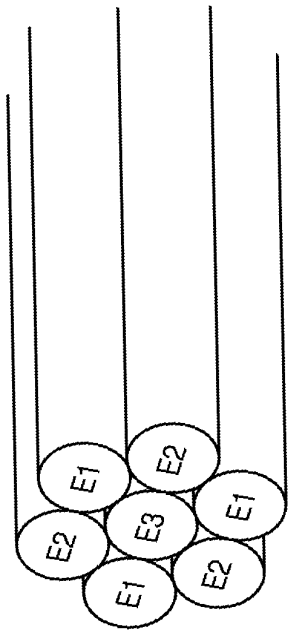


FIG. 7D

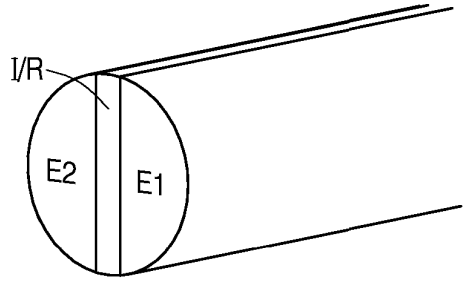


FIG. 7F

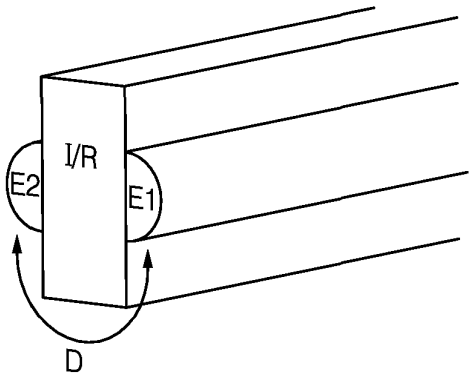


FIG. 7G

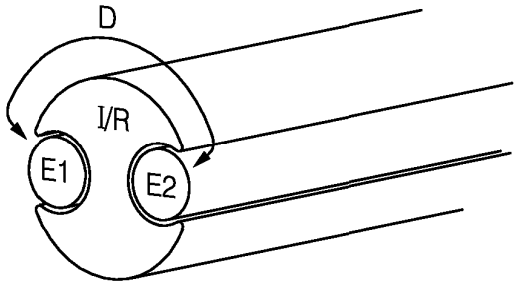


FIG. 7H

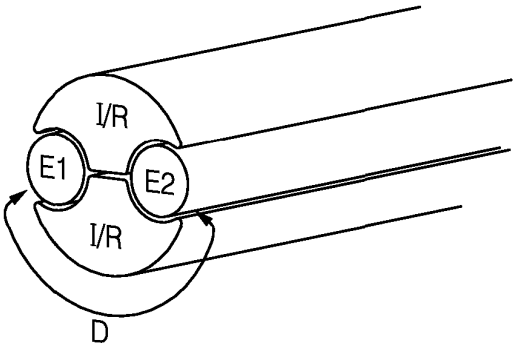


FIG. 7I

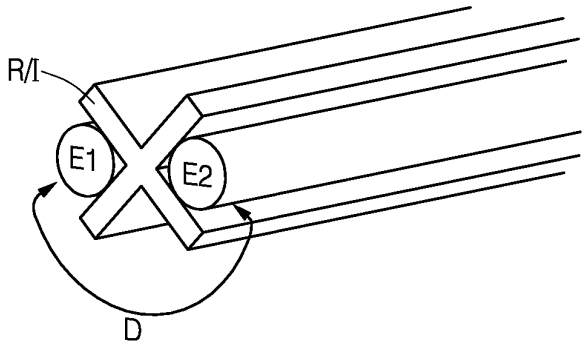


FIG. 7J

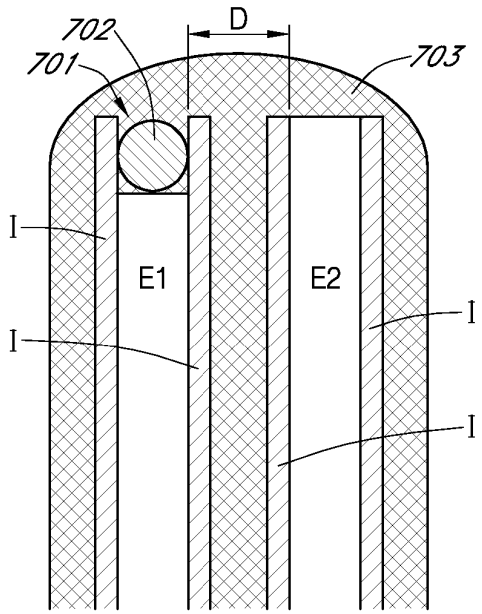


FIG. 7K

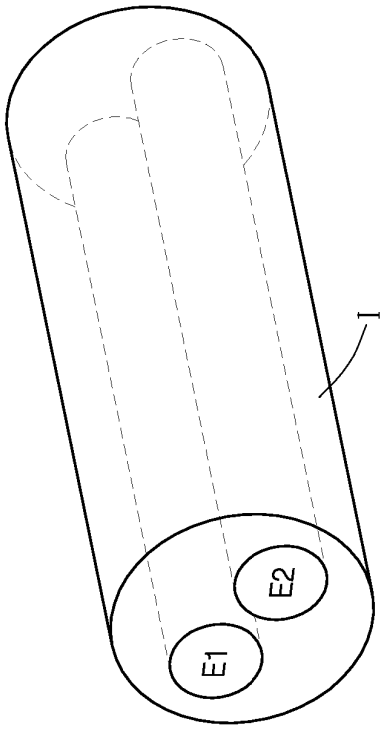


FIG. 7L

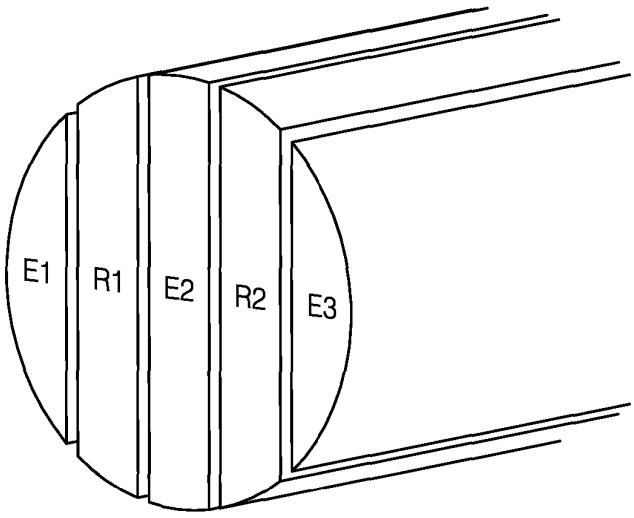


FIG. 7M

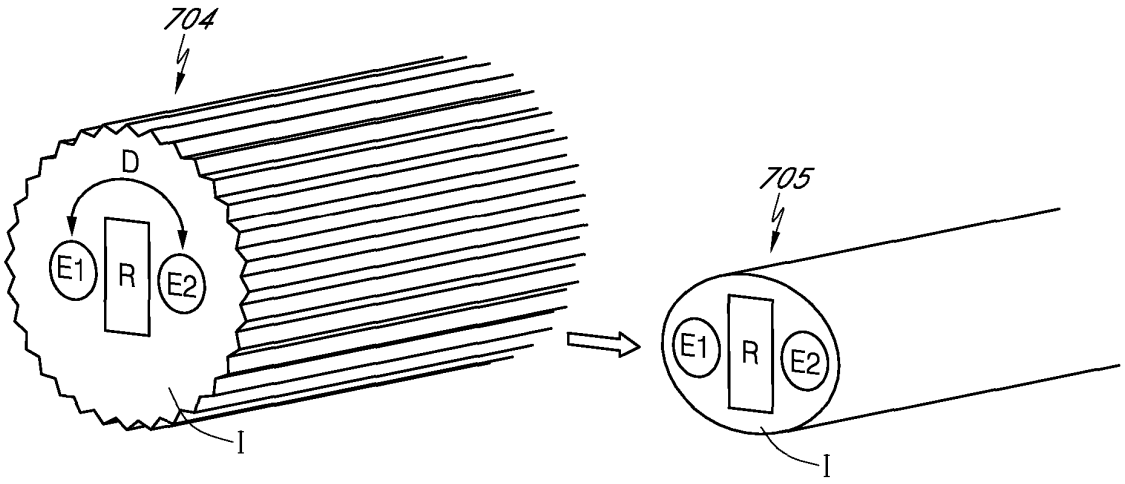


FIG. 7N

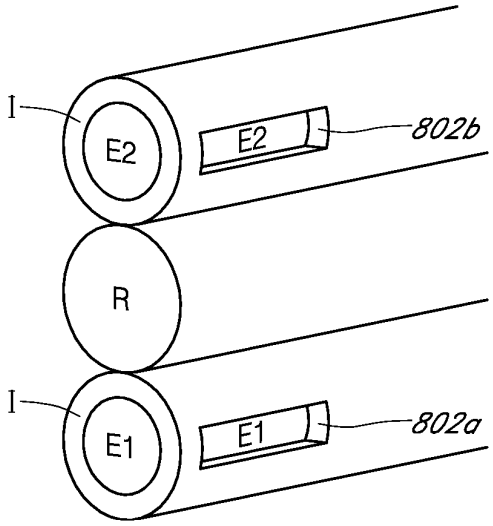


FIG. 8A

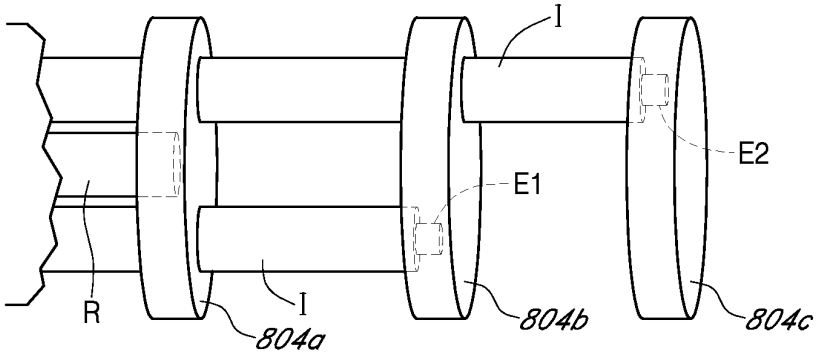


FIG. 8B

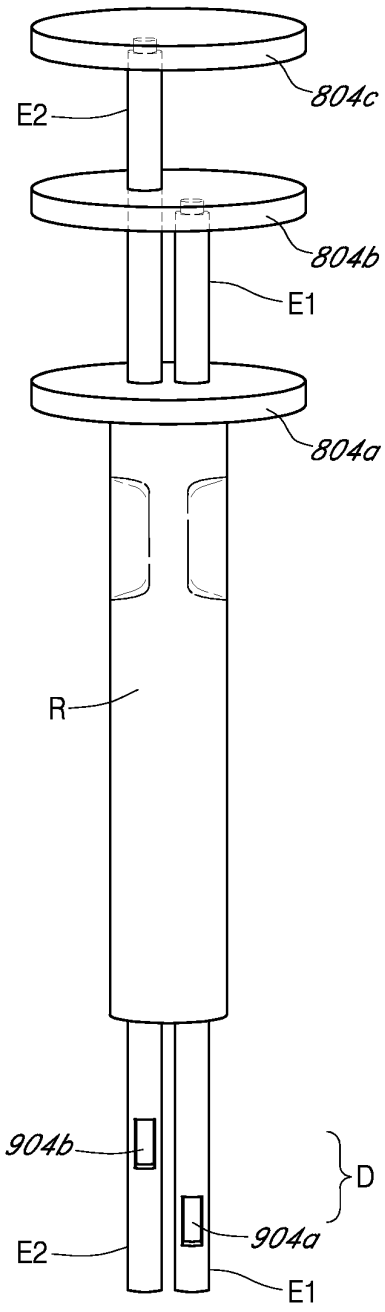

804c
E2
804b
E1
804a
R
904b
D
904a
E2
E1

FIG. 9A

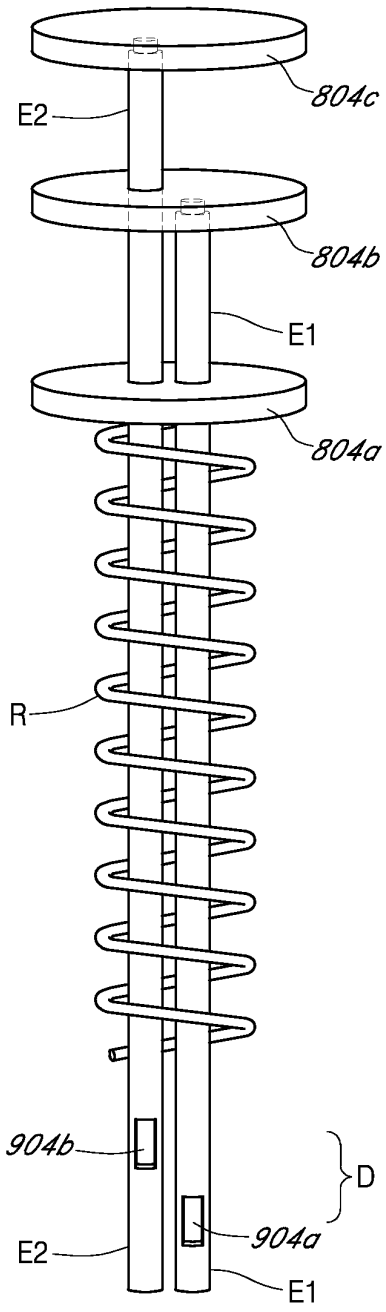

804c
E2
804b
E1
804a
R
904b
D
904a
E2
E1

FIG. 9B

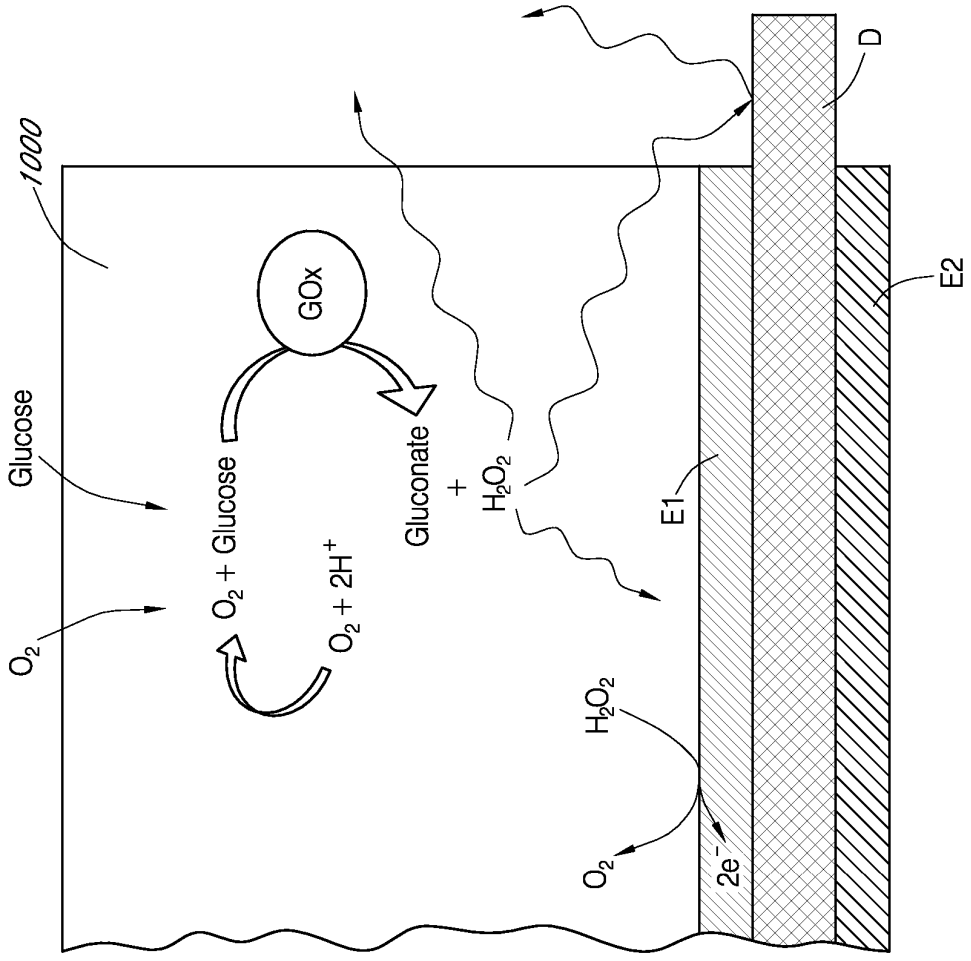

1000
D
E2
E1
GOx
Glucose
O_2
O_2 + Glucose
O_2 + $2H^+$
Gluconate
+
H_2O_2
H_2O_2
O_2
$2e^-$

FIG. 10

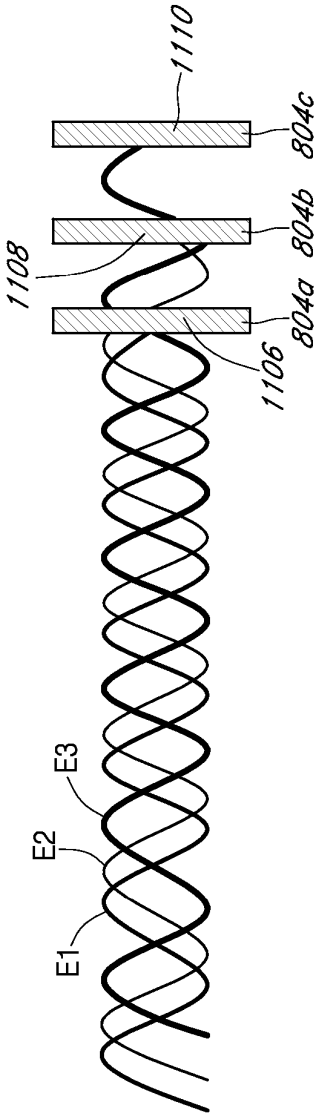


FIG. 11

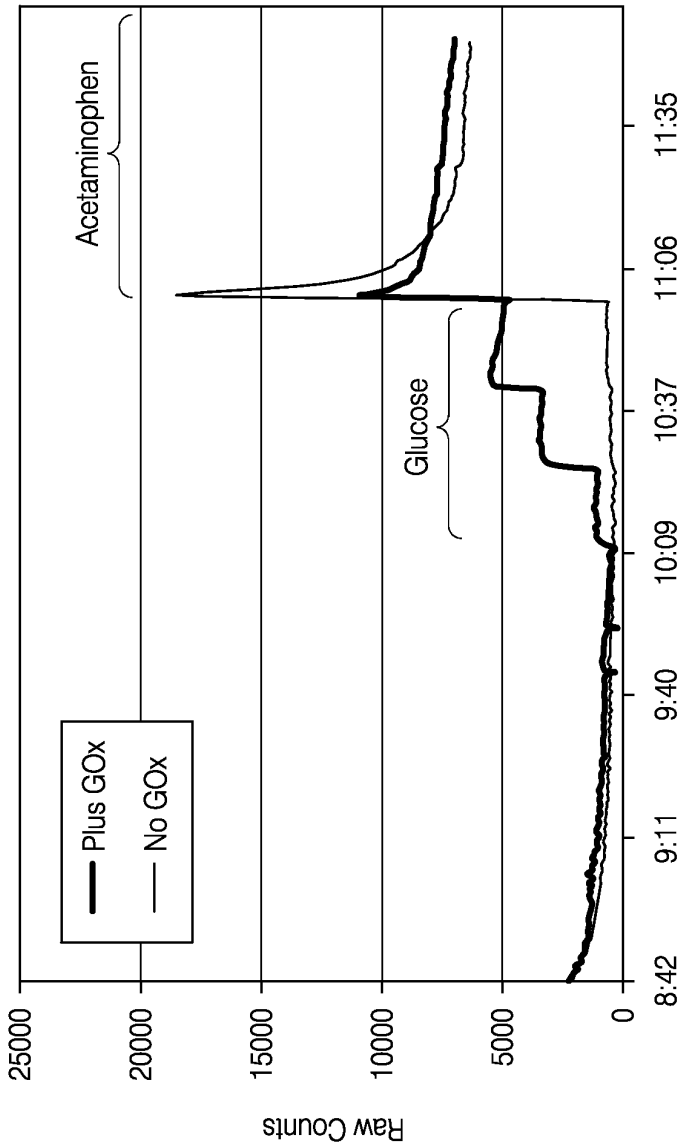

Acetaminophen
Glucose
Plus GOx
No GOx
Raw Counts
25000
20000
15000
10000
5000
0
8:42
9:11
9:40
10:09
10:37
11:06
11:35
Time (minutes)

FIG. 12

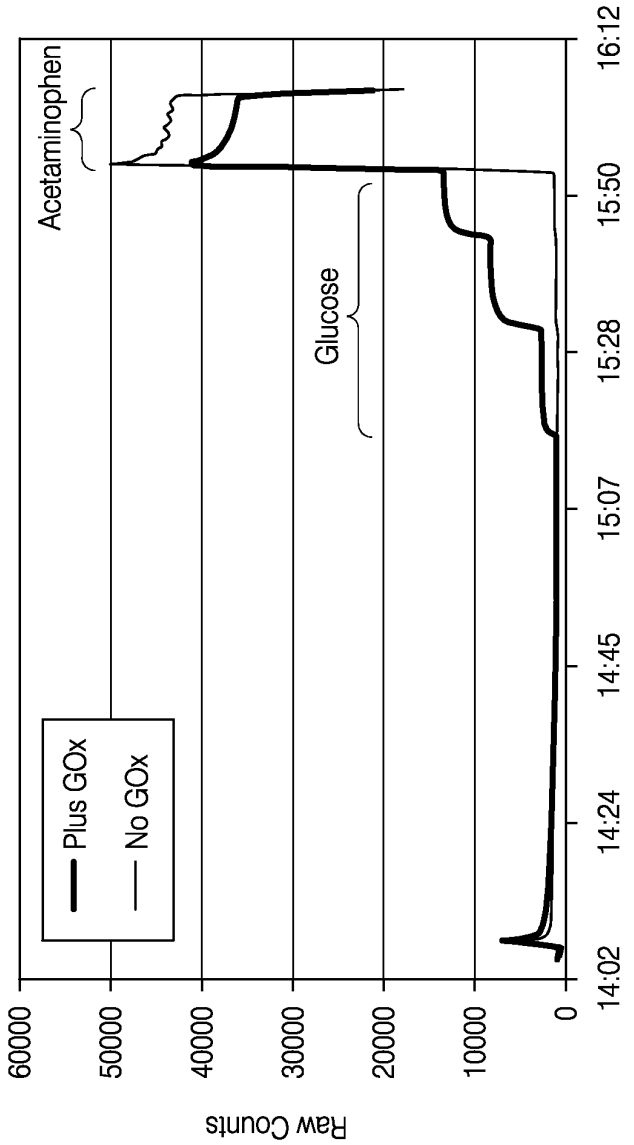

Acetaminophen
Glucose
Plus GOx
No GOx
Raw Counts
60000
50000
40000
30000
20000
10000
0
14:02
14:24
14:45
15:07
15:28
15:50
16:12
Time (minutes)

FIG. 13

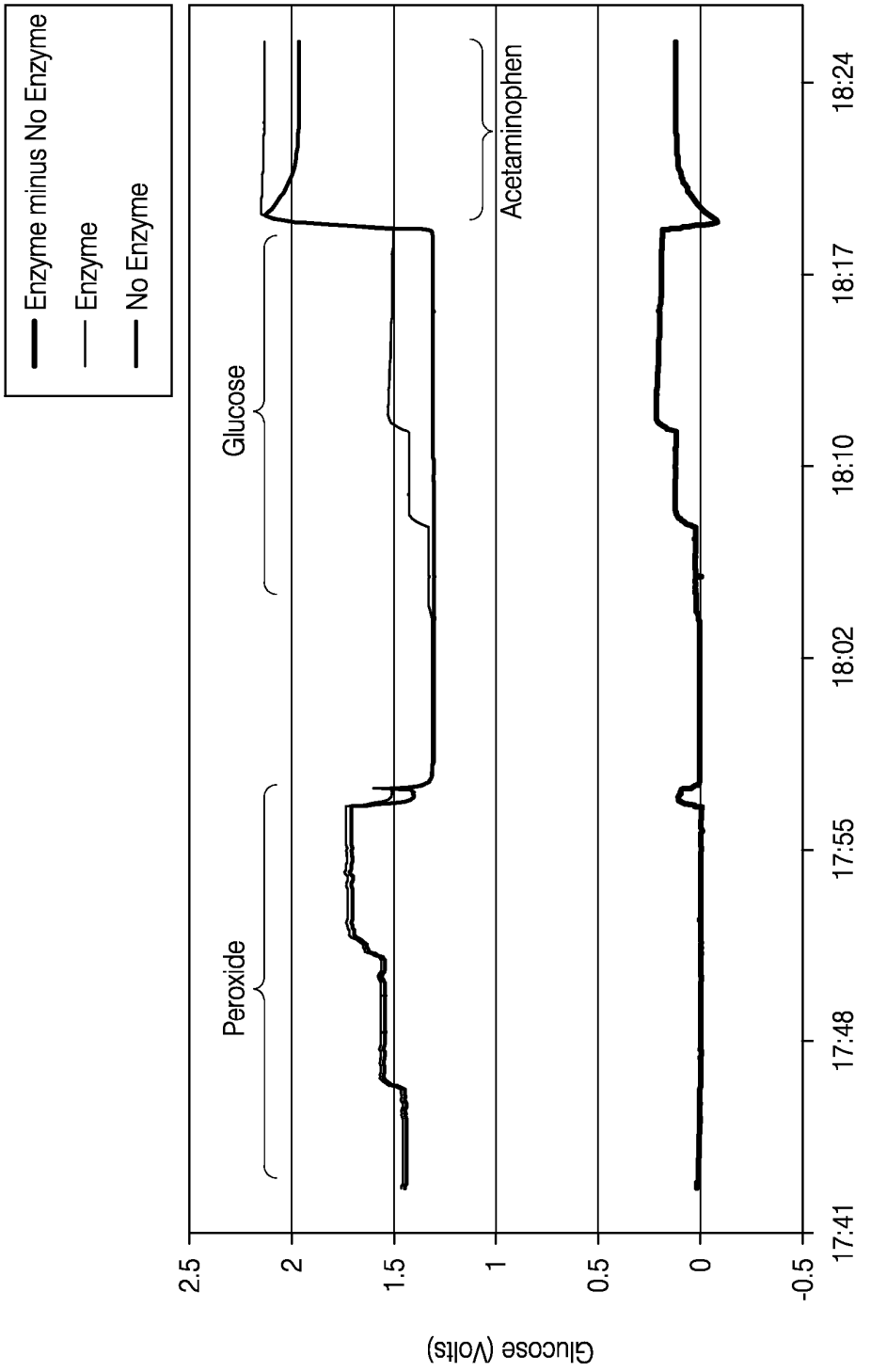

Enzyme minus No Enzyme
Enzyme
No Enzyme
Peroxide
Glucose
Acetaminophen
2.5
2
1.5
1
0.5
0
-0.5
Glucose (Volts)
17:41
17:48
17:55
18:02
18:10
18:17
18:24
Time

FIG. 14

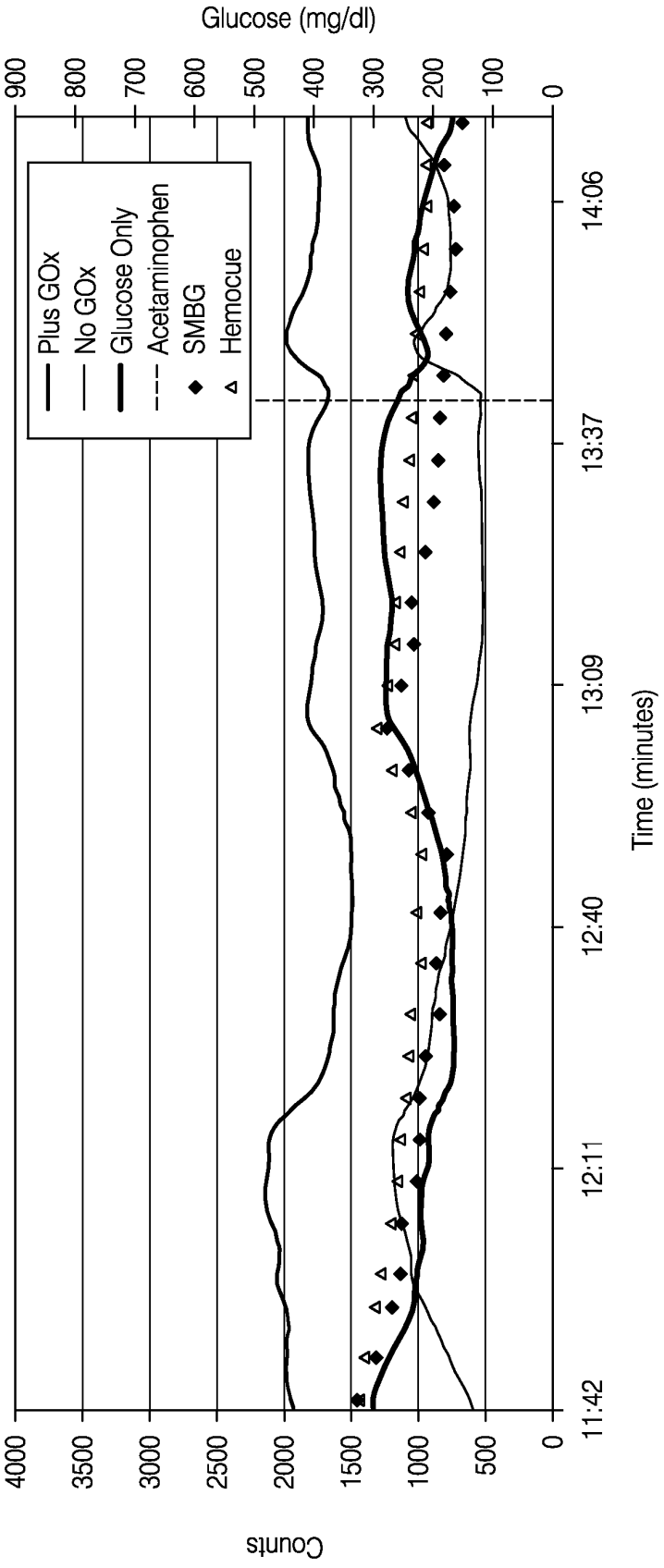

Glucose (mg/dl)
900
800
700
600
500
400
300
200
100
0
Plus GOx
No GOx
Glucose Only
Acetaminophen
SMBG
Hemocue
14:06
13:37
13:09
12:40
12:11
11:42
Time (minutes)
4000
3500
3000
2500
2000
1500
1000
500
0
Counts

FIG. 15

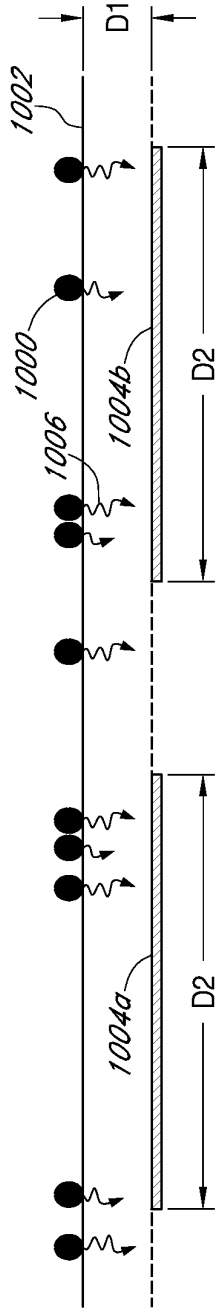


FIG. 16

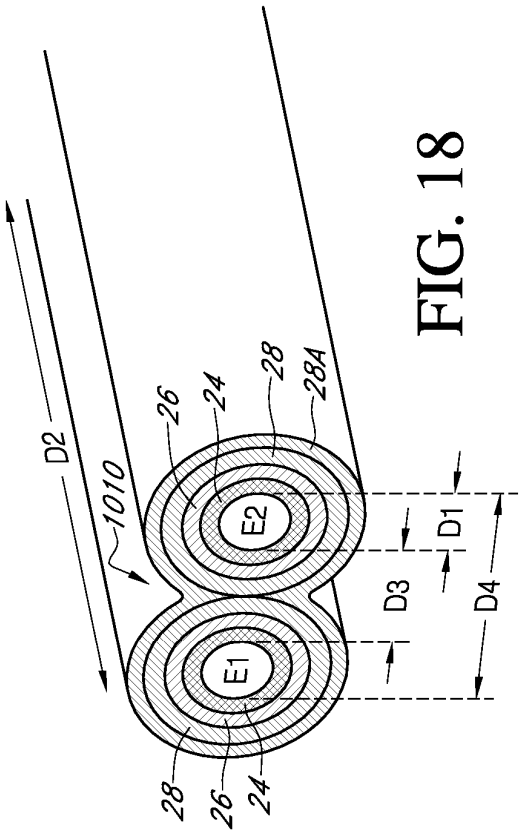


FIG. 18

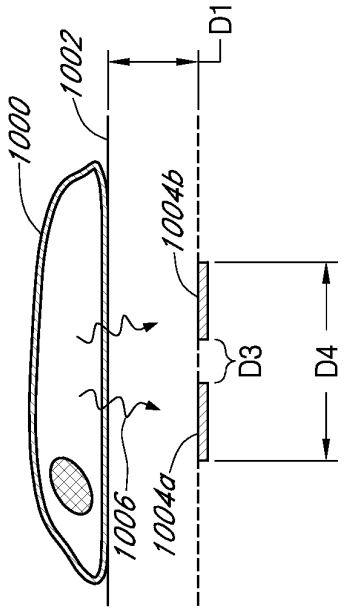


FIG. 17

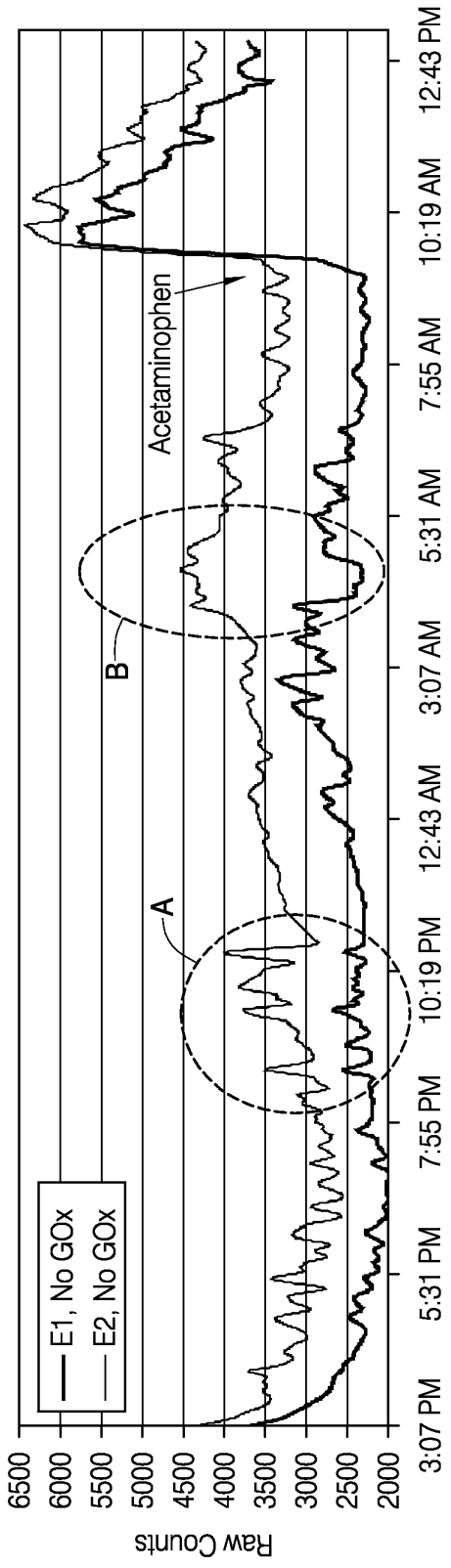

Raw Counts
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
3:07 PM
5:31 PM
7:55 PM
10:19 PM
12:43 AM
3:07 AM
5:31 AM
7:55 AM
10:19 AM
12:43 PM
E1, No GOx
E2, No GOx
A
B
Acetaminophen

FIG. 19A

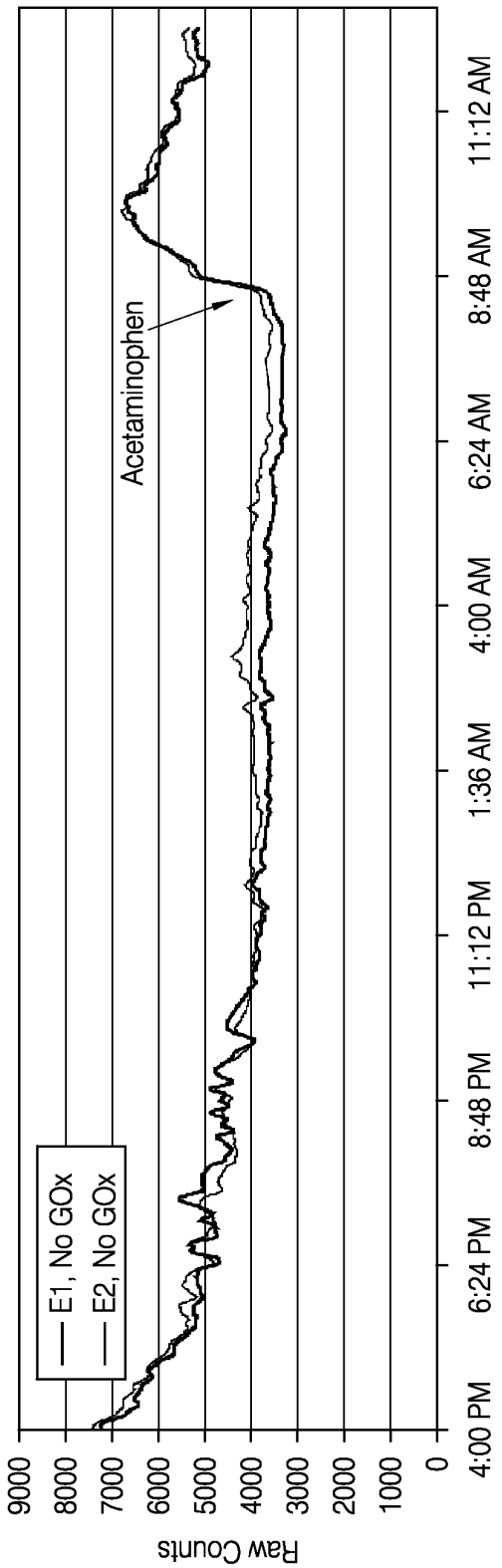

Raw Counts
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
4:00 PM
6:24 PM
8:48 PM
11:12 PM
1:36 AM
4:00 AM
6:24 AM
8:48 AM
11:12 AM
E1, No GOx
E2, No GOx
Acetaminophen

FIG. 19B

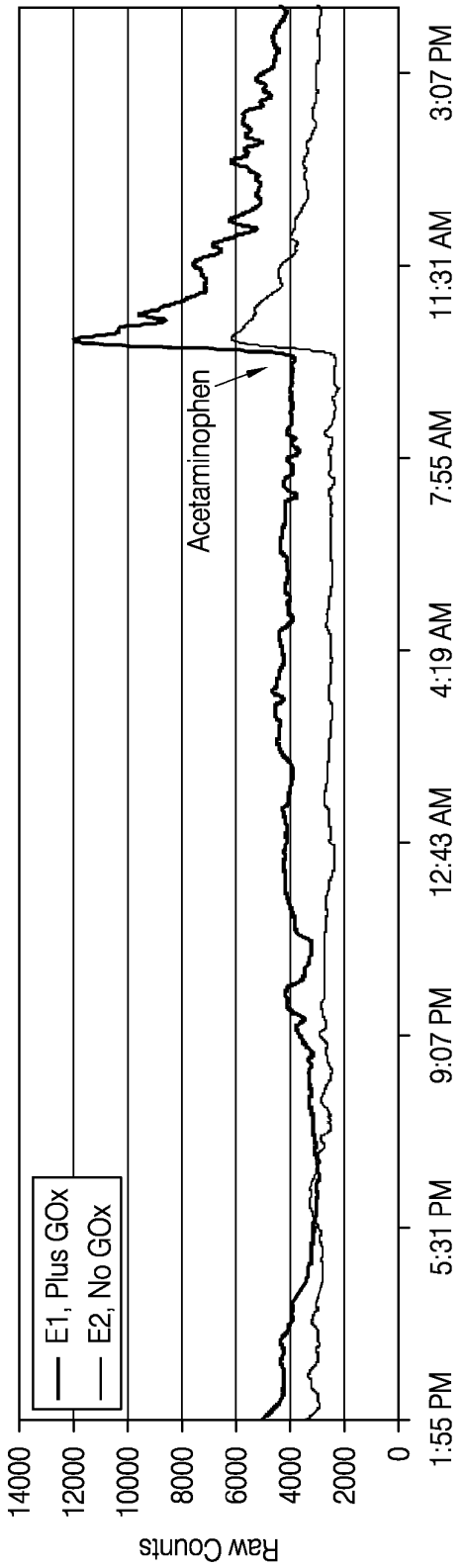

E1, Plus GOx
E2, No GOx
Acetaminophen
Raw Counts
14000
12000
10000
8000
6000
4000
2000
0
1:55 PM
5:31 PM
9:07 PM
12:43 AM
4:19 AM
7:55 AM
11:31 AM
3:07 PM

FIG. 20A

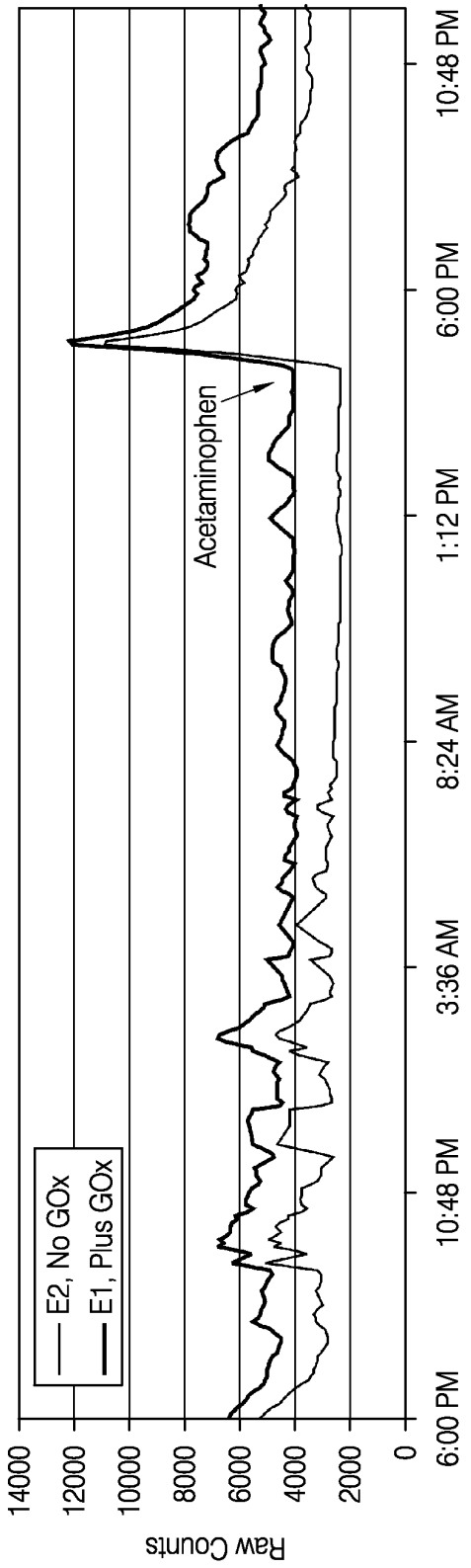

Raw Counts
14000
12000
10000
8000
6000
4000
2000
0
6:00 PM
10:48 PM
3:36 AM
8:24 AM
1:12 PM
6:00 PM
10:48 PM
E2, No GOx
E1, Plus GOx
Acetaminophen

FIG. 20B

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 April 2008 (10.04.2008)

PCT

(10) International Publication Number
WO 2008/042918 A3

(51) International Patent Classification:
G01N 27/327 (2006.01) *A61B 5/1486* (2006.01)
C12Q 1/00 (2006.01)

(21) International Application Number:
PCT/US2007/080228

(22) International Filing Date: 2 October 2007 (02.10.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

11/543,707	4 October 2006 (04.10.2006)	US
11/543,539	4 October 2006 (04.10.2006)	US
11/543,683	4 October 2006 (04.10.2006)	US
11/543,734	4 October 2006 (04.10.2006)	US
11/692,154	27 March 2007 (27.03.2007)	US
11/865,572	1 October 2007 (01.10.2007)	US

(71) Applicant *(for all designated States except US)*: **DEXCOM, INC.** [US/US]; 5555 Oberlin Drive, San Diego, CA 92121 (US).

(72) Inventors: **SIMPSON, Peter**; 227 N. Vulcan Avenue, Encinitas, California 92024 (US). **BRISTER, Mark**; 1055 Valley Side Lane, Encinitas, California 92024 (US). **WIGHTLIN, Matthew**; 8637 Jenny Avenue, San Diego, CA 92123 (US). **PRYOR, Jack**; 15590 Paseo Jenghiz, San Diego, California 92129 (US).

(74) Agent: **MALLON, Joseph, J.**; Knobbe Martens Olson & Bear LLP, 2040 Main Street 14th Floor, Irvine, CA 92614 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,

[Continued on next page]

(54) Title: DUAL ELECTRODE SYSTEM FOR A CONTINUOUS ANALYTE SENSOR

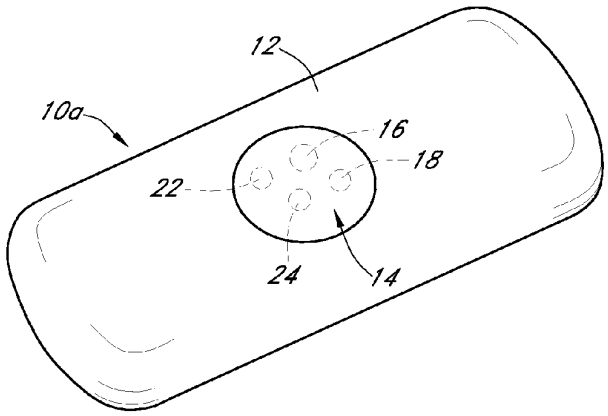


FIG. 1A

(57) Abstract: Disclosed herein are systems and methods for a continuous analyte sensor, such as a continuous glucose sensor. One such system utilizes first and second working electrodes working electrodes E1, E2 including a membrane having an electrode domain 24, an enzyme domain 26 and a resistance domain 28 to measure additional analyte or non-analyte related signal. Such measurements may provide a background and/or sensitivity measurement(s) for use in processing sensor data and may be used to trigger events such as digital filtering of data or suspending display of data.

WO 2008/042918 A3

PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
4 September 2008

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/080228

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N27/327 C12Q1/00 A61B5/1486

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/057168 A (DEXCOM INC [US]; KAMATH APURV ULLAS [US]; SIMPSON PETER C [US]; BRAUKE) 23 June 2005 (2005-06-23) cited in the application	1,17
A	page 5, paragraph 10 page 21, paragraph 83	55
X	WO 00/59373 A (SPECTRX INC [US]; KUMAR KRISHNA S [US]; PAPP JOSEPH [US]; FARQUHAR J D) 12 October 2000 (2000-10-12)	1,17
A	page 9, line 14 - line 30	55
X	WO 2005/012873 A (DEXCOM INC [US]; SIMPSON PETER C [US]; PETISCE JAMES R [US]; CARR-BREN) 10 February 2005 (2005-02-10)	1,17
Y	page 3, line 6 - line 36	1,17
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2008	07/07/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Moreno, Cristina

Form PCT/ISA/210 (second sheet) (April 2005)

Abbott Ex. 1002 - 1170/1438

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/080228

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/134347 A1 (HELLER ADAM [US] ET AL) 17 July 2003 (2003-07-17) page 1, paragraph 6 - paragraph 12 abstract	1,17
X	US 2005/139489 A1 (DAVIES OLIVER WILLIAM H [GB] ET AL) 30 June 2005 (2005-06-30) abstract	1
X	US 4 655 880 A (LIU CHUNG-CHIUN [US]) 7 April 1987 (1987-04-07) column 2, line 30 - line 60 column 3, lines 5-10; claim 1	1
A	US 5 411 866 A (LUONG JOHN H T [CA] ET AL) 2 May 1995 (1995-05-02) abstract	1,17,55
A	WO 2005/026689 A (I STAT CORP [US]; MILLER CARY JAMES [CA]; CAMPBELL JOHN LEWIS EMERSON) 24 March 2005 (2005-03-24) abstract	1,17,55

Abbott Ex. 1002 - 1171/1438

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/080228

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-35, 55-71

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Abbott Ex. 1002 - 1172/1438

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-35, 55-71

   Continuous glucose sensor comprising two working electrodes, one with an active enzymatic portion and one with an inactive or non-enzymatic portion.

   ---

2. claims: 36-54

   Continuous glucose sensor comprising two working electrodes, one having a first electroactive surface and measuring a first noise component and the second having a second electroactive surface and measuring a second noise component.

   ---

3. claims: 72-94

   Continuous glucose sensor comprising two working electrodes, one having a first resistance domain and the second having a second resistance domain, and further comprising a third resistance domain.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/080228

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005057168 A	23-06-2005	EP 1711790 A2	18-10-2006
		US 2005143635 A1	30-06-2005
WO 0059373 A	12-10-2000	AU 4216900 A	23-10-2000
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		JP 2007500336 T	11-01-2007
US 2003134347 A1	17-07-2003	NONE	
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		EP 1668347 A2	14-06-2006
		JP 2007505319 T	08-03-2007
		US 2006160164 A1	20-07-2006

Abbott Ex. 1002 - 1174/1438

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 November 2009 (12.11.2009)

PCT

(10) International Publication Number
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(51) International Patent Classification:
A61B 5/00 (2006.01)

(21) International Application Number:
PCT/IB2009/051870

(22) International Filing Date:
7 May 2009 (07.05.2009)

(25) Filing Language: Italian

(26) Publication Language: English

(30) Priority Data:
MI2008A000837 8 May 2008 (08.05.2008) IT

(71) Applicant *(for all designated States except US)*: **UNIVERSITA' DEGLI STUDI PADOVA** [IT/IT]; Via VIII Febbraio 1848, n. 2, I-35122 Padova (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SPARACINO, Giovanni** [IT/IT]; Via Forcellini, 209/B, I-35128 Padova (IT). **COBELLI, Claudio** [IT/IT]; Via S. Eufemia, 3, I-35121 Padova (IT). **FACCHINETTI, Andrea** [IT/IT]; Via Saetta, 3, I-35132 Padova (IT).

(74) Agents: **GERVASI, Gemma** et al.; Corso di Porta Vittoria 9, I-MILANO 20122 (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) **Title**: METHOD AND DEVICE FOR PROCESSING GLYCEMIA LEVEL DATA BY MEANS OF SELF-ADAPTIVE FILTERING, PREDICTING THE FUTURE GLYCEMIA LEVEL AND GENERATING ALERTS

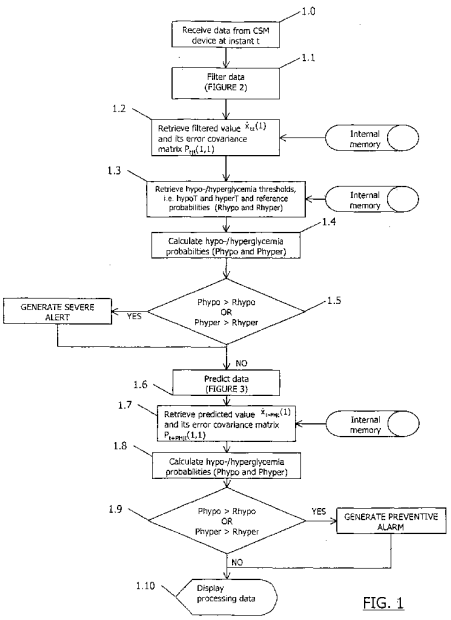


FIG. 1

(57) **Abstract**: It is described a method and device for processing glycemia level data, by means of self-adaptive filtering, future glycemia level prediction and alert generation. The device is portable and small-sized, and used in combination with Continuous Glucose Monitoring (CGM) devices, thus allowing to integrate and improve the information provided thereby. The device incorporates three innovative modules, based on statistic base algorithms for: filtering data in order to reduce the entity of the noise present therein, adapting to the sensor, to the individual and to the SNR evolution during the monitoring step, preferably by means of a "self-tuning" procedure of the filter parameters in real time and on statistic basis, with the determination of the confidence interval on the filtered glycemia level; predicting the future glycemia level with its confidence interval; generating alerts for preventing hypo-/hyperglycemia episodes based on the previously acquired statistic information.

WO 2009/136372 A1

Abbott Ex. 1002 - 1175/1438

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

"Method and device for processing glycemia level data by means of self-adaptive filtering, predicting the future glycemia level and generating alerts"

DESCRIPTION

State of the art

Diabetes - It is estimated that diabetes affects approximately 250 million people in the world today. The number is expected to rise to 350 million in less than 20 years. The rapid, constant increase of diabetic patients make this disease one of the social-health emergencies of the third millennium. Most diabetics follow a metabolic monitoring therapy based on a combination of insulin injections and/or drugs, diet and physical exercise. The therapy is determined by the physician on the basis of glycemia level measurements that the patient measures by him or herself in capillary blood 3 or 4 times a day (self-monitoring). This approach presents inevitable shortcomings due to the low amount of glycemia data available related to the high glycemia range during the day. Due to the shortcomings of the monitoring system, glycemia may exceed normal limits. Hyperglycemia (a situation in which the concentration of glucose in blood is higher than 180 mg/dl) causes various long-term complications (cardiovascular disease, hypertension, retinopathies, etc.), while on the short-term, hypoglycemia (glucose concentration lower than 70 mg/dl) may even be more dangerous (e.g. it may lead to diabetic coma) also because it may be difficult for the patient to recognize, particularly at night.

Known Continuous Glucose Monitoring (CGM) devices.

New minimally invasive or in some cases not at all invasive devices for continuously monitoring glucose levels, known as Continuous Glucose Monitoring (CGM) devices, have been developed and marketed during the past years. Such devices provide blood glycemia values at a very high frequency (from every 1 to 5 minutes, according to the sensor) and continuously stabile operation for several days (from 3 to 7 days, according to the technology).

Most of the devices known heretofore are of the "minimally invasive type", because each determination requires the "collection" of a very small amount of interstitial fluid by the sensor, in which glycemia is measured by observing a chemical reaction. The need to eliminate this limited source of invasiveness has

spurred, even more recently, to start studies on non-invasive measurement techniques. Various entirely non-invasive devices (e.g. based on ionophoresis, optic technologies, etc.) are being studied, and imaginably their use will be possible in the forthcoming years.

CGM devices are unanimously considered the most interesting due to the high glycemia monitoring frequency (e.g. from 1 minute to 5 minutes), which allows to continuously monitor glycemia levels during the entire day. Retrospective glycemia level analysis (glycemia level data can normally be downloaded by means of an appropriate software present in the device) may for example identify hypo-/hyperglycemia episodes which are not revealed by 3-4 daily measurements determined in capillary blood, and thus significantly help reviewing the specific patient's therapy.

One of the features of CGM sensors is their capacity to estimate the current glucose level in real time. This makes them particularly interesting for recognizing potentially dangerous episodes in real time, such as exceeding of the aforesaid hypo-/hyperglycemia thresholds. For this reason, some CGM sensors are provided with alert generation methods, which warn the patient when the estimated glycemia value exceeds predetermined thresholds.

The currently developed Continuous Glucose Monitoring (CGM) devices implement different technologies. Some examples of known CGM devices are briefly outlined below.

- System Gold™ Continuous Glucose Monitoring System (CGMS)®, made by Medtronic MiniMed, Northridge, CA. This device consists in a thin measuring sensor to be inserted in the abdomen and which communicates (by means of a specific wire) with a portable device (monitor) which stores the glycemia values every 3 minutes for a maximum total of 72 hours. The device does not allow to display data in real-time; data may only be retrospectively displayed after having been downloaded to a PC.

- Guardian® Real Time Continuous Glucose Monitoring System, made by Medtronic MiniMed, Northridge, CA. This device consists in a thin measuring sensor to be inserted in the abdomen, a transmitter and a portable device (monitor). Transmitter and monitor reciprocally communicate by means of wireless

technology. The monitor displays the following in real time: the measured glycemia value; a trend graph, which plots the glycemia during the last period of time (e.g. 3 hours); a trend arrow, which indicates whether the glycemia value is increasing, decreasing or stationary. The monitor is provided with an alert generator. The alerts are generated (i) when the current glycemia value exceeds certain thresholds, (ii) when the glycemia level changes (based on trend arrow) and (iii) when the prediction (which may be set from 5 to 30 minutes forward) of the glycemia level exceeds a given value.

- GlucoWatch® G2 Biographer, made by Cygnus Inc, Redwood City, CA. The monitoring system looks like a wristwatch. Glucose is measured by using a reversed ionophoresis technique through the skin using a disposable component which is stuck by means of an adhesive onto the skin, thus putting it into contact with a small electric current. The electric charges take the glucose onto the skin surface, where it is measured using a traditional glucometer. The device generates an alert in presence of a rapid change in glucose level, excessive sweating and for each measurement over or under a given threshold.

- GlucoDay® S, made by Menarini Diagnostics, Florence, Italy. This device consists in a micro-dialysis tube for collecting a sample of interstitial fluid by means of a pump and conveying it into the device itself, where glycemia is measured. The device is provided with a readout which displays the measured value in real-time.

- STS-7™ Continuous Glucose Monitoring System, made by Dexcom, San Diego, CA. The device consists of three parts: a needle sensor which makes the measurement, a wireless transmitter and a receiver. The receiver is a portable wireless device provided with a readout, which allows to display the current glycemia value in real time, and a trend graph of the previously measured values. The device can generate alerts when the measured value exceeds given thresholds.

- FreeStyle Navigator™ Continuous Glucose Monitor, made by Abbott Laboratories, Alameda, CA. The device consists of three parts: a needle sensor which makes the measurement, a wireless transmitter and a receiver. The receiver is a wireless portable device provided with a readout for displaying the current

glycemia value in real time and a trend arrow which indicates if the glycemia value is increasing, decreasing or stationary. The device can generate alerts when the measured value exceeds given thresholds.

Problems of the known devices. However, at least with regards to the real-time generation of hypo-/hyperglycemia alerts, the performance of these known CGM devices are currently disappointing, because many of the generated alerts (nearly 50%) are false. Therefore, the low reliability of such alert systems makes them useless in practice, and even potentially dangerous, because the patient cannot distinguish an alert to be taken into consideration from a false one.

One of the problems responsible for the poor hypo-hyperglycemia alert generating performance of CGM devices is constituted by the presence of "noise" in the measurements. In other words, the sensor measurement presents an error which may cause the generation of a false alert or the non-recognition of an actually occurring episode (missed alert), thus exposing the patient to risks or incorrect therapy choices.

Furthermore, it would be obviously preferable to prevent hypo-/hyper glycemia episodes, instead of simply generating alerts when such an episode occur. For example, an alert generated to indicate that without intervention a hypoglycemia situation will occur within 20 minutes would allow the patient to ingest and absorb sugar in time.

The above-mentioned problems will now be described in detail.

- SIGNAL NOISE MAKES THE MEASUREMENT UNRELIABLE. The glycemia value measured by the CGM device presents an interference component which causes an error in the glycemia level determination. In the specific case, by altering the real glucose concentration value, such an error may generate false alerts or the non-recognition of an actually occurring episode (missed alert), thus exposing the patient to risks of incorrect therapy choices. Some CGM devices contain therein algorithms for reducing this interference component in the signal, but such algorithms are evidently too "crude". For example, the filtering algorithm implemented in the CGM device is set and "blocked" once and for all. Consequently, the algorithm cannot adapt to the different intensities of the noise component actually found in different monitoring steps, nor can it adapt to the

variation of such intensity during the use of a device in a single monitoring step, variation for example due to a deterioration of the measuring sensor performance. In other terms, by maintaining the same sensor, the ratio between real signal and noise component (Signal-Noise Ratio, SNR), varies by intensity not only from individual to individual (inter-variability), but also during the monitoring step in a single individual (intra- variability).

Finally, none of the CGM devices known heretofore adopt strategies, specifically on statistic basis, for taking into consideration that the filtering needs to be adapted, in real time, to each individual's different SNR entity. Where implemented in the device, the currently used filtering methods are insensitive to SNR variations from individual to individual (inter-individual variability) and to the SNR variations during the same monitoring step (intra-individual variability).

- GLYCEMIA PREDICTION FOR PREVENTIVE PURPOSE. In the scope of preventing the consequences of diabetes, it is obviously preferable to prevent hypo-hyperglycemia episodes instead of simply generating alerts when such episodes occur. For example, an alert generated to indicate that without intervention a hypoglycemia episode will occur within 20 minutes would allow the patient to ingest and absorb sugar in time. The noise component described in the previous paragraph prevents the correct application of predictive algorithms to the obtained measurements, thus negatively affecting predictive system performance. Some articles related to techniques for predicting short-term glycemia levels (e.g. 30 - 45 - 60 minutes) are present in scientific literature.

It is worth noting that the term "prediction" is often used with various meanings also in clinical context only. Herein, the term will be related to a short-term forecast (e.g. 45 minutes) of future glycemia level useful for preventing hypo-/hyperglycemia, when obtained in real time.

For this purpose, the article by Sparacino et al., listed in literature under [1], illustrates predictive algorithms based on polynomial and self-regressive models. The articles by Palerm et al., listed in literature under [2], [3], on the identification and prediction of hypoglycemia episodes, illustrate a prediction algorithm based on Kalman Filter (KF), which however cannot adapt to the features of the noise present on the glycemia signal and in which SNR is identified on subjective basis.

In short, none of the CGM devices of those known heretofore adopt strategies, specifically on statistic basis, for predicting future glycemia by using self-adaptive signal models (i.e. customized for the monitored individual and with time-variant parameters to adapt to the variability of the glycemia signal dynamics also within the same individual).

- ALERT GENERATION. All the known CGM devices which contemplate alert generation to warn the patient about the danger of the current situation, simply base such a generation on the currently measured glycemia value. The alert is generated if the value exceeds given thresholds (in positive or negative direction). As previously mentioned, the signal noise may cause the generation of a false alert, or worse a missed alert. A high percentage of false alerts thwarts all the advantages that a CGM device introduces. In CGM devices, the alert generation system is simply based on the value measured by the sensor. If such a value exceeds predetermined thresholds, then the alert is generated. Such an alert is not very effective in presence of high signal noise, which is put into a poor accuracy of the sensor.

Finally, none of the known CGM devices adopt strategies, specifically on statistic basis, to generate hypo-/hyperglycemia alerts on the basis of filtered and/or predictive glycemia measurements on statistic and self-adaptive base.

Summary of the invention.

It is thus the object of the present invention to solve the aforesaid problems and indicate a method and device for processing glycemia level data, specifically data from Continuous Glucose Monitoring devices, capable of:

- filtering the noise which is present in said data in real time, preferably by means of a filter, the parameters of which can adapt to the variability of the noise found from individual to individual (inter-variability), as well as within the same individual (intra-variability), by means of a "self-tuning" procedure of the parameters of the filter itself;
- short term predicting the future glycemia level in real time, on the basis of the signal with SNR improved by filtering;
- generating alerts in real time for warning the patient when the glycemia value reaches a level such to imply risks for health, by exploiting the filtered and/or

predicted signal and the corresponding confidence level calculated by virtue of the statistic base of the methods.

It is the object of the present invention a small-sized portable device for use in combination with Continuous Glucose Monitoring (CGM) devices, which allows to integrate and improve the information provided thereby. Specifically, the device incorporates three innovative modules, based on original statistic based algorithms, for:

a) filtering data in order to reduce the entity of the noise present therein, adapting itself to the sensor, to the individual and to the SNR evolution during monitoring, preferably by means of a "self-tuning" procedure of the filter parameters in real time and on statistic basis, with determination of the filtered glycemia level confidence interval;

b) predicting the future glycemia level with its confidence interval;

c) generating alerts for preventing hypo-/hyperglycemia episodes, based on the previously acquired statistic information.

It is also the object of the present invention a method for processing glycemia level data, said glycemia level data being generated by a device of the Continuous Glucose Monitoring (CGM) type, characterized in that it comprises the steps of:

- filtering the noise from said glycemia level data, thus obtaining filtered values $\hat{x}_{t|t}(1)$ and measuring the error variance $P_{t|t}(1,1)$ thereof (on the basis of which the so-called standard confidence interval is constructed);
- calculating the probability of hypoglycemia Phypo and hyperglycemia Phyper, using said filtered values $\hat{x}_{t|t}(1)$ and error variance $P_{t|t}(1,1)$, hypoglycemia thresholds hypoT and hyperglycemia hyperT, and comparing such probabilities with respectively correlated reference thresholds Rhypo and Rhyper;
- generating a hypo- or hyperglycaemia "SEVERE ALERT" condition if Phypo is higher than Rhypo, or if Phyper is higher than Rhyper.

Furthermore, the method optionally contemplates obtaining said noise filtering of glycemia level data by means of a filter the parameters of which are estimated using a "self-tuning" procedure so as to adapt the filter to the noise variability.

Furthermore, the method optionally comprises the further steps of:

- calculating a predictive algorithm on said filtered values $\hat{x}_{t|t}(1)$ and with estimated error variance $P_{t|t}(1,1)$, thus obtaining a predicted glycemia value $\hat{x}_{t|t+PH}(1)$ referred to a given number (PH) of instants forward in time, and the corresponding error variance $P_{t+PH|t}(1,1)$ (from the root of which the prediction confidence interval is constructed);
- calculating the probability of hypoglycemia Phypo and hyperglycemia Phyper on said predicted glycemia value and corresponding confidence interval;
- generating a hypo- or hyperglycemia "PREDICTIVE ALERT" condition if Phypo is higher than Rhypo, or if Phyper is higher than Rhyper.

It is important to note that the method and the device presented here are independent from the CGM sensor technology, which may be either minimally invasive (needle, micro-dialysis, etc.) or non-invasive (optical, ionoforesis, etc.).

It is the particular object of the present invention a method and device for processing glycemia level data by means of real-time, self-adaptive filtering future glycemia level prediction, as better described in the claims, which form an integral part of the present description.

Brief description of the figures.

Further objects and advantages of the present invention will be apparent from the detailed description that follows of an example of embodiment of the same (and its vatiants) and the accompanying drawings given by way of non-limitative example, in which:

FIG. 1 shows a flow chart of the main operations carried out by the device object of the invention;

FIGS. 2.1, 2.2, 2.3 show flow charts of the data filtering operation in FIG. 1;

FIG. 3 shows flow charts of the glycemia level prediction operation in FIG. 1;

FIG. 4 shows a block diagram of the device object of the present invention.

The same numbers and reference letters in the figures refer to the same elements or components.

Detailed description.

The data processing method according to the invention is described below.

The operations shown in the flow chart in FIG. 1 are carried out when the data are

received from the CGM device, as illustrated in detail below.

Table 1 below contains a list of the symbols used in the flow charts in the figures (with corresponding meanings).

Table 1

Symbol	Description
t	(Discrete) time instant corresponding to the reception of a new glycemia level
hypoT (hyperT)	Hypo- (hyper-)glycemia thresholds (in mg/dl or mg/mmol)
Rhypo (Rhyper)	Reference hypo- (hyper-)glycemia probability threshold
n	Number of selected samples
y	Vector (n x 1) of the last n glycemia measurements provided by the sensor
u	Vector (n x 1) of the last n "ideal" glycemia measurements (without noise)
$\hat{u}$	Estimated vector (n x 1) of vector u
v	vector (n x 1) of additive noise
G	Identity matrix (n x n)
F	Lower triangle Toeplitz matrix (n x n) (first column = $[1\ -1\ 0\ \ldots\ 0]^T$ in case of random-walk model, or $[1\ -2\ 1\ 0\ \ldots\ 0]^T$ in the case of integrated random-walk model)
σ^2	Error variance ("noise") with which glycemia is detected (variable from sensor to sensor, from individual to individual, and also within the time of the same monitoring step)
λ^2	*A priori* model variance parameter, random-walk or integrated random-walk, of the glycemia signal (λ^2 variable from individual to individual, and also in the time for the same individual)

γ	Ratio between σ^2 and λ^2
γmax	γ maximum value
γmin	γ minimum value
WRSS	Quadratic sum of weighed residues
WESS	Quadratic sum of $\hat{u}$ estimates weighed for F
$q(\gamma)$	Equivalent degrees of freedom, $q(\gamma) = \text{trace}\,(G(G^TG+\gamma F^TF)^{-1}G^T)$
x_t	state vector at time t, of dimension n_x dependent on the *a priori* model used to describe glycemia, in which position 1 is occupied by the glycemia value at time t
$\hat{x}_{t\|t}$	Vector of dimension n_x, state vector x_t estimate at time t (given the glycemia values measured by the sensor until time t included)
$\hat{x}_{t+1\|t}$	State vector x_t prediction at time t+1, calculated using only the glycemia values measured by the sensor until time t (included)
PH	Scalar parameter providing the number of sampling periods corresponding to the Prediction Horizon
$\hat{x}_{t+PH\|t}$	State vector x_t prediction at time t+PH, calculated using the glycemia values measured by the sensor until time t only (included)
A	State transition matrix ($n_x \times n_x$)
y_t	Glycemia value measured by sensor at time t
H	matrix $1 \times n_x$ which links the state vector to measurement y_t at time t
v_t	Noise on measurement y_t
w_t	Vector dimension of the measurement noise n_x in the evolution model of state x_t
R	Measurement noise covariance matrix v_t
Q	covariance matrix of vector w_t
$P_{t\|t}$	Estimation error covariance matrix related to vector

	$\hat{x}_{t\|t}$
$P_{t+1\|t}$	Estimation error covariance matrix related to vector $\hat{x}_{t+1\|t}$
$P_{t+PH\|t}$	Estimation error covariance matrix related to vector $\hat{x}_{t+PH\|t}$
K	Kalman filter "gain" matrix

With reference to FIG. 1, filtering and prediction operations are carried out in real time on the glycemia level measured by a CGM device.

In detail, the device according to the invention receives the glycemia value (in mg/dl or mg/mmol) measured by the CGM sensor in combination with which is it used as an input (step 1.0) at time instant t. The value is filtered ($\hat{x}_{t|t}(1)$) according to the operations which will be described below in detail with reference to FIG. 2 (step 1.1). The newly obtained filtered value of $\hat{x}_{t|t}(1)$ is provided (step 1.2) with $P_{t|t}(1,1)$, which corresponds to the obtained data estimation error variance, and which is in direct relationship with the confidence interval of the filtered glycemia measurement.

The next step consists in retrieving the hypo- and hyperglycemia threshold values (hypoT and hyperT, respectively) (step 1.3) and the correlated reference probability thresholds (Rhypo and Rhyper) from the system memory. Assuming that the filtered glycemia punctually has a probability plot describable with a Gaussian distribution with average $\hat{x}_{t|t}(1)$ and variance $P_{t|t}(1,1)$, the hypo- and hyperglycemia probabilities (Phypo and Phyper) are easily calculated (step 1.4) by using the hypoT and hyperT values as a reference. A hypo- and hyperglycemia "SEVERE ALERT" is generated (step 1.5) if Phypo is higher than Rhypo, or if Phyper is higher than Rhyper, otherwise no alert is generated. The filtered data (along with the confidence interval) and the possible alert are shown on a readout.

A predictive algorithm is then applied (step 1.6) (an embodiment of which is shown in FIG. 3 and shown in detail below) and the glycemia value predicted for a certain

number (PH) of sampling times ahead in time is obtained. The estimate error variance, and thus its confidence interval, is also available for the predicted value. Assuming again a Gaussian distribution, the hypo- and hyperglycemia probabilities (Phypo and Phyper) are calculated (step 1.8). A hypo- and hyperglycemia "PREVENTIVE ALERT" is generated (step 1.9) if Phypo is higher than Rhypo, or if Phyper is higher than Rhyper, otherwise no alert is generated. The predicted data (along with the confidence interval) and the possible alert are shown on the display (step 1.10).

With reference to FIG. 2.1, 2.2 and 2.3, the filtering operation of the signal fed back by the CGM device exploits models (named *a priori*), which make bland, yet realistic assumptions concerning the two contributions in play, i.e. "measurement noise" and "true CGM signal":

- the measurement noise is additive and may be assimilated to a white noise process, with zero average and unknown variance σ^2 (such a variance may be variable in time);
- the "true" CGM signal (i.e. without noise) can be assimilated to the creation of a so-called random-walk (or an integrated random-walk) process driven by white noise of zero average and unknown variance λ^2 (such a variance may be variable in time).

The parameters σ^2 and λ^2 determine the filtering action because their ratio is related to the data signal-noise ratio (SNR). However, in each single acquisition by means of the sensor, their value is unknown, and may even vary in time. According to the invention, the filtering algorithm uses a statistic criterion for estimating the values of σ^2 and λ^2 , from the data only, by means of a "self-tuning" procedure, shown in the steps going from 2-20 to 2-29. Such an estimate may be carried out in real time and may even be updated whenever a new sensor measurement is received, so as to adapt to SNR variability in time.

The estimation process of σ^2 and λ^2 is as follows.

The glycemia value (in mg/dl or mg/mmol) measured by the CGM sensor in combination with which is it used is received as an input at time instant t (step 2.11). The data is stored (step 2.12) in the device. The last received unfiltered values n are loaded (step 2.14) in vector y (dimension n x 1).

The vector y is given by:

$$y = Gu + v \quad (1)$$

where u is a column vector (n x 1) which represents the vector of the noise-free data, G is an identity matrix (dimension n x n, step 2.15), and the vector v represents the measurement noise (zero average and variance σ^2).

The vector u has an *a priori* covariance matrix given by $\lambda^2 (F^TF)^{-1}$.

Specifically, F is an n x n matrix (step 2.15) obtained from a Toeplitz lower triangle matrix, with first column given by $[1\ -1\ 0\ \ldots\ 0]^T$, multiplied by itself a number of times (ord) equal to the number ord of integrators used to describe the signal regularity expectations (e.g., ord=1 if the process u is described as a random-walk, ord=2 if the process u is described as an integrated random-walk, etc.). Matrix F will thus again be a Toeplitz lower triangle with first column given for example by $[1\ -1\ 0\ \ldots\ 0]^T$ if the process u is described as a random-walk, by $[1\ -2\ 1\ 0\ \ldots\ 0]^T$ in the case of *a priori* integrated random-walk model.

The algorithm thus determines the minimum error variance linear estimate. Numerically, the method proceeds by seeking the vector $\hat{u}$ which minimizes a cost function constituted by two terms: the first (step 2.25) relates to data adherence (specifically given by $WRSS=(y-G\hat{u})^T(y-G\hat{u})$, quadratic sum of the weighed residues), while the second term (step 2.26) provides the signal regularity ($WESS=\hat{u}^TF^TF\hat{u}$, quadratic sum of weighed estimates). The second term is weighed by the parameter $\gamma = \sigma^2/\lambda^2$ which, as mentioned above, is unknown. If γ were known, the vector u would be found by means of the formula (step 2.24):

$$\hat{u} = (G^TG+\gamma F^TF)^{-1}G^Ty \quad (2)$$

A statistic base criterion is used in order to determine γ, described for example in the article listed in literature under [4]. In practice, a trial and error type of procedure is used, in logarithmic scale in order to speed up the operation.

Initially, a tentative value of $\gamma = 10\exp((\log_{10}(\gamma max)+\log_{10}(\gamma min))/2)$ is employed (step 2.21), where γmax and γmin are the extreme values that γ may assume.

After having calculated $\hat{u}$ with tentative γ value, (eq. 2), the consequent WRSS and WESS and $q(\gamma)= \text{trace}(G(G^TG+\gamma F^TF)^{-1}G^T)$ are calculated (degrees of freedom, Cf. [4]). If the following inequality (step 2.28) is fulfilled:

$$\left|\frac{WRSS(\gamma)}{n-q(\gamma)}-\gamma\frac{WESS(\gamma)}{q(\gamma)}\right|<\rho \qquad (3)$$

where ρ is a predetermined threshold value, then the newly tested tentative value of γ is the final value, and the measurement noise variance is determined (step 2.29) as:

$$\sigma^2=\frac{WRSS}{n-q(\gamma)} \qquad (4)$$

and subsequently that of the signal as $\lambda^2 = \sigma^2/\gamma$. If (3) is not fulfilled, the method evaluates (step 2.20) which of the two terms in the module is higher and consequently modifies either γmax or γmin. The entire process described heretofore is thus repeated, recalculating both γ and u until (3) is satisfied or until the maximum predetermined number of iterations is reached. Such values of λ^2 and σ^2 are thus individualized, i.e. different not only from sensor to sensor but also from individual to individual. Because the vector y can be updated at each new sampling instant t (as if the measurements n contained therein refer to a sliding window), the parameters λ^2 and σ^2 may be periodically updated, so as to adapt to the possible SNR variations which occur during the various monitoring days due to the prolonged immersion of part of the sensor in the biological fluids (e.g. 5-7 days).

After having estimated the values of σ^2 and λ^2 (step 2.30), the *a priori* information are translated in the corresponding state model:

$$\begin{cases}\mathbf{x}_{t+1}=\mathbf{A}\mathbf{x}_t+\mathbf{w}_t\\ \mathbf{y}_t=\mathbf{H}\mathbf{x}_t+\mathbf{v}_t\end{cases} \qquad (5)$$

where x_t represents the state vector (the first component of which precisely coincides with the filtered signal), A and H are transition matrixes, and using the notation used until here, y_t represents the scalar glycemia value measured by the

CGM device at instant t. Vectors v_t and w_t are respectively the vectors of the noises related to measurement and state. The method assumes that v_t and w_t are reciprocally independent, with covariance matrixes R and Q. R is scalar and equal to σ^2, Q is scalar and equal to λ^2 in the case of a priori type random-walk model, and is of 2x2 dimension instead in case of a priori integrated random-walk model, with $Q(1,1)= \lambda^2$ and all other elements zero. The state can be estimated from observations by employing Bayes estimate, implemented in static manner or recursive manner by means of the known Kalman Filter (KF).

In our case, we chose to implement the recursive approach of this second alternative. The equations are typical KF equations, described for example in the book listed in literature under [5]. In the equations shown in the flow chart in Figure 2, the matrix $P_{t|t}$ represents (step 2.35) the state estimate covariance matrix error at instant t given the measurements made until the instant t included.

The method related to the glycemia level prediction for sampling periods PH ahead is shown in Figure 3.

The part which comprises the predictive algorithm may be implemented in different manners. An example of implementation based on the cyclic use of the KF predictive step only is shown below.

At instant t, $\hat{x}_{t|t}$ and $P_{t|t}$ are available, i.e. the estimate of the state vector (containing the filtered glycemia value in first position) with corresponding uncertainty (step 3.1). The KF predictive step consists of the one-step state prediction equation:

$$\hat{x}_{t+1|t} = A\hat{x}_{t|t} \qquad (6)$$

and of the equation which describes the relative uncertainty:

$$P_{t+1|t} = AP_{t|t}A^T + Q \qquad (7)$$

Having indicated with PH the number of sampling periods ahead for which the glycemia value will be predicted, the equations (6-7) (steps from 3.2 to 3.6) will be iterated PH times, replacing from the second iteration onwards, $\hat{x}_{t+i|t+i}$ with $\hat{x}_{t+i|t}$

and $P_{t+i|t+i}$ with $P_{t+i|t}$, (i being the index representing the iteration cycle) in order to calculate the predicted value ($\hat{x}_{t+PH|t}(1)$) and its error variance ($P_{t+PH|t}(1,1)$) .

The use of the Kalman filter KF on CGM data is already known per se, having been previously used for example in [3], where however the matrixes Q and R were fixed in equal manner for all individuals (as if there were no inter-individual variability) and once and for all (as if there were no intra-individual variability). Conversely, a statistic-based method is used for the first time in the present invention which allows to identify the unknown parameters σ^2 and λ^2 which determine the matrixes Q and R of the KF in real time and similarly to periodically update them in automated manner, even at each sampling instant. The personalised estimate, which may be adjusted in time, of the matrixes Q and R which determine the KF allows for the first time to adapt the CGM filtering action to SNR variations which may occur during the various monitoring days (e.g. due to deterioration of sensor performance).

With reference to FIG. 4, there are described the features and advantages introduced by the device in accordance with the invention.

In the described embodiment, the device is configured as a portable one, and it processes the data received (via wireless connection) from any Continuous Glucose Monitoring (CGM) device and comprises the following components:

- READOUT D. This is used to communicate:
- A first number: the glycemia value obtained at the end of the processing/filtering process.
- A second number: the predicted glycemia value for PH sampling periods ahead (the prediction horizontal expressed in minutes thus results by multiplying PH for the sampling time of the CGM sensor, expressed in minutes).
- WIRELESS RECEIVER RW for receiving data from CGM devices.
- PROCESSOR CPU for processing.
- MEMORY MEM for temporarily storing data.
- SOUND DEVICE DS for emitting an alert if the hypo-hyperglycemia probabilities are beyond the predetermined threshold.
- BUTTONS/INTERFACE PI for allowing the user to interact with the device.

More in detail, the most immediate manner for implementing the device object of the present invention is to use a Personal Digital Assistant (PDA) and an operating system.

The PDA presents all the necessary hardware features, the processor for processing (sufficient to run the data processing operations in satisfactory time), the RAM for temporarily storing data, a fixed memory for storage, IrDA and Bluetooth communication cards for dialoguing with the CGM devices, a Wi-Fi/LAN/802.11 card for connecting for example a personal computer (for downloading and analysing processing data off-line), a touch-screen display which acts as user interface, for displaying processing results and for entering information (button function).

The operating system comprises all the software needed to dialogue with the hardware (processor, I/O peripherals, wireless devices, etc.) and further allows to install a processing code. There are different operating systems which may be installed on a PDA, such as Palm OS, Windows Mobile and Symbian OS. The use of Symbian OS is recommended here.

Briefly, the PDA - operating system pair solves the following problems:

- running a series of data processing operations which are difficult to be encoded directly in machine language to be then directly run by a microprocessor. By using such an operating system, the data processing and displaying software for implementing the above-described method may be encoded in high-level programming language, such as for example C++ (or Java).

- graphically displaying the results of the data processing operation, i.e. showing the user the current and future glycemia values and possibly also the graphic plot of the glycemia profile monitored over the past hours. Such graphic operations may be easily reproduced by means of a graphic display, which requires a graphic interface.

- wirelessly communicating with CGM device via, for example, Bluetooth technology.

- storing the processing results.

- generating both graphic and acoustic critical glycemia level alerts.

The processing, data display and alert generation software is described

above with reference to figures 1, 2.1, 2.2, 2.3.

With regards to this part of the software, the device contemplates setting the filtering algorithm so that:

- the parameters σ^2 and λ^2 of the filter are estimated, although on statistic basis, only once in the initial interval (named *burn-in interval*, and equivalent to assume that SNR remains constant);

- the estimate on statistic basis of the parameters of the filter σ^2 and λ^2 is periodically updated. For example, it is possible to have the parameters updated each hour or also more frequently or even at each new measuring step, e.g. every 60 seconds with the Navigator (Abbott Diabetes Care) sensor or every 3 minutes with the Glucoday (Menarini Diagnostics) sensors, so as to ensure the filter response as stressed as possible by the possible SNR variations occurring during monitoring.

As mentioned, the various previously suggested CGM devices use alert generation for warning individuals of the risk of a critical episode. The device object of the invention however contemplates an innovative alert generation system. Indeed, the invention uses an algorithm for generating alerts which is not blindly based on the data obtained by the CGM device, but rather on the probability that a certain episode may occur. The calculation of such a probability is only possible in virtue of the previous use of stochastic algorithm for filtering and predicting, in which, in addition to the punctual value, the uncertainty (confidence interval) which characterizes the filtered and predicted glycemia, and from which the hypo-/hyper glycemia can indeed be calculated, is also obtained. The suggested device generates the alert only if such a probability exceeds a predetermined threshold.

The advantage of such an alert generation system is indeed based not only on the punctual value but also on the accuracy of the measurement (given by value uncertainty).

The above-described method with reference to Figures 1, 2.1, 2.2, 2.3 and 3 may be implemented with a high-level programming language, such as C++ or Java. These encoding languages also contemplate the use of libraries for interfacing with graphic devices (e.g. a readout). In this manner, it is easier to make a code

which shows the processing output on screen.

The part of the method object of the present invention may thus be advantageously implemented by means of a computer program which comprises encoding means for implementing one or more steps of the method, when this program is run on a computer. Therefore it is intended that the scope of protection is extended to said computer program and also to computer-readable means which comprise a recorded message, said computer-readable means comprising program encoding means for implementing one or more steps of the method, when said program is run on a computer.

The advantages deriving from the application of the present invention are apparent.

The main strength consists in the accuracy of the supplied measurements, crucial for obtaining real-time indications, e.g. danger warnings of past or imminent hypo-/hyperglycemia episodes. The device object of the invention improves clinical performance of known CGM devices.

During prototype use on retrospectively analysed data, the filtering algorithm has proven to work very satisfactorily. Specifically, the noise removal being equal, the algorithm introduces a considerably smaller delay than that observed by implementing the known mobile average filtering techniques as described above.

A fundamental advantage is due to the capacity of the device to adapt to variability between sensors to variability between individuals and also above all to intra-individual variability. Such a particularity is significantly important in clinical perspective, given the expected variability of sensor performance during monitoring, induced, for example, by the prolonged immersion by the sensor itself (e.g. by its needle) in biological fluids. Prototype results obtained from retrospectively analysed data show that by fixing confidence at 90%, it is possible to reach sensitivity in the order of 95% and specificity of over 70%, maintaining an average time gain of approximately 20 minutes, sufficient for example to compensate in time for the possible hypoglycemia episode by orally ingesting sugar.

The major feature which characterizes the originality of the device is that it can adapt to the different SNR caused by sensor technology (inter-sensor variability), it

is adaptable to the SNR caused by sensor operation in the given individual (inter-individual adaptability), and it can be updated in real time to SNR variations which occur during monitoring (intra-individual variability). Indeed, the parameters σ^2 and λ^2 which characterize the action (and the performance) of the filter not only are self-adaptive by means of a "self-tuning" procedure, to the single sensor and to the single individual, but may be periodically updated, in the most extreme case, whenever the device receives new data.

The device may interface with CGM sensor of all types, e.g. both minimally invasive (subcutaneous, micro-dialysis, etc.) which are entirely non-invasive (optical, ionophoresis, etc.).

Other possible variants of the described non-limitative example are possible, without because of this departing from the scope of protection of the present invention, comprising all the equivalent implementations for a person skilled in the art.

From the above description, a person skilled in the art will be capable of implementing the object of the invention without introducing further constructive details.

Literature quoted in the description

[1] Sparacino G., Zanderigo F., Corazza S., Maran A., Facchinetti A., Cobelli C., "Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series", IEEE Trans Biomed Eng, 2007 May;54(5):931-7.

[2] Palerm C.C., Willis J.P., Desemone J., Bequette B.W., "Hypoglycemia prediction and detection using optimal estimation", Diabetes Technol Ther, 2005 Feb;7(1):3-14.

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[4] Sparacino G., Cobelli C., "A stochastic deconvolution approach to reconstruct insulin secretion rate after a glucose stimulus", IEEE Trans Biomed Eng, 1996 May;43(5):512-29.

[5] Anderson B.D.O., Moore J., "Optimal Filtering", Dover Publications, 2005.

CLAIMS

1. A method for processing glycemia level data, said glycemia level data being generated by a device of the' Continuous Glucose Monitoring (CGM) type, characterized in that it comprises the steps of:

- filtering the noise from said glycemia level data, obtaining filtered values $\hat{x}_{t|t}(1)$ and measuring the error variance $P_{t|t}(1,1)$ thereof (on the basis of which the so-called standard confidence interval is constructed);

- calculating the probability of hypoglycemia Phyper and hyperglycemia Phyper, by using said filtered values $\hat{x}_{t|t}(1)$ and error variance $P_{t|t}(1,1)$, hypoglycemia thresholds hypoT and hyperglycemia hyperT, and comparing such probabilities with respectively correlated reference thresholds Rhypo and Rhyper;

- generating hypo- or hyperglycemia "SEVERE ALERT" condition if Phypo is higher than Rhypo, or if Phyper is higher than Rhyper.

2. A method for processing glycemia level data according to claim 1, characterized in that said noise filtering of said glycemia level data is obtained by means of a filter, the parameters of which are estimated with a "self-tuning" procedure so as to adapt the filter to noise variability.

3. A method for processing glycemia level data according to claim 2, characterized in that it comprises the further steps of:

- calculating a predictive algorithm on said filtered values $\hat{x}_{t|t}(1)$ and error variance $P_{t|t}(1,1)$, thus obtaining a predicted glycemia value for a given number of instants (PH) forward in time, and a corresponding error variance and thus a confidence interval;

- calculating the probability of hypoglycemia Phypo and hyperglycemia Phyper on said predicted glycemia value and corresponding confidence interval;

- generating a hypo- or hyperglycemia "PREDICTIVE ALERT" condition if Phypo is higher than Rhypo, or if Phyper is higher than Rhyper.

4. A method for processing glycemia level data, according to claim 2, characterized in that said step of noise filtering comprises processing said glycemia level data for estimating unknown variance parameters σ^2 and λ^2, said glycemia level data comprising:

- an additive measurement noise, which may be assimilated to a white noise process, with zero average and known variance σ^2, possibly variable in time and different from individual to individual;

- a 'real" glycemia signal, without noise, which may be assimilated *a priori* to a process of the so-called multi-integrated white noise type, where the noise has zero average and unknown variance λ^2, possibly variable in time, and however different from individual to individual;

- said unknown variance parameters σ^2 and λ^2 determining the filtering action, so that their ratio is related to the data signal-interference ratio (SNR) of the glycemia level data.

5. A method for processing glycemia level data according to claim 4, characterized in that said unknown variance parameter estimate σ^2 and λ^2 is generated by means of an automated "self-tuning" procedure of the parameters which comprises:

- composing a vector y (dimension n x 1) with the last n non-filtered glycemia level data values, the vector being $y = Gu + v$,

where u is a column vector (n x 1) which represents the vector of the noise-free data, G is an identity matrix (dimension n x n), and the vector v represents the measurement noise (zero average and variance σ^2);

said vector u having *a priori* covariance matrix given by $\lambda^2 (F^TF)^{-1}$, F being a Toeplitz lower triangular matrix n x n, with a first column given by $[1\ -1\ 0\ \ldots\ 0]^T$ in the case of random-walk *a priori* model, $[1\ -2\ 1\ 0\ \ldots\ 0]^T$ in the case of *a priori* integrated random-walk type model;

- determining a linear estimate with minimum error variance, searching for the vector $\hat{u}$ which minimizes a cost function constituted by two addenda:

  - the first related to data adherence, given by $WRSS=(y-G\hat{u})^T(y-G\hat{u})$, quadratic sum of weighed residues,

  - the second provides the signal regularity, given by $WESS=\hat{u}^TF^TF\hat{u}$, quadratic sum of weighed estimates, said second term being weighed by a parameter $\gamma = \sigma^2/\lambda^2$;

- determining said vector $\hat{u}$ by means of the formula

$$\hat{u} = (G^TG+\gamma F^TF)^{-1}G^Ty$$

- determining γ by means of a statistic trial and error type criterion, in which the method initially starts with a tentative value of

$$\gamma = 10\exp((\log_{10}(\gamma max)+\log_{10}(\gamma min))/2),$$

where γmax and γmin are the extreme values that γ may assume;

- after having calculated û with tentative value of γ, calculating said values WRSS, and WESS and $q(\gamma)=\text{trace}(G(G^TG+\gamma F^TF)^{-1}G^T)$

- if the following inequality is fulfilled:

$\left|\frac{WRSS(\gamma)}{n-q(\gamma)}-\gamma\frac{WESS(\gamma)}{q(\gamma)}\right|<\rho$ where ρ is a predetermined threshold value, then the newly tested tentative value of γ is the final value, and the measurement noise variance is determined as:

$$\sigma^2=\frac{\text{WRSS}}{n-q(\gamma)}$$

and subsequently that of the signal as $\lambda^2 = \sigma^2/\gamma$;

- if instead said inequality is not fulfilled, the method evaluates which of the two terms within the inequality module is higher, and consequently modifies either γmax or γmin;

- the entire process is thus repeated, by recalculating both γ and u until either the inequality is fulfilled or until the maximum predetermined number of iterations is reached.

6. A method for processing glycemia level data according to claim 5, characterized in that, after said estimation of unknown variance parameters σ^2 and λ^2 , it comprises the steps of:

- translating the *a priori* information into a corresponding state model:

$$\begin{cases}\mathbf{x}_{t+1}=\mathbf{A}\mathbf{x}_t+\mathbf{w}_t\\ \mathbf{y}_t=\mathbf{H}\mathbf{x}_t+\mathbf{v}_t\end{cases}$$

where x_t represents the state vector, in which the first component coincides with said filtered signal, A and H are transition matrixes, y_t is the non-filtered glycemia level data at instant t, vectors v_t and w_t are respectively the vectors of the noises linked to measurement and state, assuming v_t and w_t being reciprocally

independent, with covariance matrixes R and Q, containing said estimates of σ^2 and λ^2 respectively.

7. A method for processing glycemia level data according to claim 3, characterized in that it said step of calculating of a predictive algorithm comprises the steps of:

- cyclically using only the predictive step of a Kalman Filter KF, having the estimate of the state vector $\hat{x}_{t|t}$ containing in first position the filtered glycemia value, and corresponding uncertainty $P_{t|t}$ available at instant t,
- said predictive step of the Kalman Filter (KF) comprising the state prediction equation:

$$\hat{x}_{t+1|t} = A\hat{x}_{t|t}$$

and the prediction equation of its uncertainty:

$$P_{t+1|t} = AP_{t|t}A^T + Q$$

- indicated by PH the number of sampling periods ahead for which to predict the glycemia value, iterating equations $\hat{x}_{t+1|t} = A\hat{x}_{t|t}$ and $P_{t+1|t} = AP_{t|t}A^T + Q$ for PH times, replacing from the second iteration onwards, $\hat{x}_{t+i|t+i}$ with $\hat{x}_{t+i|t}$ and $P_{t+i|t+i}$ with $P_{t+i|t}$, (index i representing the iteration cycle), thus obtaining said predicted glycemia value ($x_{t+PH|t}(1)$) and its uncertainty ($P_{t+PH|t}(1,1)$).

8. A device for processing glycemia level data, specifically for implementing the method in accordance with any of the preceding claims, said glycemia level data being generated by a Continuous Glucose Monitoring (CGM) device, characterized in that it comprises:

- at least one displaying element of at least:
  - said glycemia value obtained at the end of the processing/filtering process;
  - said predicted glycemia value PH minutes ahead in time;
- at least one receiver for receiving said glycemia data;
- at least one processing unit, provided with memory;
- at least one device for emitting an alert if the hypo-hyperglycemia probabilities

are beyond the predetermined threshold;

- devices for allowing user interaction.

9. A device according to claim 8, characterized in that said at least one processing unit comprises a Personal Digital Assistant (PDA) and an operating system.

5

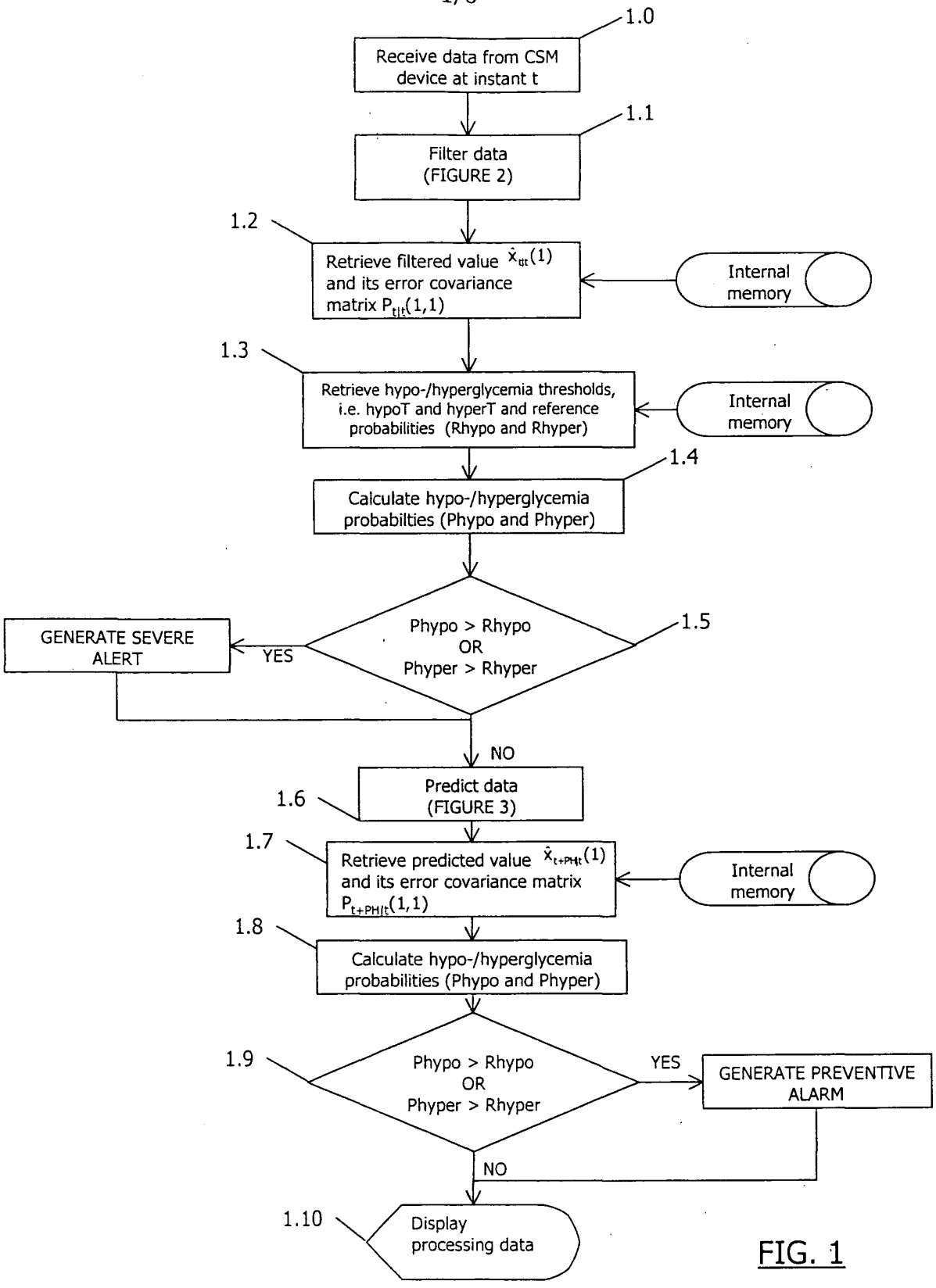

1.0
Receive data from CSM device at instant t
1.1
Filter data (FIGURE 2)
1.2
Retrieve filtered value $\hat{x}_{t|t}(1)$ and its error covariance matrix $P_{t|t}(1,1)$
Internal memory
1.3
Retrieve hypo-/hyperglycemia thresholds, i.e. hypoT and hyperT and reference probabilities (Rhypo and Rhyper)
Internal memory
1.4
Calculate hypo-/hyperglycemia probabilties (Phypo and Phyper)
1.5
Phypo > Rhypo OR Phyper > Rhyper
YES
GENERATE SEVERE ALERT
NO
1.6
Predict data (FIGURE 3)
1.7
Retrieve predicted value $\hat{x}_{t+PH|t}(1)$ and its error covariance matrix $P_{t+PH|t}(1,1)$
Internal memory
1.8
Calculate hypo-/hyperglycemia probabilities (Phypo and Phyper)
1.9
Phypo > Rhypo OR Phyper > Rhyper
YES
GENERATE PREVENTIVE ALARM
NO
1.10
Display processing data

FIG. 1

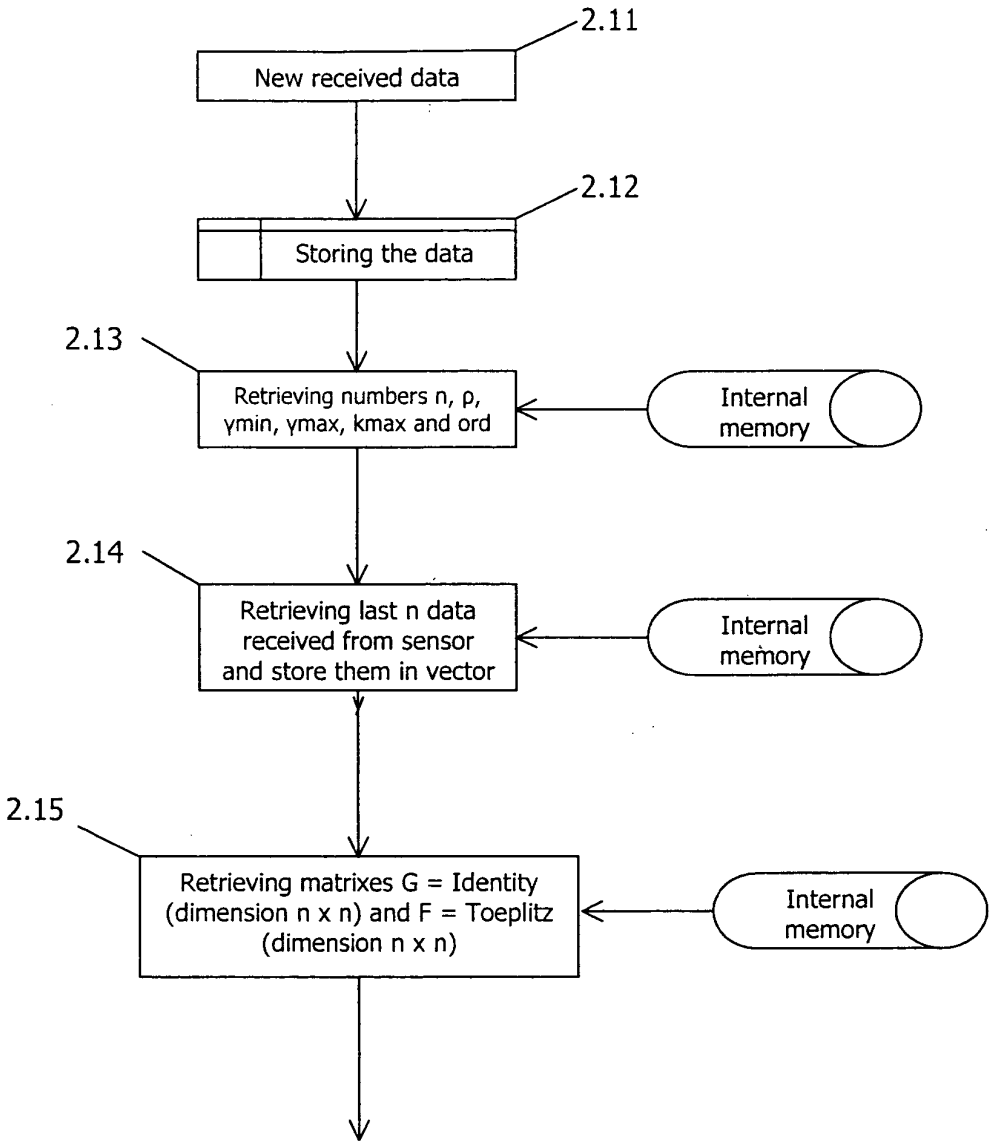

2.11
New received data
2.12
Storing the data
2.13
Retrieving numbers n, ρ, γmin, γmax, kmax and ord
Internal memory
2.14
Retrieving last n data received from sensor and store them in vector
Internal memory
2.15
Retrieving matrixes G = Identity (dimension n x n) and F = Toeplitz (dimension n x n)
Internal memory

FIG. 2.1

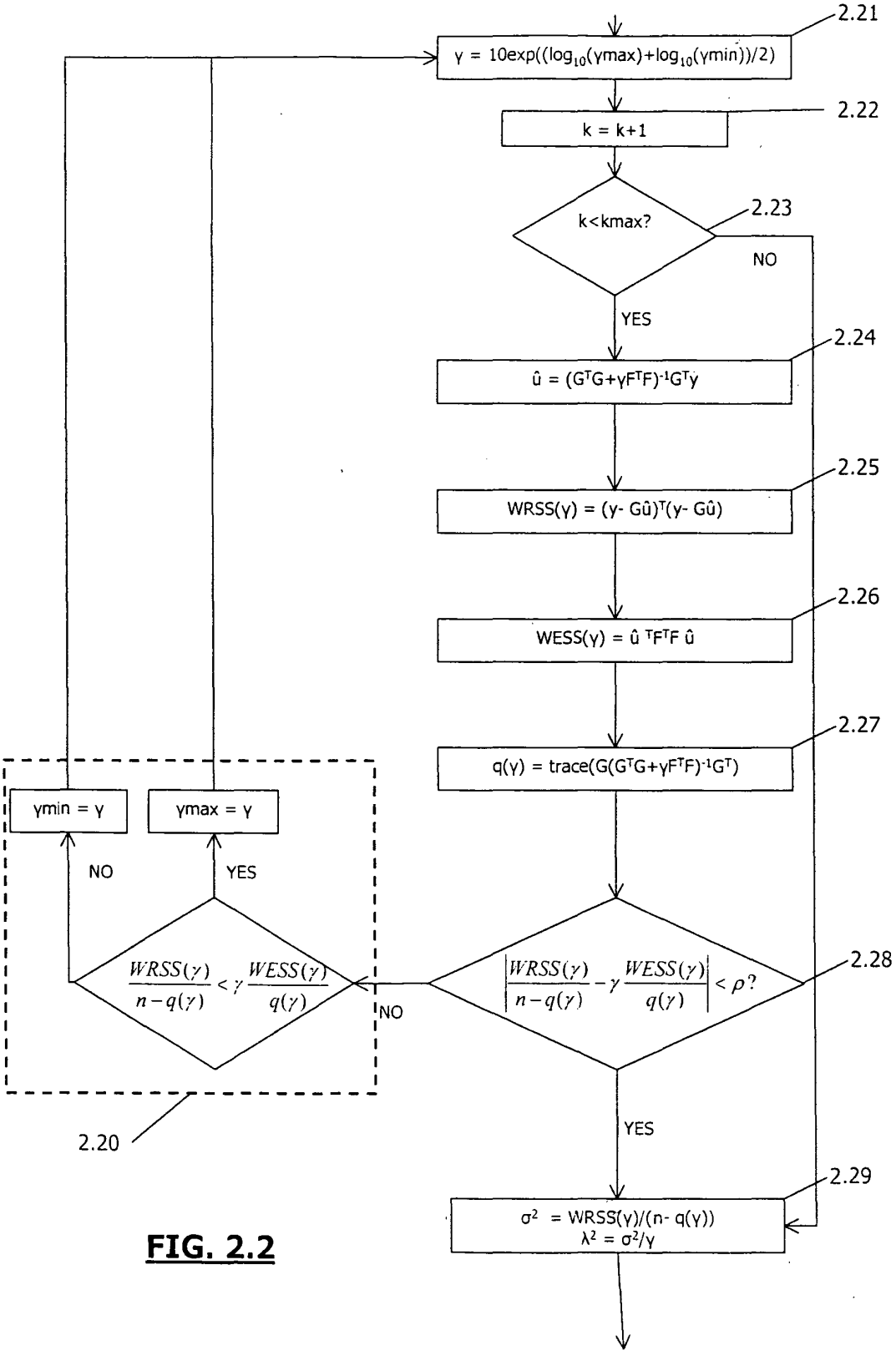

2.21
γ = 10exp((log10(γmax)+log10(γmin))/2)
2.22
k = k+1
2.23
k<kmax?
NO
YES
2.24
û = (GTG+γFTF)-1GTy
2.25
WRSS(γ) = (y- Gû)T(y- Gû)
2.26
WESS(γ) = û TFTF û
2.27
q(γ) = trace(G(GTG+γFTF)-1GT)
γmin = γ
γmax = γ
NO
YES
$\frac{WRSS(\gamma)}{n-q(\gamma)} < \gamma \frac{WESS(\gamma)}{q(\gamma)}$
NO
$\left|\frac{WRSS(\gamma)}{n-q(\gamma)} - \gamma \frac{WESS(\gamma)}{q(\gamma)}\right| < \rho ?$
2.28
YES
2.29
σ2 = WRSS(γ)/(n- q(γ))
λ2 = σ2/γ
2.20

FIG. 2.2

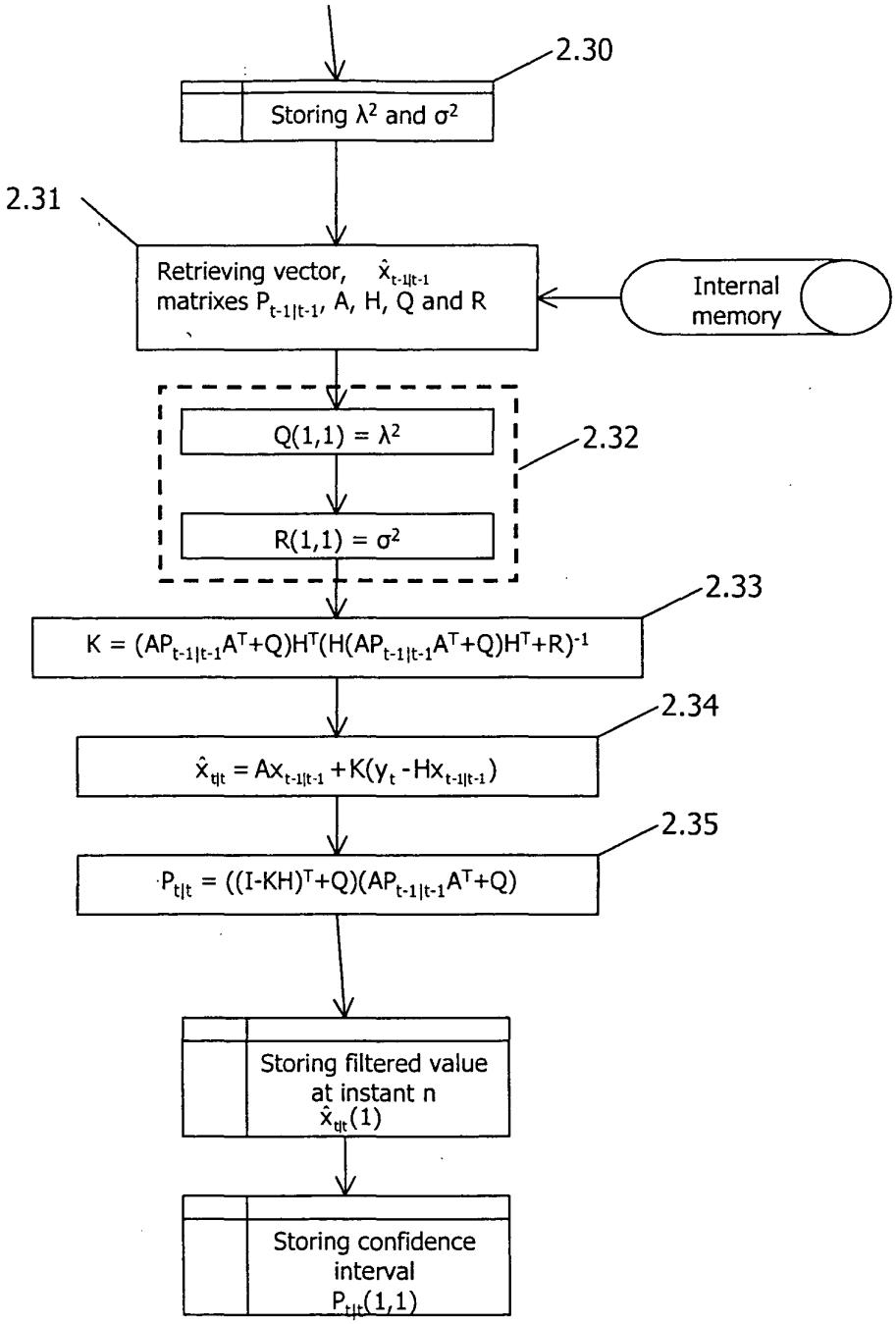

2.30
Storing λ^2 and σ^2
2.31
Retrieving vector, $\hat{x}_{t-1|t-1}$
matrixes $P_{t-1|t-1}$, A, H, Q and R
Internal memory
$Q(1,1) = \lambda^2$
2.32
$R(1,1) = \sigma^2$
2.33
$K = (AP_{t-1|t-1}A^T+Q)H^T(H(AP_{t-1|t-1}A^T+Q)H^T+R)^{-1}$
2.34
$\hat{x}_{t|t} = Ax_{t-1|t-1} + K(y_t - Hx_{t-1|t-1})$
2.35
$P_{t|t} = ((I-KH)^T+Q)(AP_{t-1|t-1}A^T+Q)$
Storing filtered value at instant n
$\hat{x}_{t|t}(1)$
Storing confidence interval
$P_{t|t}(1,1)$

FIG. 2.3

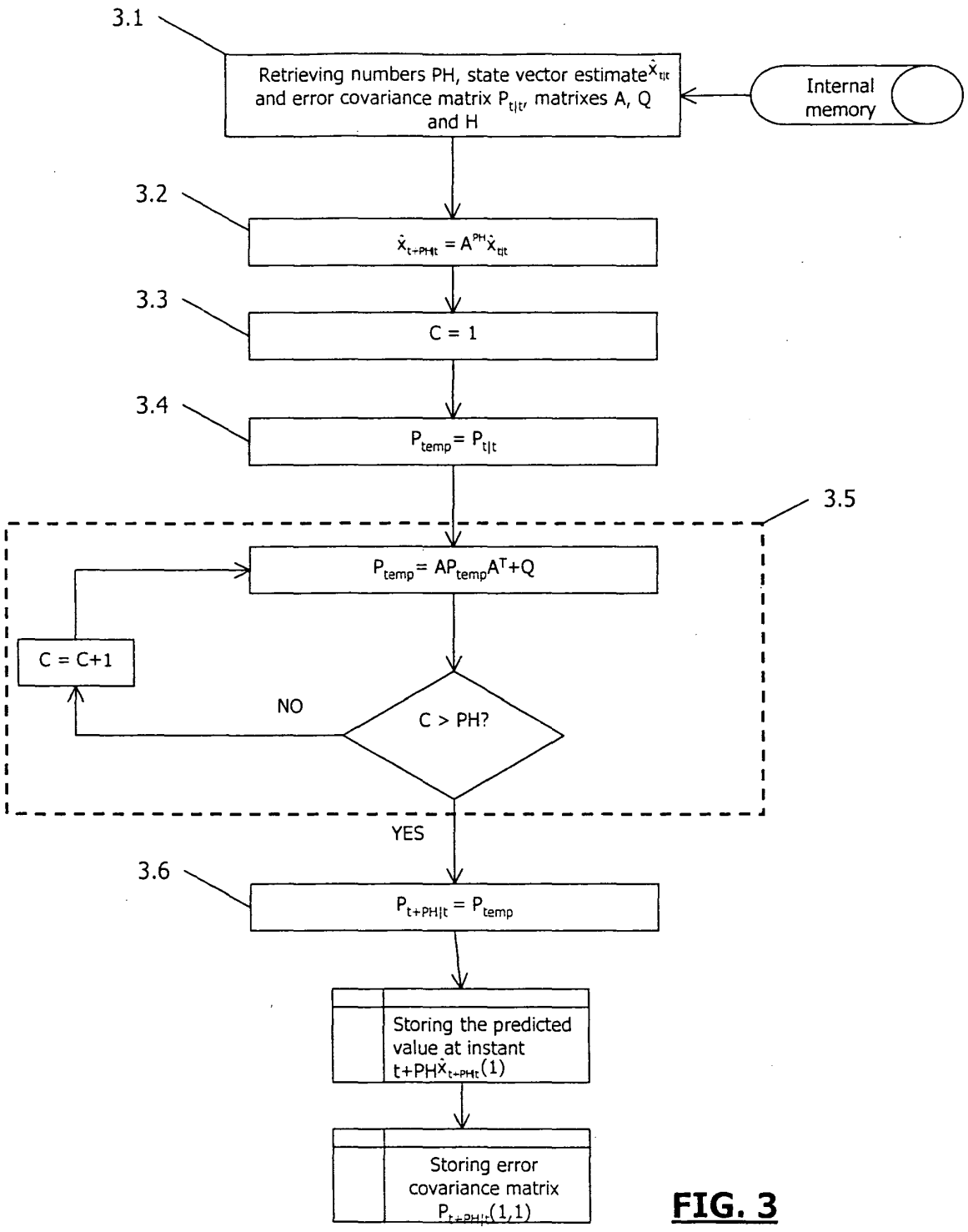

3.1
Retrieving numbers PH, state vector estimate $\hat{x}_{t|t}$ and error covariance matrix $P_{t|t}$, matrixes A, Q and H
Internal memory
3.2
$\hat{x}_{t+PH|t} = A^{PH}\hat{x}_{t|t}$
3.3
C = 1
3.4
$P_{temp} = P_{t|t}$
3.5
$P_{temp} = AP_{temp}A^T+Q$
C = C+1
NO
C > PH?
YES
3.6
$P_{t+PH|t} = P_{temp}$
Storing the predicted value at instant $t+PH\hat{x}_{t+PH|t}(1)$
Storing error covariance matrix $P_{t+PH|t}(1,1)$

FIG. 3

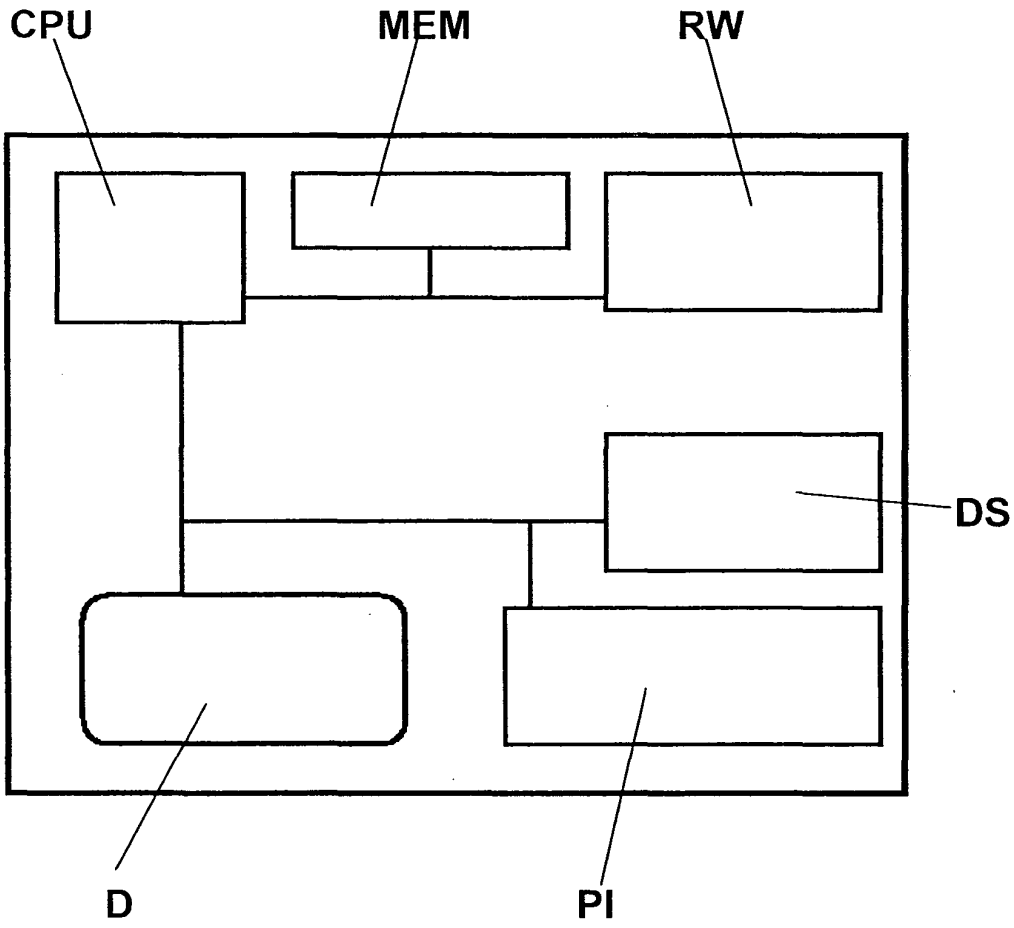


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/051870

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/025931 A1 (ROSEN RICHARD [US] ET AL) 2 February 2006 (2006-02-02) paragraphs [0031] - [0034] paragraphs [0078] - [0087]	1-9
A	US 2003/125609 A1 (BECKER ROBERT [US]) 3 July 2003 (2003-07-03) paragraphs [0005], [0026], [0027]	1-9
A	US 4 974 162 A (SIEGEL JOHN H [US] ET AL) 27 November 1990 (1990-11-27) column 10, lines 29-58	1-9
A	US 6 272 480 B1 (TRESP VOLKER [DE] ET AL) 7 August 2001 (2001-08-07) the whole document	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2009	28/09/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Trachterna, Morten

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006025931 A1	02-02-2006	NONE	
US 2003125609 A1	03-07-2003	NONE	
US 4974162 A	27-11-1990	US 5365426 A	15-11-1994
US 6272480 B1	07-08-2001	EP 0910023 A2	21-04-1999

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(74) Agent: **WITTMANN, Günther**; Boschetsriederstrasse 67, 81379 München (DE).

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Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) **Title**: METHOD TO RECALIBRATE CONTINUOUS GLUCOSE MONITORING DATA ON-LINE

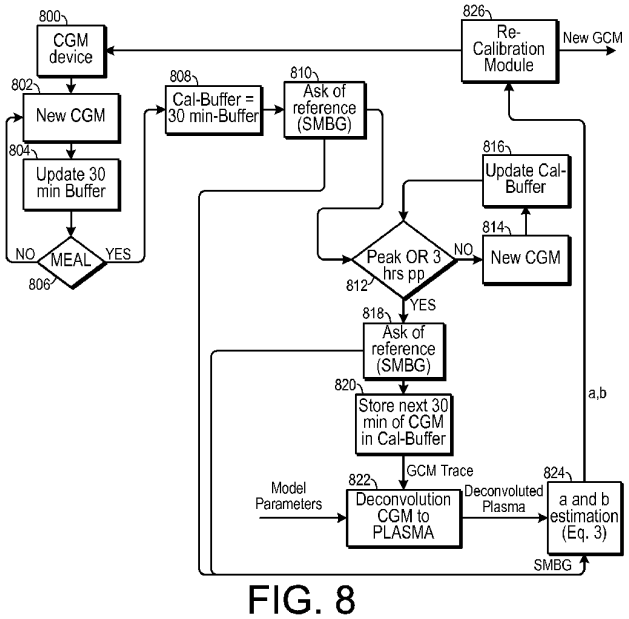


FIG. 8

(57) Abstract: In a method of recalibrating continuous glucose monitoring data from a user, operable on a digital processor, an indication from the user that the user has taken a meal is received (806). A self-monitored of blood glucose levels from the user (810) at two separate times during a day corresponding to when the user has taken a meal. A glucose signal is received from a continuous glucose monitoring sensor (818) at times corresponding to the two separate times that the user has taken a meal. Two reconstructed blood glucose values based on the glucose signal from the continuous monitoring sensor at times when the at least two self-monitored of blood glucose levels are received from the user. A linear regression is performed (822) using y = ax + b, wherein x corresponds to the two reconstructed blood glucose values and y corresponds to the two self-monitored of blood glucose levels thereby generating an estimation of a and b. A recalibration signal, including the estimation of a and b, is transmitted to the continuous glucose monitoring sensor (824) based on the linear regression.

WO 2011/051922 A2

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

METHOD TO RECALIBRATE CONTINUOUS GLUCOSE MONITORING DATA ON-LINE

BACKGROUND OF THE INVENTION

[0001] Field of the Invention

[0002] The present invention relates to glucose monitoring systems and, more specifically, to a method of recalibrating continuous glucose monitoring data.

[0003] Description of the Prior Art

[0004] The standard therapy for diabetes is based on insulin and drug administration, diet, and physical exercise, tuned according to self-monitoring of blood glucose (SMBG) levels 3-4 times a day. However, given the inefficiency of SMBG approach in capturing the actual extent of glucose dynamics during the daily life, blood glucose concentration in diabetic patients often goes outside the normal range (70-180 mg/dl). In the last 10 years, new possibilities in diabetes therapy have been opened thanks to the availability of continuous glucose monitoring (CGM) sensors. CGM systems are noninvasive or minimally-invasive, and, in many cases, the fact that they are portable can allow their use in patient daily life for several days (up to a week).

[0005] Diabetes is a chronic disease characterized by the inefficiency of the pancreas to produce insulin (Type-1 diabetes), or by malfunctions in both insulin secretion and action (Type-2 diabetes). As a result, in a diabetic subject the plasma glycaemic level exceeds the normal range, with several long and short term complications. Diabetes is taking on epidemic proportions with over 220 million individuals affected by this disease worldwide (1 over 20 adults, 95% of whom have Type-2 diabetes), a number which is expected to grow to 366 million by the year 2030. The rapid, constant increase of diabetic patients make this disease one of the social-health emergencies of the third millennium. Most diabetics follow a metabolic monitoring therapy based on a combination of insulin injections and/or drugs, diet and physical exercise. The therapy is determined by the physician on the basis of glycaemia level measurements that the patient measures by him or herself in capillary blood 3 or 4 times a day (self-monitoring). This approach presents

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inevitable shortcomings due to the low amount of glycaemia data available related to the high glycaemia range during the day. Due to the shortcomings of the monitoring system, glycaemia may exceed normal limits (between 70 and 180 mg/dl). Hyperglycaemia (a situation in which the concentration of glucose in blood is higher than 180 mg/dl) causes various long-term complications (cardiovascular disease, hypertension, retinopathies, etc.), while on the short-term, hypoglycaemia (glucose concentration lower than 70 mg/dl) may even be more dangerous (e.g. it may lead to diabetic coma) also because it may be difficult for the patient to recognize, particularly at night.

[0006] New minimally invasive or in some cases not at all invasive devices for continuously monitoring glucose levels, known as Continuous Glucose Monitoring (CGM) devices, have been developed and marketed during the past years. CGM devices can compensate the lack of information of the traditional 3 or 4 Self Monitoring Blood Glucose (SMBG) measurements. In fact, they can measure, in real-time, the glycaemia level at a continuous time (from every 1 to 5 minutes, according to the sensor) for up to several days (from 3 to 7 days, according to the technology), allowing the improvement of diabetes management. Retrospective CGM data analysis (glycaemia level data can normally be downloaded by means of an appropriate software present in the device) may for example identify hypo/hyperglycaemic episodes which are not revealed by 3-4 daily measurements determined in capillary blood, and thus significantly help reviewing the specific patient's therapy. One of the features of CGM sensors is their capacity to estimate the current glucose level in real time. This makes them particularly interesting for recognizing potentially dangerous episodes in real time, such as exceeding of the aforesaid hypo/hyperglycaemic thresholds. For this reason, some CGM sensors are provided with alert generation methods, which warn the patient when the estimated glycaemia value exceeds predetermined thresholds.

[0007] Most of the commercialized CGM systems, e.g. the Seven® (DexCom Inc, San Diego, CA), the FreeStyle Navigator™ (Abbott Diabetes Care, Alameda, CA), and the CGMS® (Medtronic Minimed Inc, Northridge, CA), exploit the glucose-oxidase principle, which requires that the current levels (e.g. in mA) are transformed into glucose levels (e.g. mg/dl) by exploiting a transformation rule with parameters determined using one or more references, e.g. SMBG. This step is commonly referred to as a calibration. In addition, in order to reduce invasiveness, CGM sensors measure interstitial glucose (IG) rather than

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blood glucose (BG) concentration. In dynamic conditions, IG and BG differ because of the existence of a BG-to-IG kinetics.

[0008] To show this, FIG. 1 displays a comparison between BG references, collected every 15 minutes (measured with YSI, Yellow Springs, OH), and a CGM profile collected using a subcutaneous sensor (FreeStyle Navigator™, Abbott Diabetes Care, Alameda, CA) (these data were taken from the literature and are used for representative purposes only). Discrepancies between BG and CGM time series due to the BG-to-IG kinetics (e.g. amplitude and phase distortion) are rather evident.

[0009] BG-to-IG kinetics is usually described by the two-compartment model as shown in FIG. 2. From the model, BG and IG concentrations can be related through the following continuous-time differential equation:

$$\frac{dC_2(t)}{dt} = -(k_{02} + k_{12})C_2(t) + k_{21}\frac{V_1}{V_2}C_1(t) \qquad (1)$$

where $C_1(t)$ and $C_2(t)$ are BG and IG concentration, respectively, V_1 and V_2 are BG and IG volumes, and k_{ij} denote the transfer rate from compartment j to compartment i. Eq. (1) can be transformed in:

$$\frac{dC_2(t)}{dt} = -\frac{1}{\tau}C_2(t) + \frac{g}{\tau}C_1(t) \qquad (2)$$

where $g=(k_{21}V_1/V_2)\tau$ and $\tau=1/(k_{02}+k_{12})$. In summary, IG can be interpreted as the output of a first order linear system driven by BG, where g represents the "static gain" of the physiological BG-to-IG system (which we can consider equal to 1 without any loss of generality), and τ is the time constant of the system, which could vary between individuals. The system acts as a low-pass filter, and introduces a distortion (attenuation in amplitude and distortion in phase) which is well observable e.g. in time window 2-8 hours shown in FIG. 1.

[0010] The BG-to-IG kinetics is not able to explain the whole discrepancy between the CGM readings and the true plasma profile. An example of this fact can be inferred from FIG. 1, in the interval 25-33, where discrepancies which cannot be attributed to the physiological component can be visualized along the y-axis. In this case, we can see that the mean values of BG and CGM data are very different. This difference should be principally attributed to technological aspects and in particular to the change of behaviour

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of the CGM sensor performance after its initial calibration. Furthermore, by looking at FIG. 1, this source of error seems to have a time-varying nature, which has been modelled by [ref] as a multiplicative error in affecting sensor calibration.

[0011] The fact that CGM time series may differ from BG profiles because of calibration problems can be critical in several applications resorting to CGM sensors, e.g. artificial pancreas methods relying on CGM output. Real-time recalibration of CGM data is therefore an important task to deal with. Of note, these problems inevitably affect all the CGM traces, since a natural degradation of the sensor itself always occurs, but it is important to note that they can be recovered at a software level via a re-adjustment of the calibration that translates current readings into glucose concentration values.

[0012] Real-time recalibration of CGM sensors is hence necessary to increase the accuracy of their measurements. An accurate and precise CGM device can be extremely useful to improve the management of diabetes therapy, helping the patient in a tighter glucose concentration control, and hence reducing both long- and short-term complications.

[0013] Calibration is the most critical aspect in CGM devices. The calibration should transform the raw current level measured by the sensor into an IG level by exploiting one or more capillary BG measurements. The most adopted calibration strategy exploits is the so-called 2-point linear regression model reported in eq. (3)

$$y = ax + b \qquad (3)$$

where a and b are calibration parameters which are determined by fitting them against a couple of BG (y) and raw current CGM (x) levels collected at the same time. However, this procedure is less than suboptimal, because it does not take into account the distortion introduced by the BG-to-IG kinetics. In fact, by comparing BG and IG concentrations when glucose is changing rapidly, e.g. just after a meal, one could note that their level could be significantly different (e.g. 20 mg/dl). Therefore, drawing the calibration sample in such a point, i.e. while the raw current is not proportional to real BG level, could introduce a bias in CGM readings (e.g. in the 28-31 hour time interval of FIG. 1). In order to improve CGM accuracy, many other different recalibration procedures have been proposed in the literature.

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[0014] A first attempt has been performed by DirecNet Study Group, which analyzed the improvement in CGMS sensor accuracy by retrospectively modifying the number and timing of the calibration points. Results evidenced the fact that the timing of the calibration points is even more important than the number. In particular, performing calibrations during periods of relative glucose stability, i.e. where the point-to-point difference due to the BG-to-IG kinetics is minimized, significantly improves the accuracy.

[0015] A second recalibration procedure is based on the same linear regression model of eq.(3), and works by exploiting all the BG references that one can have available. A first weak point of this procedure is that it can be applied only retrospectively. In addition, it does not take into account the BG-to-IG kinetics. Finally, it cannot deal with a possible time-varying behaviour of sensor performance (i.e. the parameters of eq. (3) are equal throughout the monitoring).

[0016] In another approach a dual-rate Kalman filter is presented to improve the accuracy of CGM data. The procedure exploits sparse SMBG measurements and estimates in real-time the sensor gain. A critical aspect of this algorithm is that it does not embed any BG-to-IG kinetics model. As a consequence, it is suboptimal because it considers SMBG and CGM measurements as if they were collected in the same site.

[0017] In a comprehensive description of the CGM measurement process, the BG-to-IG kinetics model was explicitly taken into account in order to reconstruct BG levels at continuous time from CGM measurements. To such a scope, a state-space Bayesian framework exploiting a priori knowledge of the unknown variables was adopted and an extended Kalman Filter (EKF) was implemented to perform state estimation.

[0018] In the most widely used technique for the recalibration of CGM profiles, a linear regression model is used to make two points of blood samples (see, e.g., FIG. 3) to match correspondent values of the original CGM trace sampled at the same time. This recalibration method (hereafter we will refer at this as gold standard) has been used to improve the accuracy of CGM time series is some recent studies.

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[0019] Even if it is proved that this technique allows improving the quality of CGM traces, some important issues remain uncovered. In order to point out some of these open problems that cannot be faced with it, some simulated examples are here reported.

[0020] *Example #1.* In FIG. 3 shows data relative to the first simulation, i.e. the plasma glucose concentration (red line), inferred from 5 minute sampling traces, the interstitial glucose concentration, calculated feeding the plasma profile to the Rebrin BG-to-IG model, and the CGM profile, obtained multiplying the IG concentration by a profile which simulates a lack of calibration (in this example a non linear stretch of IG is used) and adding a measurement error. The CGM profile clearly suffers from lack of calibration. In order to recalibrate the data, the existing method is applied. Once the two pairs of measurements are collected (the two BG samples and the correspondent CGM data, see FIG. 3), the parameters of the linear regression of eq.(3) are calculated. Then, the whole CGM profile is adjusted by using the regression, obtaining the profile shown in FIG. 4. In this case, the gold standard technique performs satisfactorily. However, the gold standard technique is not robust. This can be shown with the following example.

[0021] *Example #2.* FIG. 5 shows data used in this second simulation. Applying the gold standard method by using the two pairs of values highlighted in the Figure, the recalibration leads to a large deviation from real data, even worse than the original CGM data. Results are displayed in FIG. 6.

[0022] The reason why the gold standard fails in recalibrating CGM data is due to the fact that the two pairs of values (i.e. the red and black circles) refer to two different compartments, i.e. BG and IG in FIG. 4. In fact, the whole BG-to-IG dynamic system acts like a filter, which has the effect of distorting and delaying the plasmatic profile. As a consequence, the IG concentration is a *distorted* and *delayed* version of BG. For this reason, if BG and IG concentrations are compared when glucose is changing rapidly, their level could be significantly different (e.g. 20 mg/dl). This is exactly the case of this second example. While in the first example the two points have been chosen when BG and IG levels are similar, in the second case the second of the two pairs have been selected during the rise up after the meal. If the BG-to-IG kinetics is not taken into account (as it happens in the gold standard procedure), this difference could be wrongly misread as a loss of

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accuracy of the sensor, introducing a bias in the estimation of the parameters of the regressor.

[0023] Therefore, any algorithm for the recalibration con CGM data which uses "inhomogeneous" quantities (i.e. BG and IG) for the estimation of its parameters should not ignore the dynamics between them.

[0024] It is currently believed that all the up-to-date available methods for recalibration use both CGM and BG values without considering any BG-to-IG kinetics.

[0025] The inclusion of a model of the BG-to-IG dynamic system can improve CGM recalibration algorithms, making them more physiology-aware, with great benefit for the precision of CGM devices.

[0026] Most of the CGM devices exploit the glucose-oxidase principle, i.e. they measure, within the subcutaneous tissue, an electrical current, proportional to the glucose level in the interstitium, which is then converted into a glucose level in an "internal" calibration step (which requires suitable blood glucose (BG) references taken at times empirically determined). However, in practical situations, a possible deterioration of sensor gain may occur, which leads the CGM output to be significantly different from the true glucose profile. Especially in real-time applications, this calls for CGM recalibration algorithms.

[0027] Existing state-of-the-art recalibration algorithms present several limitations. In particular, they do not take into account that: a) CGM devices measure glucose into the interstitium compartment rather than into the blood compartment where the reference BG samples are taken; b) the times at which reference BG samples are collected for calibration should be accurately determined by means of exhaustive computer simulations; c) CGM sensors accuracy may change in time, and calibration should be continuously reassessed. As a consequence of a), b) and c), the recalibration provided by the state-of-the-art methods is suboptimal.

[0028] Therefore, there is a need for a device that includes a recalibration algorithm that explicitly takes into account: the physiology of the signals into play and, in particular,

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the existence of a plasma-to-interstitium glucose kinetics; the possibility of including the reference BG sampling times among the design variables; and the possible time-varying behavior of the sensor accuracy.

SUMMARY OF THE INVENTION

[0029] The disadvantages of the prior art are overcome by the present invention which, in one aspect, is a system employing an algorithm that can be described as it follows. A deconvolution procedure is employed (by using the sensor CGM signal and a "population" impulse response) to reconstruct a profile which is then scaled, by means of a regression model, in order to fit the available reference BG samples (at least two). Optimal times at which these BG references should be collected by the patient are suggested from the algorithm (on the basis of an exhaustive numerical simulation made in the phase of algorithm design). Once the parameters of the regressor have been estimated, the measured CGM data are recalibrated by employing the regressor itself. In order to track possible changes in the sensor performance, the recalibration algorithm can be launched every time a new pair of reference BG samples is available (e.g. typically twice a day, at breakfast and at dinner).

[0030] The new algorithm works on-line. Numerical simulations demonstrate that it is largely superior to the state-of-the-art algorithms, in terms of both accuracy and robustness

[0031] One embodiment of the invention here proposed includes in a recalibration method, which aims to a dynamics-aware on-line recovering of CGM data, in order to obtain a more accurate and precise glucose concentration. The invention can either be embedded in a commercialized CGM device or be a part of a separate system, which receives CGM data as input and returns the recalibrated CGM data as output. The algorithm recalibrates CGM readings comparing values which belong to the same compartment. In fact, BG and CGM data is typically not directly compared, because of the distortion introduced by the BG-to-IG dynamics. Thanks to the exploitation of a model describing the BG-to-IG dynamic system, the invention converts CGM data into BG concentration before comparing it with BG references collected for calibrating the device.

[0032] The algorithm which is part of the invention receives as inputs:

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- the CGM readings;
- the time of meals;
- population parameters describing the BG-to-IG dynamics of the system;
- some SMBG references (at least 2);
- the time in which SMBG references have been collected.

[0033] The inputs required by the algorithm are compatible with every CGM device which exploits one or more SMBG to be calibrated. In addition, the calibration procedure we propose can be used in series with the CGM device (see FIG. 9): the raw CGM signal is fed to the calibration module, that will calibrate it exploiting only some simple input information from the patient (SMBG and meal announcements). The information provided by the patient is perfectly compatible with standard self monitoring he or she is used to perform, in fact, only few (4 per day) SMBG samples are required.

[0034] These and other aspects of the invention will become apparent from the following description of the preferred embodiments taken in conjunction with the following drawings. As would be obvious to one skilled in the art, many variations and modifications of the invention may be effected without departing from the spirit and scope of the novel concepts of the disclosure.

BRIEF DESCRIPTION OF THE FIGURES OF THE DRAWINGS

[0035] **FIG. 1** is a graph relating BG references to CGM data profiles.

[0036] **FIG. 2** is a two-compartmental model describing relationship and exchanges between BG (compartment 1) and IG (compartment 2) concentrations.

[0037] **FIG. 3** is a graph showing BG, IG, and CGM values, respectively, including two pairs of values selected and used for recalibrating CGM data with the gold standard method.

[0038] **FIG. 4** is a graph showing results of the application of the gold standard to recalibrate CGM data showing true IG and CGM data and recalibrated CGM by using the gold standard and the two pairs of values.

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[0039] **FIG. 5** is a graph showing data used in Example #2.

[0040] **FIG. 6** is a graph showing Results of the application of the gold standard to recalibrate CGM data.

[0041] **FIG. 7** is a schematic diagram showing one embodiment of a recalibration module and input information that has to be inserted by the patient.

[0042] **FIG. 8** is a flowchart describing one procedure for recalibration.

[0043] **FIG. 9** is a graph showing results of the application of the gold standard and model-based recalibration techniques to recalibrate CGM data of Example #1.

[0044] **FIG. 10** is a graph showing results of the application of the gold standard and model-based recalibration techniques to recalibrate CGM data of Example #2.

DETAILED DESCRIPTION OF THE INVENTION

[0045] A preferred embodiment of the invention is now described in detail. Referring to the drawings, like numbers indicate like parts throughout the views. Unless otherwise specifically indicated in the disclosure that follows, the drawings are not necessarily drawn to scale. As used in the description herein and throughout the claims, the following terms take the meanings explicitly associated herein, unless the context clearly dictates otherwise: the meaning of "a," "an," and "the" includes plural reference, the meaning of "in" includes "in" and "on." Also, as used herein, "global computer network" includes the Internet.

[0046] A recalibration method for dynamics-aware on-line recovering of CGM data is configured to obtain a more accurate and precise glucose concentration. Either be embedded in a commercialized CGM device or be a part of a separate system, which receives CGM data as input and returns the recalibrated CGM data as output, the algorithm recalibrates CGM readings comparing values which belong to the same compartment. BG and CGM data cannot be directly compared, because of the distortion introduced by the BG-to-IG dynamics. Employing a model describing the BG-to-IG dynamic system, the

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method converts CGM data into BG concentration before comparing it with BG references collected for calibrating the device.

[0047] As shown in FIG. 7, one embodiment includes a calibration module **700** that receives a raw glucose signal from a continuous glucose monitoring device **702** and that receives both meal information and self monitored blood glucose data from a patient **704**. The recalibration module **700** would typically be executable on a digital computer and the data from the patient **704** could be received by the processor via the global computer network.

[0048] The recalibration method part of the invention leans on a linear regression which exploits two pairs of glucose measures. The first pair consists of two reference BG measures (e.g. SMBG, received in input), the second pair consists of two reconstructed blood glucose (RBG) values, obtained converting the CGM data (received in input) into a "potential" plasma glucose concentration. exploiting the BG-to-IG kinetics and a deconvolution procedure. In details, the recalibration algorithm works as follow:

- Measurements received from the CGM device are stored;
- CGM data is converted into RBG data, which can have theoretically generated it, by exploiting a deconvolution procedure based on a dynamic model of the BG-to-IG system (the parameters of the BG-to-IG model can be either individual or population parameters);
- Two RBG values are extracted from the RBG profiles in correspondence to the times in which the two BG references have been collected;
- The parameters (a,b) of a linear regressor y =ax + b are estimated by using as x data the pair of RBG and as y data the pair of BG;
- The regressor is hence used to recalibrate in real time CGM data, obtaining new CGM data as output of the system.new CGM = aCGM + b

[0049] With this procedure, the couples of measures which are used inside eq.(3) (above) belong to the same compartment, i.e. BG, and therefore the estimation of the parameters of eq.(3) is performed among "homogeneous" quantities. As it has been described in the last point of the procedure, once the parameters of the regressor are obtained, the regressor can be on-line applied to the original CGM traces (thanks to the linearity of the whole system) to obtain in real time the new recalibrated profile.

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[0050] A flowchart describing the suggested procedure for the recalibration with dynamics-aware tool is shown in FIG. 8. Starting from the CGM data stream **800** (e.g. a new glucose value every 1 or 5 minutes **802**), the algorithm buffers at least 30 minutes of data **804** (the buffer must be updated at each new incoming measure). If no meal announcement arrives **806**, the algorithm keeps on updating the buffer **804** at each measure **802**. When a meal is announced (information that must be given in input by the patient), the algorithm stores the actual 30-minute-buffer in the so called Cal-Buffer **808**, which stores the trace of CGM we intend to use for deconvolution purposes. As soon as a meal is announced, a SMBG reference is required (patient dependent input) **810**. The SMBG value should be given in input by the patient in the 10-minute window after it is required; otherwise the recalibration procedure is aborted. After meal the algorithm stores every new CGM value **814** in the Cal-Buffer **816** until a postprandial peak is reached OR for a maximum of 3 hours after the meal **812** if the postprandial peak has not yet been reached. When one of the two conditions is satisfied, the patient is asked for a second SMBG reference **818**. The SMBG value has to be given in input by the patient in the 10-minute window after it is requested, otherwise the recalibration procedure is aborted. Information about SMBG is stored **820**, as well as the Cal-Buffer, which is updated for the 30 minutes following the collection of the second SMBG. Then, the "theoretical" plasma profile that should have generated the CGM data till here stored is reconstructed by exploiting a deconvolution based procedure **822**, which uses a BG-to-IG kinetics model (individualized or population parameters can be used) to take into account the distortion of the dynamics between the two compartments. SMBG and corresponding deconvoluted plasma values are fed to the linear regression to estimate the correction parameters **824** (such as that shown in Equation 3, above), which in turn are fed to the CGM device or to the final user of the CGM trace, who will be able to correct the original CGM data.

[0051] There could be many different model-based procedures to reconstruct a plasmatic profile from CGM readings. Here, two possible procedures are shown: the first performs a parametric deconvolution by exploiting a polynomial-based model, the second performs a non-parametric deconvolution; both are based on literature state-of-art BG-to-IG model , exploiting individual/population values for the model parameters. The two algorithms here suggested can be easily performed online, since they yield a close-form solution. The whole calibration process is then condensed in a chain of matrix products.

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[0052] FIGS. 9 and 10 show results of the application of the two new recalibration methods on the simulated examples seen in Figures 3 and 5. In both simulations, both methods provide a satisfactory recalibration profiles significantly better than the one obtained by using the gold standard (the "POLY" and the "DEC" profiles are obtained by using the polynomial–based parametric deconvolution and the non-parametric deconvolution recalibration approaches, respectively).

[0053] CGM devices may lead to fundamental improvement for the management of diabetes, since they can provide an insight on glycaemic trends. Their high-frequent information can be fed to control and prediction systems for the optimal management of the disease. However, CGM sensor accuracy is not always satisfactory because of both the degradation of sensor performance during the whole monitoring and possibly bad-calibration of the device. On-line recalibration of CGM sensors becomes a crucial issue for the correction of these technology-relates problems and for the improvement of sensors performance.

[0054] Many different recalibration algorithms have proposed in the CGM field literature. The most used is able to improve the accuracy of CGM readings by exploiting a linear regressor which parameters are estimated by comparing two BG references and the corresponding measured CGM data; however this procedure is not stable, because in many situations it produces a CGM value which is even less accurate than original. The inability of improving CGM data accuracy is due to the fact that the procedure ignores the dynamic system that correlates IG to BG concentrations, which acts as a low-pass filter, distorting the IG concentration. If one of the recalibration points is collected e.g. on a rising front of glucose concentration, BG and IG point-to-point difference could be even higher than 15/20 mg/dl. If the BG-to-IG kinetics is not taken into account, this difference could be wrongly considered as a loss of accuracy of the sensor, introducing a bias in the estimation of the parameters of the regressor. It is important to note that likely all state-of-the-art methods try to match these inhomogeneous quantities (i.e. IG and BG), hence suffering from dynamics related problems.

[0055] The recalibration method here proposed is able to improve CGM data accuracy in all situations, because it embeds a model of the BG-to-IG kinetics. In fact, first the

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"theoretical" plasma glucose concentration that could have generated CGM data is reconstructed by using a deconvolution-based procedure and a model of the BG-to-IG kinetics, and then the parameters of the linear regressor are estimated. In this way, the estimation is performed comparing homogeneous quantities, i.e. BG references (e.g. a pair of SMBG measurements) and the correspondent RBG samples taken from the reconstructed plasma profile. The limitation of state-of-the-art recalibration procedures is overcome, and the possibility of obtaining a recalibrated CGM value worse than original CGM data is avoided.

[0056] One of the most important features of this new method is that it works on-line. Once the parameters of the regressor have been estimated, the regressor can be directly applied to original CGM data, adjusting their values.

[0057] The above described embodiments, while including the preferred embodiment and the best mode of the invention known to the inventor at the time of filing, are given as illustrative examples only. It will be readily appreciated that many deviations may be made from the specific embodiments disclosed in this specification without departing from the spirit and scope of the invention. Accordingly, the scope of the invention is to be determined by the claims below rather than being limited to the specifically described embodiments above.

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CLAIMS

What is claimed is:

1. A system for recalibrating continuous glucose monitoring data from a user, comprising:
   a. a digital processor;
   b. a continuous glucose monitoring sensor, in communication with the digital processor, configured to generate a glucose signal;
   c. a recalibration module, configured to:
      i. receive at least two self-monitored of blood glucose levels from the user;
      ii. receive meal information from the user;
      iii. receive the glucose signal from the continuous glucose monitoring sensor;
      iv. generate two reconstructed blood glucose values based on the glucose signal from the continuous monitoring sensor at times when the at least two self-monitored of blood glucose levels are received from the user;
      v. perform a linear regression using $y = ax + b$, wherein x corresponds to the two reconstructed blood glucose values and y corresponds to the two self-monitored of blood glucose levels thereby generating an estimation of a and b; and
      vi. transmit a recalibration signal, including the estimation of a and b, to the continuous glucose monitoring sensor based on the linear regression.

2. The system of Claim 1, wherein the calibration module is configured to generate two reconstructed blood glucose values by converting the glucose signal from the continuous glucose monitoring sensor into a potential plasma glucose concentration.

3. The system of Claim 1, wherein the calibration module converts continuous glucose monitoring data in the glucose signal into reconstructed blood glucose data with a

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deconvolution procedure based on a dynamic model of a blood glucose to interstitial glucose system.

4. The system of Claim 1, wherein the calibration module is configured to generate a request to the user for a self monitored blood glucose level at a first predetermined period after the user has had a meal.

5. The system of Claim 4, wherein the first predetermined period comprises thirty minutes.

6. The system of Claim 5, wherein the calibration module is configured to generate a request to the user for a self monitored blood glucose level at a second predetermined period after the user has had a meal.

7. The system of Claim 6, wherein the first predetermined period comprises three hours.

8. The system of Claim 1, wherein the processor and the continuous glucose monitoring sensor are in communication with each other via a global computer network.

9. The system of Claim 1, wherein the recalibration module is further configured to execute each day after the user has taken two different meals.

10. A method of recalibrating continuous glucose monitoring data from a user, operable on a digital processor, comprising the steps of:
    a. receiving an indication from the user that the user has taken a meal;
    b. receiving a self-monitored of blood glucose levels from the user at two separate times during a day corresponding to when the user has taken a meal;
    c. receiving a glucose signal from a continuous glucose monitoring sensor at times corresponding to the two separate times that the user has taken a meal;

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d. generating two reconstructed blood glucose values based on the glucose signal from the continuous monitoring sensor at times when the at least two self-monitored of blood glucose levels are received from the user;

e. performing a linear regression using $y = ax + b$, wherein x corresponds to the two reconstructed blood glucose values and y corresponds to the two self-monitored of blood glucose levels thereby generating an estimation of a and b; and

f. transmitting a recalibration signal, including the estimation of a and b, to the continuous glucose monitoring sensor based on the linear regression.

11. The method of Claim 10, wherein the step of generating two reconstructed blood glucose comprises converting the glucose signal from the continuous glucose monitoring sensor into a potential plasma glucose concentration.

12. The method of Claim 10, further comprising the step of converting continuous glucose monitoring data in the glucose signal into reconstructed blood glucose data using a deconvolution procedure based on a dynamic model of a blood glucose to interstitial glucose system.

13. The method of Claim 10, further comprising the step of generating a request to the user for a self monitored blood glucose level at a first predetermined period after the user has had a meal.

14. The method of Claim 13, wherein the first predetermined period comprises thirty minutes.

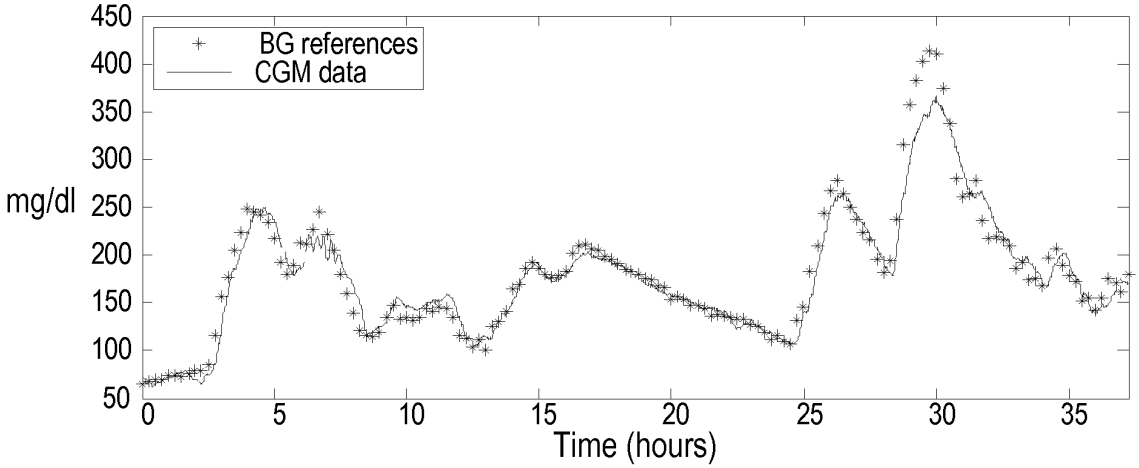
15. The method of Claim 14, further comprising the step of generating a request to the user for a self monitored blood glucose level at a second predetermined period after the user has had a meal.

16. The method of Claim 15, wherein the first predetermined period comprises three hours.

Abbott Ex. 1002 - 1228/1438

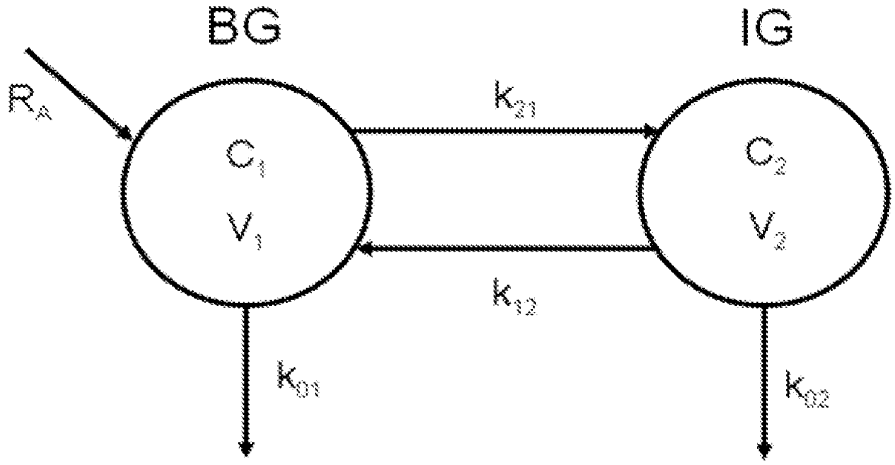
17. The method of Claim 10, further comprising the step of communicating data from the continuous glucose monitoring sensor to the processor and from the processor to the continuous glucose monitoring sensor via a global computer network.

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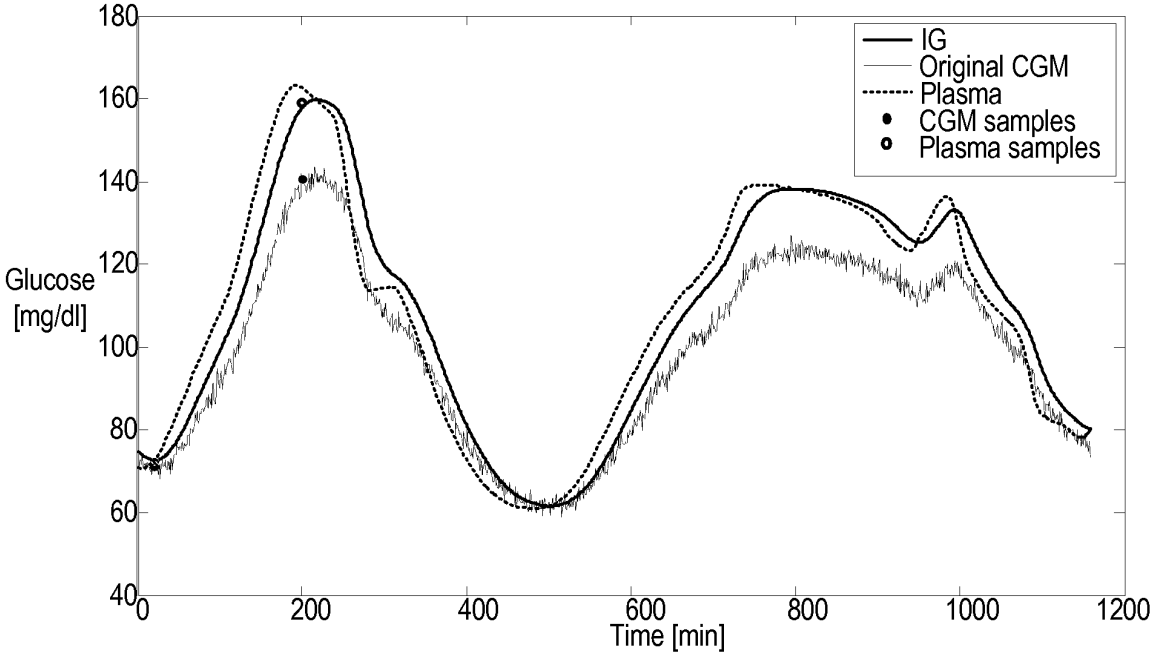
PRIOR ART

FIG. 1



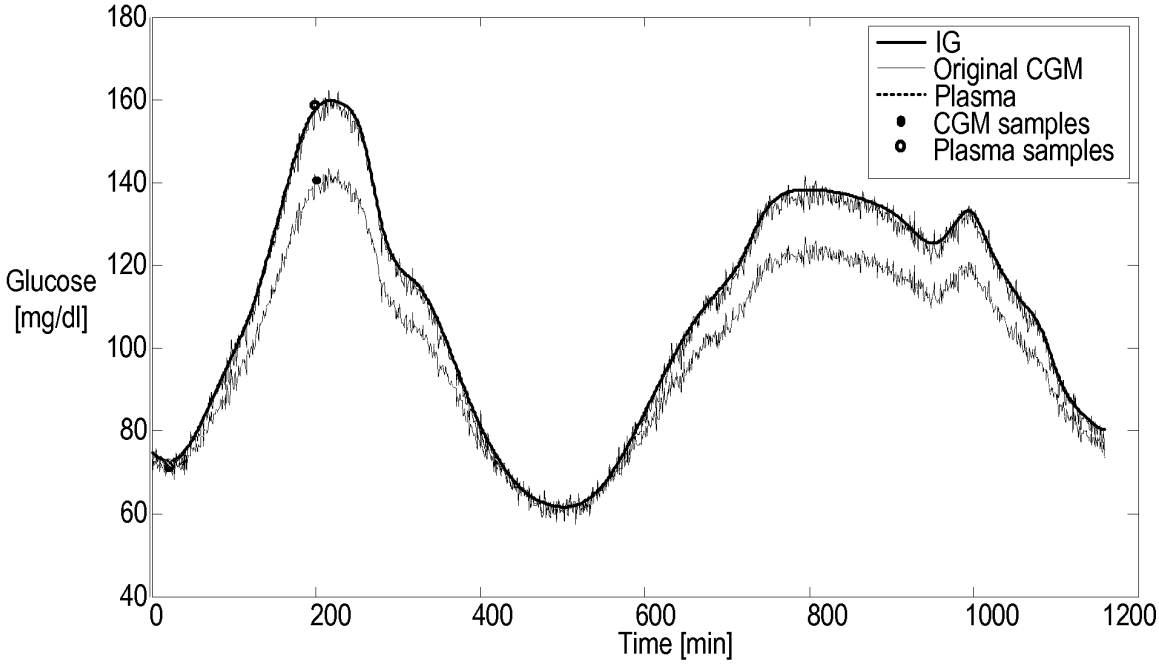
PRIOR ART

FIG. 2



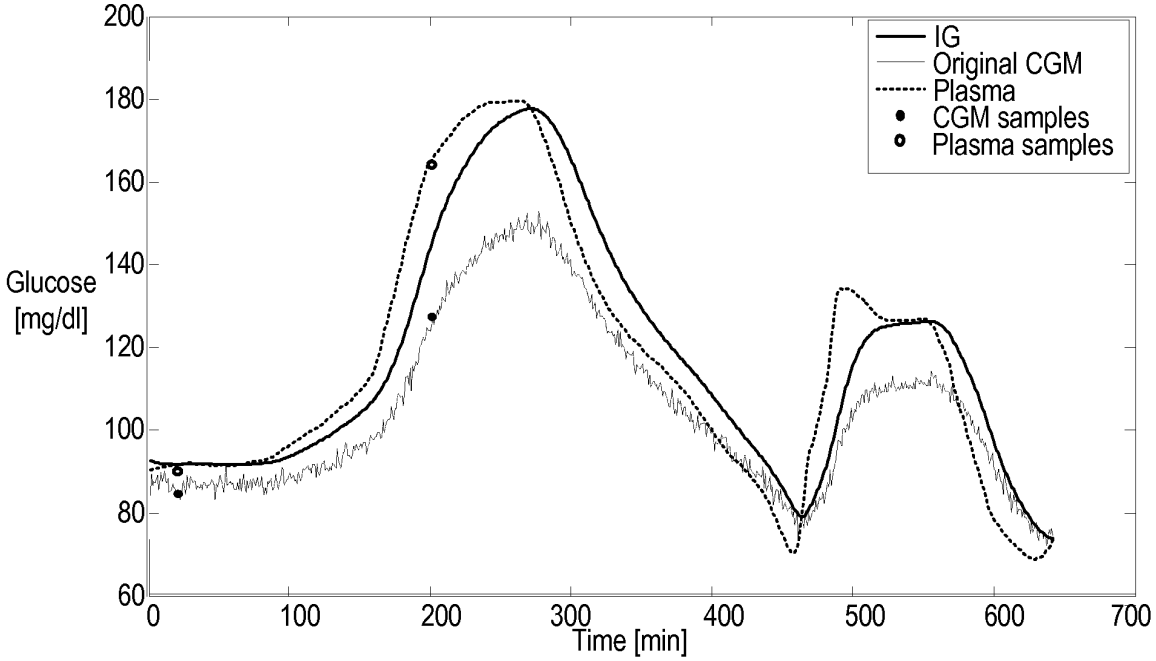
PRIOR ART

FIG. 3



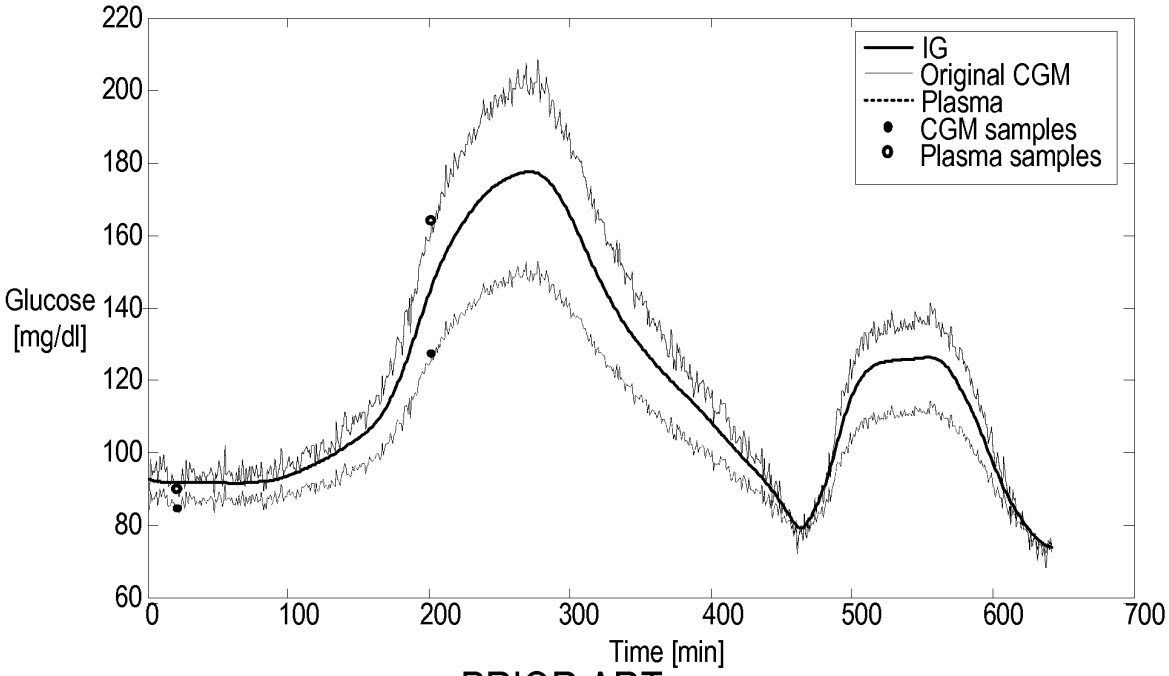
PRIOR ART

FIG. 4



PRIOR ART

FIG. 5



PRIOR ART

FIG. 6

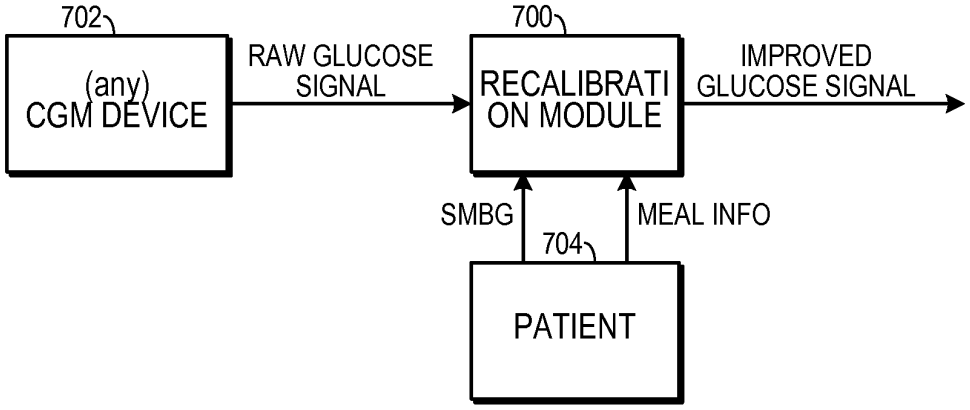

702
(any)
CGM DEVICE
RAW GLUCOSE
SIGNAL
700
RECALIBRATI
ON MODULE
IMPROVED
GLUCOSE SIGNAL
SMBG
MEAL INFO
704
PATIENT

FIG. 7

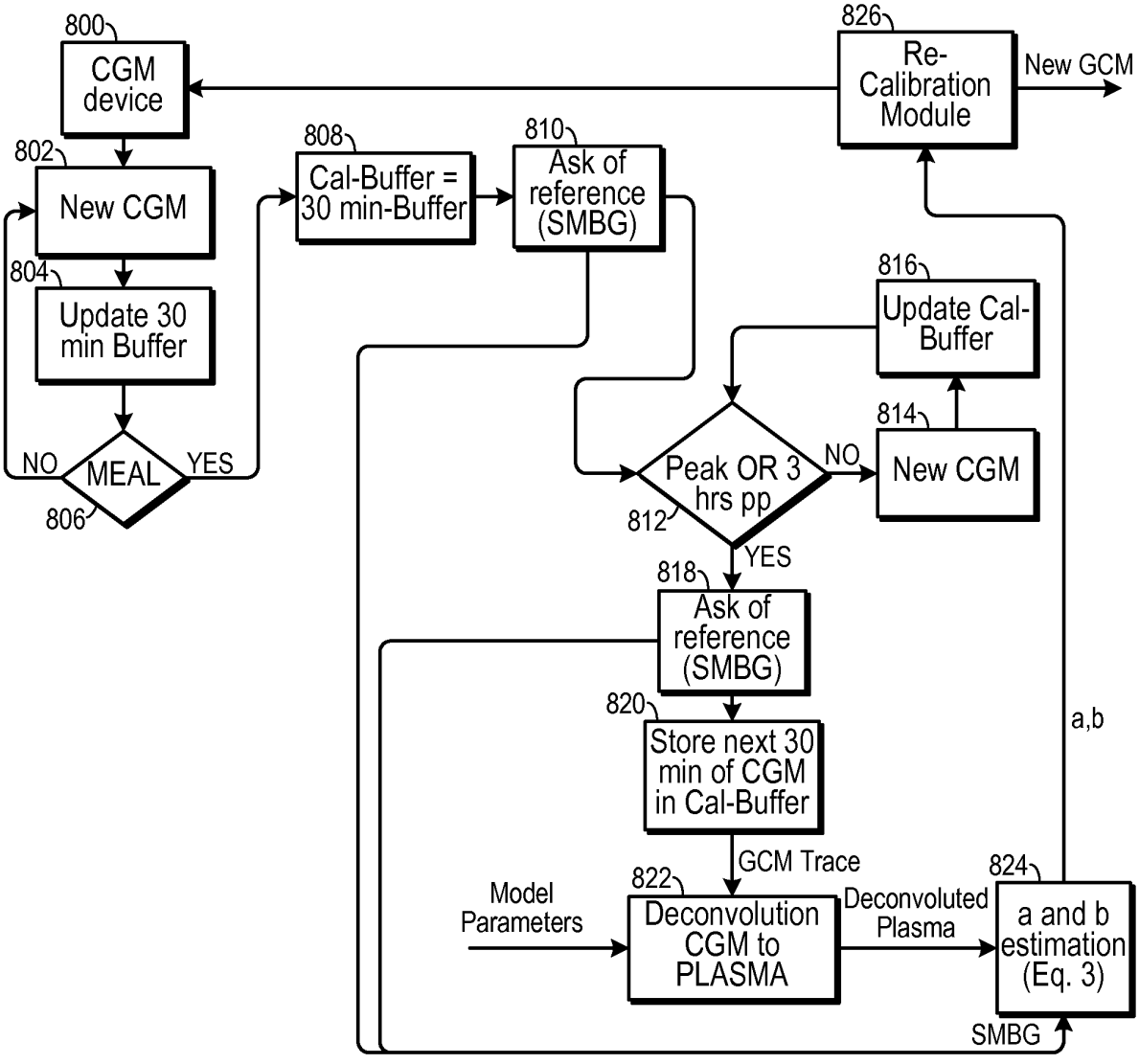

800
CGM
device
826
Re-
Calibration
Module
New GCM
802
New CGM
808
Cal-Buffer =
30 min-Buffer
810
Ask of
reference
(SMBG)
804
Update 30
min Buffer
816
Update Cal-
Buffer
NO
MEAL
YES
806
Peak OR 3
hrs pp
NO
814
New CGM
812
YES
818
Ask of
reference
(SMBG)
820
Store next 30
min of CGM
in Cal-Buffer
a,b
GCM Trace
Model
Parameters
822
Deconvolution
CGM to
PLASMA
Deconvoluted
Plasma
824
a and b
estimation
(Eq. 3)
SMBG

FIG. 8

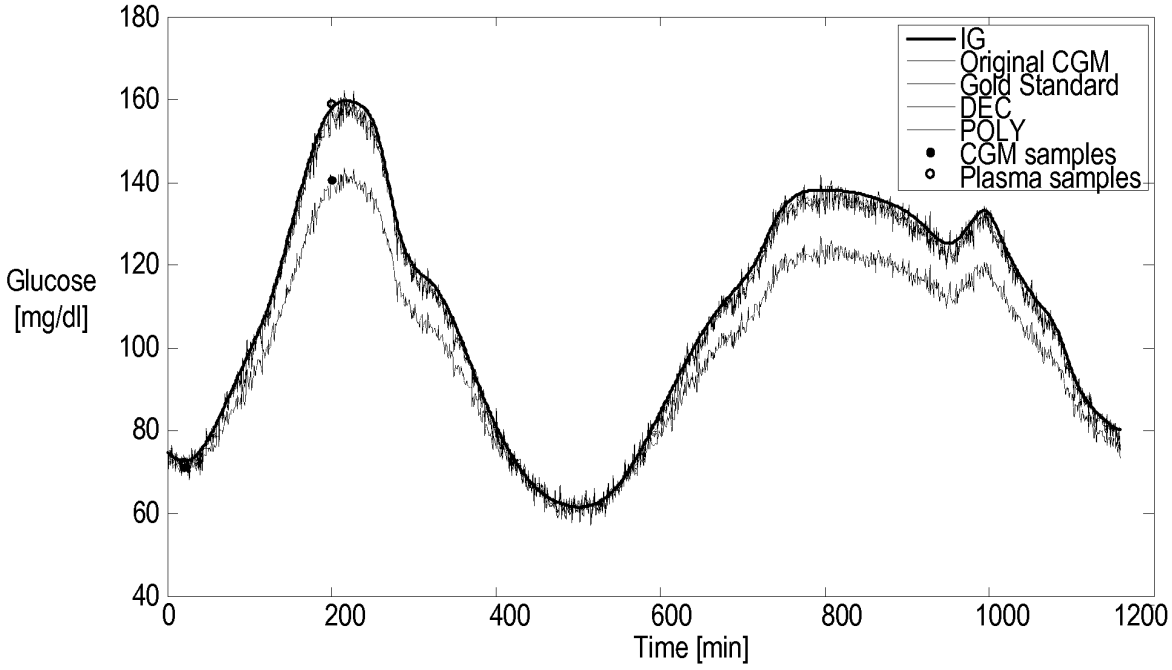

180
160
140
120
100
80
60
40
Glucose [mg/dl]
0
200
400
600
800
1000
1200
Time [min]
IG
Original CGM
Gold Standard
DEC
POLY
CGM samples
Plasma samples

FIG. 9

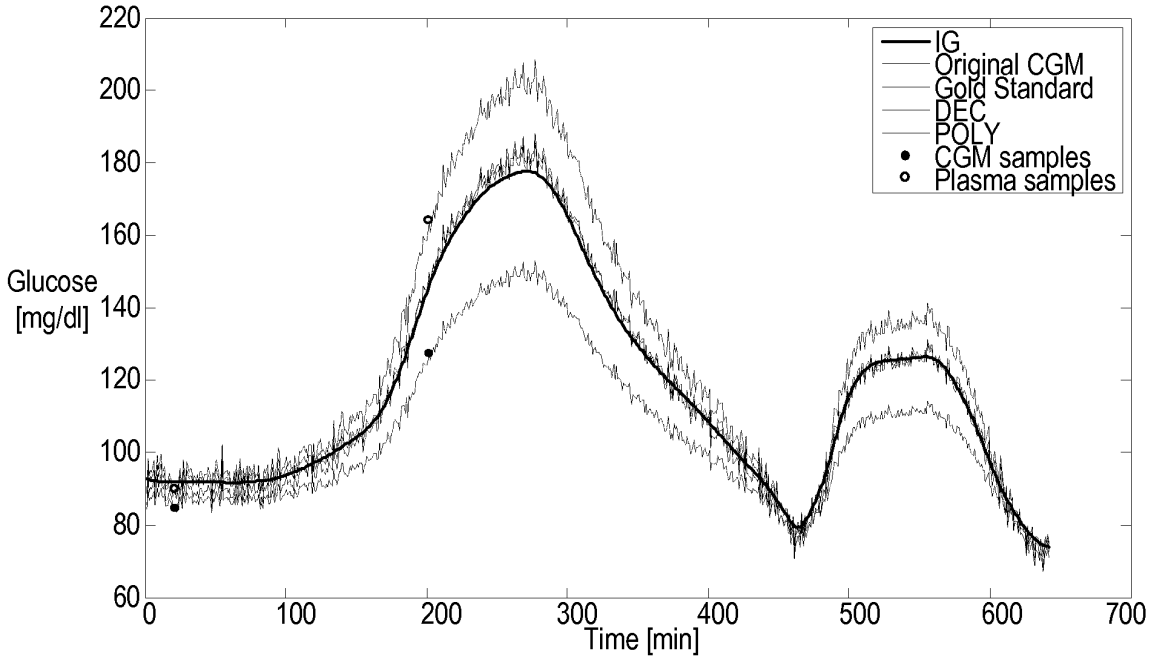

220
200
180
160
140
120
100
80
60
Glucose [mg/dl]
0
100
200
300
400
500
600
700
Time [min]
IG
Original CGM
Gold Standard
DEC
POLY
CGM samples
Plasma samples

FIG. 10

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(22) International Filing Date:
2 November 2010 (02.11.2010)

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61/257,288 2 November 2009 (02.11.2009) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITÀ DEGLI STUDI DI PADOVA** [IT/IT]; Area trasfermiento di tecnologia, Via 8 febbraio, 2, I-35122 Padova (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COBELLI, Claudio** [IT/IT]; Via S. Eufemia 3, I-35121 Padova PD (IT). **DE NICOLAO, Giuseppe** [IT/IT]; Viale Argonne 53, I-20133 Milano MI (IT). **FACCHINETTI, Andrea** [IT/IT]; Via Saetta 3, I-35132 Padova PD (IT). **GUERRA, Stefania** [IT/IT]; Via Pra' Secco 27, I-36010 Carrè VI (IT). **SPARACINO, Giovanni** [IT/IT]; Via Forcellini 209/B, I-35128 Padova PD (IT).

(74) Agent: **WITTMANN, Günther**; Boschetsriederstrasse 67, 81379 München (DE).

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[Continued on next page]

(54) **Title**: METHOD TO RECALIBRATE CONTINUOUS GLUCOSE MONITORING DATA IN REAL-TIME

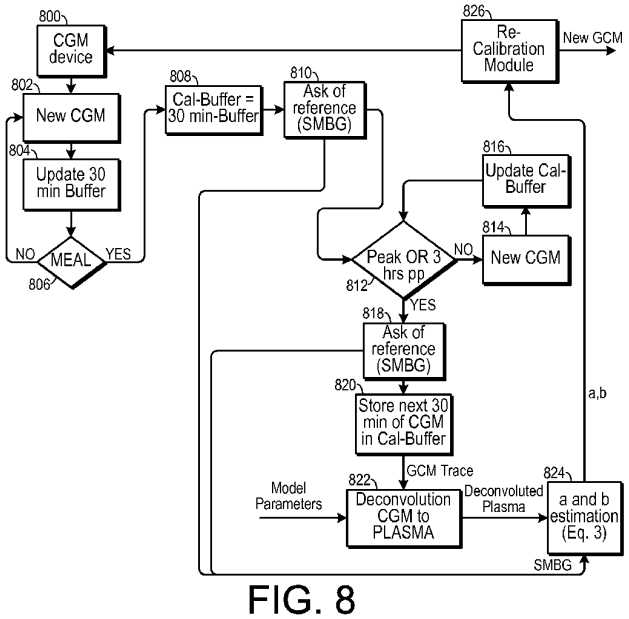


FIG. 8

(57) Abstract: In a method of recalibrating continuous glucose monitoring data from a user, operable on a digital processor, an indication from the user that the user has taken a meal is received (806). A self-monitored of blood glucose levels from the user (810) at two separate times during a day corresponding to when the user has taken a meal. A glucose signal is received from a continuous glucose monitoring sensor (818) at times corresponding to the two separate times that the user has taken a meal. Two reconstructed blood glucose values based on the glucose signal from the continuous monitoring sensor at times when the at least two self-monitored of blood glucose levels are received from the user. A linear regression is performed (822) using y = ax + b, wherein x corresponds to the two reconstructed blood glucose values and y corresponds to the two self-monitored of blood glucose levels thereby generating an estimation of a and b. A recalibration signal, including the estimation of a and b, is transmitted to the continuous glucose monitoring sensor (824) based on the linear regression.

WO 2011/051922 A3

Abbott Ex. 1002 - 1235/1438

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— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
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Abbott Ex. 1002 - 1236/1438

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/054947

A. CLASSIFICATION OF SUBJECT MATTER
INV. G06F19/00 A61B5/1495
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FACCHINETTI A, SPARACINO G, COBELLI C.: "Reconstruction of glucose in plasma from interstitial fluid continuous glucose monitoring data: role of sensor calibration", J DIABETES SCI TECHNOL., vol. 1, no. 5, September 2007 (2007-09), pages 617-623, XP002650522, the whole document	3,12
X	US 2009/156924 A1 (SHARIATI MOHAMMAD ALI [US] ET AL) 18 June 2009 (2009-06-18)	1,2, 4-11, 13-17
Y	paragraphs [0302] - [0405]; figures 6A, 6B	3,12

☐ Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2011	11/08/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Chabros, Cezary

1

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International application No
PCT/IB2010/054947

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009156924 A1	18-06-2009	US 2009192745 A1	30-07-2009
		US 2009192722 A1	30-07-2009
		US 2009192380 A1	30-07-2009
		WO 2009055736 A1	30-04-2009

Docket No. DEXCOM.217A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Claudio Cobelli et al.
App. No	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	LEE, Benjamin C.
Art Unit	:	2684
Conf #	:	6142

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By: Renee Zavala

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Respectfully submitted,

DEXCOM, INC.

Dated: Sept. 11, 2013

By: Laura J. Johnson

Laura J. Johnson, PTO Reg. No. 48,208

Customer Number 68851
DEXCOM, INC.
6340 Sequence Drive
San Diego, CA 92121
Telephone: 858.875.9786

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Complete if Known	
Application Number	13742694
Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	1	Bremer et al., Diabetes 48:445-451 (March 1999): Is Blood Glucose Predictable From Previous Values? A Solicitation for Data	

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International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Laura Jeanette Johnson/Renee Zavala
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Attorney Docket Number:	DEXCOM.217A
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Filing Date:	16-JAN-2013
Time Stamp:	12:39:44
Application Type:	Utility under 35 USC 111(a)

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Docket No. DEXCOM.217A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Filed	:	January 16, 2013
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Examiner	:	LEE, Benjamin C.
Art Unit	:	2684
Conf #	:	6142

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Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 20050033254	2/7/2008	Kamath et al.	
	2	US- 20110193704	8/11/2011	Harper, Wesley Scott	
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Sheet 2 of 2

Complete if Known	
Application Number	13742694
Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	Palerm et al., 2007, J. Diabetes Sciences and Technology 1(5):624-629. Hypoglycemia detection and prediction using continuous glucose monitoring - a study on hypoglycemic cl	
	2	Sandham et al., 1998, IX European Signal Processing Conference, 1998, pages 673-676. Blood glucose prediction for diabetes therapy using a recurrent artificial neural network	
	3	Sparacino et al., 2007, IEEE Transactions on Biomedical Engineering 54(5):931-937. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sen	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	18355922
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Laura Jeanette Johnson/Renee Zavala
Filer Authorized By:	Laura Jeanette Johnson
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	03-MAR-2014
Filing Date:	16-JAN-2013
Time Stamp:	19:30:49
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2014-0303-SupplDS-217A.pdf	296574 e1297d58198485ed56ca1012d3c4c8f8672 1bfd3	yes	4

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	4	
Warnings:					
Information:					
2	Non Patent Literature	X-Palerm-JDiabSciTech-2007.pdf	1265344 6d27adfe2a5fc67b977ebeb7e1d6f45595eca80b	no	6
Warnings:					
Information:					
3	Non Patent Literature	X-Sandham-EUSigProcCOnf-1998.pdf	947473 373305186cb025b0dcc0c55737cd1935f8746bb8	no	4
Warnings:					
Information:					
4	Non Patent Literature	X-Sparacino-IEEETxnBiomedEng-2007.pdf	1100166 8c0e7e03faf2b4cd07226cd56b94da9336493299	no	7
Warnings:					
Information:					
		Total Files Size (in bytes):	3609557		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. DEXCOM.217A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Claudio Cobelli et al.
App. No	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	McNALLY, Kerri L.
Art Unit	:	2682
Conf #	:	6142

CERTIFICATE OF TRANSMITTAL UNDER 37 C.F.R. 1.8

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being filed electronically via EFS-Web at the United States Patent and Trademark Office on the date indicated.

By: Renee Zavala

Date: March 03, 2014

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Submitted herewith in the above-identified application is an Information Disclosure Statement listing references for consideration. In accordance with 37 C.F.R. §1.98(a)(2)(ii), Applicant submits herewith copies of all cited references, other than copies of U.S. patents or U.S. patent publications.

It is respectfully requested that the Examiner initial and return a copy of the enclosed Form PTO/SB/08, and indicate in the official file wrapper oaf this patent application that the documents listed therein have been considered.

This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance.

I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. §1.97(e)(1). Consequently, Applicants believe that no fee is due. If this is incorrect, and a fee is due, the Commissioner is hereby authorized to charge the appropriate

amount to Deposit Account No. 506176, referencing Applicant Docket No. DEXCOM.217A.

Further, the Commissioner is hereby authorized to charge all fees and credit all overpayments to Deposit Account No. 506176 during the pendency of this application.

Respectfully submitted,
DEXCOM, INC.

Dated: 3/3/14

By: _____
Laura J. Johnson, PTO Reg. No. 48,208

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Telephone: 858.875.9786

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A

CONFIRMATION NO. 6142

68851
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IRVINE, CA 92614

PUBLICATION NOTICE

OC000000068168455

Title:SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

Publication No.US-2014-0118138-A1
Publication Date:05/01/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Abbott Ex. 1002 - 1250/1438

PLUS Search Results for S/N 13742694, Searched Wed Sep 03 14:04:49 EDT 2014

The Patent Linguistics Utility System (PLUS) is a USPTO automated search system for U.S. Patents from 1971 to the present PLUS is a query-by-example search system which produces a list of patents that are most closely related linguistically to the application searched. This search was prepared by the staff of the Scientific and Technical Information Center, SIRA.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

68851 7590 10/02/2014

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EXAMINER	
MCNALLY, KERRI L	
ART UNIT	PAPER NUMBER
2682	

NOTIFICATION DATE	DELIVERY MODE
10/02/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jayna.cartee@knobbe.com
efiling@knobbe.com

Office Action Summary	Application No. 13/742,694	Applicant(s) COBELLI ET AL.	
	Examiner KERRI MCNALLY	Art Unit 2682	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/16/13*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-38* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8,10-27 and 29-38* is/are rejected.

8)☒ Claim(s) *9 and 28* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *1/16/13* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of the Claims

1. Claims 1-38 are currently pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. **Claims 15 and 16** are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Specifically, in each of claims 15 and 16, "the processor module" lacks antecedent basis.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. **Claims 1-5, 10, 12, 17, 18, 20-24, 29, 31, 36, and 37** are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by US Patent Application Publication No. 2011/0193704 (Harper et al.).

Regarding claim 1, Harper discloses a method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria;

activating a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and

providing an output based on the activated hypoglycemic indicator

(display for an analyte monitoring device wherein user may select varying glucose threshold levels at which various alarms will sound for low glucose levels or projected low glucose levels [0201] - [0203]).

Regarding claim 2, Harper further discloses the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria

comprises determining whether the real-time glucose value passes a glucose threshold (Abstract; [0201] - [0203]).

Regarding claim 3, Harper further discloses wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion (amplitude of rate of change and direction of rate of change [0134]).

Regarding claim 4, Harper further discloses wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value (current glucose measurement is compared to a threshold level in order to determine if glucose is low or not - low glucose threshold level a static or fixed number [0201] – [0203]).

Regarding claim 5, Harper further discloses wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value (historical values or moving average, for example; [0134]; [0201] – [0203]).

Regarding claim 10, Harper further discloses wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function (harper discloses not only detected low glucose but projected low glucose, which allows for increased warning time before low glucose; [0201] - [0203]; furthermore the user can customize the alerts, including the timing and frequency [0201]).

Regarding claim 12, Harper further discloses wherein the one or more first criteria comprises a first threshold that is configured to be user settable [0202]).

Regarding claim 17, Harper further discloses wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria (each of the specific thresholds or alarms can be customized with different alarm settings, for example, low glucose can be customized with a different tone, timing, volume, vibration, than a projected low glucose alarm; [0198] - [0203]).

Regarding claim 18, Harper further discloses wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria (each of the specific thresholds or alarms can be customized with different alarm settings, for example, low glucose can be customized with a different tone, timing, volume, vibration, than a projected low glucose alarm; [0198] - [0203]).

Regarding claim 20, Harper discloses a system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body (Abstract; [0052]); and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria;

activate a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and

provide an output based on the activated hypoglycemic indicator

(display for an analyte monitoring device wherein user may select varying glucose threshold levels at which various alarms will sound for low glucose levels or projected low glucose levels [0201] - [0203]).

Regarding claim 21, Harper further discloses wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria comprises determining whether the real-time glucose value passes a glucose threshold (Abstract; [0201] - [0203]).

Regarding claim 22, Harper further discloses wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion (amplitude of rate of change and direction of rate of change [0134]).

Regarding claim 23, Harper further discloses wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value (current glucose measurement is compared to a threshold level in order to determine if glucose is low or not - low glucose threshold level a static or fixed number [0201] – [0203]).

Regarding claim 24, Harper further discloses wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value (historical values or moving average, for example; [0134]; [0201] – [0203]).

Regarding claim 29, Harper further discloses wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function (harper discloses not only detected low glucose but projected low glucose, which allows for increased warning time before low glucose; [0201] - [0203]; furthermore the user can customize the alerts, including the timing and frequency [0201]).

Regarding claim 31, Harper further discloses wherein the one or more first criteria comprises a first threshold that is configured to be user settable ([0202]).

Regarding claim 36, Harper further discloses wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria (each of the specific

thresholds or alarms can be customized with different alarm settings, for example, low glucose can be customized with a different tone, timing, volume, vibration, than a projected low glucose alarm; [0198] - [0203]).

Regarding claim 37, Harper further discloses wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria (each of the specific thresholds or alarms can be customized with different alarm settings, for example, low glucose can be customized with a different tone, timing, volume, vibration, than a projected low glucose alarm; [0198] - [0203]).

Claim Rejections - 35 USC § 103

6. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. **Claims 6 and 25** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper et al.) in view of US Patent Application Publication No. 2011/0225112 (Cameron et al.).

Regarding claims 6 and 25, Harper discloses the system and method of claims 1 and 20, respectively, as discussed above. Harper fails to expressly disclose wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness, or surgery to determine the predicted glucose value. However, Cameron discusses using a neural network to predict glucose values ([0247] - [0257]) and analyzing data such as stress levels and activity when determining the future predicted glucose values [0300] and [0301]. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper and utilize a neural network with as much data as possible when predicting future glucose levels in order to get a more accurate result for the patient. Furthermore, the use of neural networks to determine a predicted future value is old and well known in the prior art, as evidenced by Cameron.

8. **Claims 7, 8, 19, 26, 27, and 38** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper et al.) in view of US Patent Application Publication No. 2011/0106011 (Cinar et al.).

Regarding claims 7 and 26, Harper discloses the method and system of claims 1 and 20, respectively, as discussed above. Harper fails to expressly disclose the second function utilizes a first order autoregressive model to determine the predicted glucose value.

However, Cinar discloses an automatic insulin pump system using autoregressive moving-average models, including low order and first order autoregressive models [0079] and [0097]. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper and utilize a first order autoregressive model to better predict glucose levels and to get a more accurate result for the patient. Furthermore, as evidenced by Cinar, the use of autoregressive models is old and well known in the prior art for predicting future values and the selection of which order of autoregressive model could be easily selected or chosen by one of ordinary skill in the art depending on the specific purpose or desired result.

Regarding claims 8 and 27, Harper and Cinar disclose the method and system of claims 7 and 26 as discussed above.

Cinar further discloses wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received (Lambda is estimated recursively when data is received; [0086] and [0087]). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper and utilize the autoregressive scheme as described in Cinar including estimating lambda recursively "in order to capture unpredicted glycemic disturbances rapidly and to provide quick response to such conditions" [0087] and thus better predict glucose levels to get a more accurate result for the patient.

Regarding claims 19 and 38, Harper discloses the method and system of claims 1 and 20 as discussed above. Harper fails to expressly disclose wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of suspending insulin delivery, initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, controlling insulin delivery or informaitno associated with the hypoglycemia indicator.

However, Cinar discloses an insulin pump system with added hypoglycemia warning that stops insulin infusion when measured glucose values drop below specified limits [0005]). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper with a pump system like Cinar such that when glucose drops too low, the pump can stop insulin infusion to try to stabilize the patient's glucose better.

9. **Claims 11, 15, 16, 30, 34, and 35 a**re rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper et al.) in view of US Patent Application Publication No. 2011/0184267 (Duke et al.).

Regarding claims 11 and 30, Harper discloses the method and system of claims 1 and 20 as discussed above. Harper fails to expressly disclose wherein the second function comprises a Kalman filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.
However, Duke discloses methods and systems for processing glucose measurements from a person having diabetes wherein a Kalman filter is used to predict future glucose levels over future time based on past sensed data [0048]). Thus the Kalman filter inherently has an at least one input of an estimated rate of change (based on past readings), otherwise future predictions would not be able to be calculated. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper and utilize a Kalman filter to better predict future glucose levels and thus give the patient better and more accurate treatment.

Regarding claims 15, 16, 34, and 35, Harper discloses the method and system of claim 12 as discussed above. Harper fails to expressly disclose wherein the one or more second criteria comprises a second threshold that is adaptively set by the processor

module based on the first threshold or wherein the second function comprises a prediction horizon that is adaptively set by the processor module based on the first threshold.

Duke discloses methods and systems for processing glucose measurements from a person having diabetes wherein a second (critieria), ie. threshold, ie. prediction hypoglycemic threshold, is set based on the first threshold (hypoglycemic threshold) and that is used when determining the prediction horizon (future values over time) [0048]). The thresholds are uniquely determined for each person based on activity. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to set the prediction threshold based on the first or hypoglycemic threshold and wherein the second function comprises a prediction horizon based on the first threshold in order to keep the alarms consistent for the patient.

10. **Claims 13, 14, 32, and 33** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper et al.).

Regarding claims 13 and 32, Harper discloses the method and system of claims 12 and 31, respectively, as discussed above. While Harper discloses the second threshold (rate of change for example; [0134]; [0136]; [0201] - [0203], Harper states that the threshold can may be selected by the user or the healthcare provider and does not explicitly state it is not user settable. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have the rate of change

threshold be not settable by the user and instead be set by only the healthcare provider who programs the device with the most appropriate thresholds for medical safety.

Regarding claims 14 and 33, Harper discloses the method and system of claims 12 and 31, respectively, as discussed above. While Harper discloses the second function comprises a prediction horizon (projected alarm with time horizon for the alarm projection; [0253]), Harper does not explicitly disclose that the prediction horizon is not user settable. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have the prediction horizon be not settable by the user and instead be set by a healthcare provider who programs the device with the most appropriate thresholds for medical safety.

Allowable Subject Matter

11. Claims 9 and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KERRI MCNALLY whose telephone number is

(571)270-1840. The examiner can normally be reached on Tues - Thurs 6:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Bugg can be reached on 571-272-2998. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KERRI MCNALLY/
Primary Examiner, Art Unit 2682

Notice of References Cited	Application/Control No. 13/742,694	Applicant(s)/Patent Under Reexamination COBELLI ET AL.	
	Examiner KERRI MCNALLY	Art Unit 2682	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2011/0193704	08-2011	Harper et al.	340/573.1
*	B	US-2011/0225112	09-2011	Cameron et al.	706/20
*	C	US-2011/0106011	05-2011	Cinar et al.	604/151
*	D	US-2011/0184267	07-2011	Duke et al.	600/365
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

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	S					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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BIB DATA SHEET

CONFIRMATION NO. 6142

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/742,694	01/16/2013	340	2682	DEXCOM.217A

APPLICANTS
DEXCOM, INC., San Diego, CA

INVENTORS
Claudio Cobelli, Padova, ITALY;
Giovanni Sparacino, Padova, ITALY;
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Anna Leigh Rack-Gomer, San Diego, CA;
Chiara Zecchin, Pernumia, ITALY;
Naresh C. Bhavaraju, San Diego, CA;
Apurv Ullas Kamath, San Diego, CA;

**** CONTINUING DATA ***************************
This appln claims benefit of 61/720,286 10/30/2012

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
02/08/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /KERRI L MCNALLY/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		ITALY	18	38	2

ADDRESS
KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614
UNITED STATES

TITLE
SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	**Art Unit**
	KERRI MCNALLY	2682

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/25/2014								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
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	29	✓								
	30	✓								
	31	✓								
	32	✓								
	33	✓								
	34	✓								
	35	✓								
	36	✓								

Abbott Ex. 1002 - 1271/1438

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CLAIM		DATE								
Final	Original	09/25/2014								
	37	✓								
	38	✓								

Abbott Ex. 1002 - 1272/1438

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
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CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
340	539.12	9/24/14	KLM

SEARCH NOTES		
Search Notes	Date	Examiner
PLUS Search	9/25/14	KLM
Inventor name search	9/24/14	KLM
Keyword search - see attached EAST history	9/24/14	KLM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/KERRI MCNALLY/ Primary Examiner.Art Unit 2682

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	~~2684~~ 2682
Examiner Name	~~LEE, Benjamin C.~~ Kerri McNally
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	2	US- 5390671	2/21/1995	Lord et al.	
	3	US- 5568806	10/29/1996	Cheney et al.	
	4	US- 5586553	12/24/1996	Halili et al.	
	5	US- 5680858	10/28/1997	Henrik-Egesborg et al.	
	6	US- 5851197	12/22/1998	Marano et al.	
	7	US- 5971922	10/26/1999	Arita et al.	
	8	US- 5993411	11/30/1999	Choi, Soo Bong	
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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	1	EP 1077634-B1	2003-07-30	Cygnus, Inc.		
	2	EP 1078258-B1	2003-07-30	Cygnus, Inc.		
	3	EP 1102559-B1	2003-06-04	Cygnus, Inc.		
	4	EP 1119637-B1	2004-03-24	Therasense, Inc.		
	5	EP 1144028-B1	2004-06-23	Novo Nordisk A/S		
	6	EP 1437674-B1	2008-08-13	Novo Nordisk A/S		

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

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Sheet 2 of 10

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Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

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	20	US- 6553244	4/22/2003	Lesho et al.	
	21	US- 6558351	5/6/2003	Steil et al.	
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	7	EP 1473050-B1	2009-12-09	Medtronic MiniMed, Inc.		
	8	EP 1503660-B1	2007-01-17	Medtronic Minimed, Inc.		
	9	EP 1518495-B1	2010-03-31	Roche Diagnostics GmbH		
	10	EP 1703839-B1	2012-02-08	Medtronic MiniMed, Inc.		
	11	EP 1706022-B1	2008-10-29	Medtronic MiniMed, Inc.		
	12	EP 1759201-B1	2010-10-13	Medtronic Minimed, Inc.		

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Sheet 3 of 10

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Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	39	US- 7003336	2/21/2006	Holker et al.	
	40	US- 7003341	2/21/2006	Say et al.	
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	47	US- 7282029	10/16/2007	Poulsen et al.	
	48	US- 7299082	11/20/2007	Feldman et al.	
	49	US- 7310544	12/18/2007	Brister et al.	
	50	US- 7318816	1/15/2008	Bobroff et al.	
	51	US- 7343188	3/11/2008	Sohrab, Borzu	
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	55	US- 7399277	7/15/2008	Saidara et al.	
	56	US- 7402153	7/22/2008	Steil et al.	
	57	US- 7494465	2/24/2009	Brister et al.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	13	EP 1890597-B1	2012-02-22	Abbott Diabetes Care, Inc		
	14	EP 1927602-B1	2012-01-11	Abbott Diabetes Care, Inc		
	15	EP 1931253-B1	2012-02-22	Abbott Diabetes Care, Inc		
	16	EP 2051620-B1	2010-04-28	Koninklijke Philips Elect		
	17	EP 2069771-B1	2011-11-02	Abbott Diabetes Care, Inc		
	18	WO 1999/058051	1999-11-18	Cygnus, Inc		

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

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Sheet 4 of 10

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Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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	58	US- 7582059	9/1/2009	Funderburk et al.	
	59	US- 7602310	10/13/2009	Mann et al.	
	60	US- 7618369	11/17/2009	Hayter et al.	
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	70	US- 7697967	4/13/2010	Stafford, Gary Ashley	
	71	US- 7699807	4/20/2010	Faust et al.	
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	73	US- 7729737	6/1/2010	Ward, W. Kenneth	
	74	US- 7731657	6/8/2010	Stafford, Gary Ashley	
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	76	US- 7736310	6/15/2010	Taub, Mark B.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	19	WO 2002/082989	2002-10-24	Abbott Laboratories		
	20	WO 2008/042918	2008-04-10	Dexcom, Inc.		
	21	WO 2009/136372	2009-12-12	Universita Degli Studi Pa		
	22	WO 2011/051922	2011-05-05	Universita Degli Studi di		

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U.S. PATENT DOCUMENTS

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	77	US- 7736338	6/15/2010	Kavazov et al.	
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	79	US- 7740613	6/22/2010	Yokoi et al.	
	80	US- 7744589	6/29/2010	Mounce et al.	
	81	US- 7762793	7/27/2010	Gray et al.	
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Sheet 6 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

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	96	US- 7869853	1/11/2011	Say et al.	
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Sheet 7 of 10

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Application Number	13/742694
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First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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Sheet 8 of 10

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Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

NON PATENT LITERATURE DOCUMENTS			
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	1	Arnold et al., IEEE Transactions on Biomedical Engineering 45(5):553-562 (1998): Adaptive AR Modeling of Nonstationary by Means of Kalman Filtering	
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Sheet 9 of 10

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First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

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Sheet 1 of 2

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First Named Inventor	Cobelli, Claudio
Art Unit	~~2684~~ 2682
Examiner Name	LEE, Benjamin C. Kerri McNally
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 20050033254	2/7/2008	Kamath et al.	
	2	US- 20110193704	8/11/2011	Harper, Wesley Scott	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13742694
Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	Palerm et al., 2007, J. Diabetes Sciences and Technology 1(5):624-629. Hypoglycemia detection and prediction using continuous glucose monitoring - a study on hypoglycemic cl	
	2	Sandham et al., 1998, IX European Signal Processing Conference, 1998, pages 673-676. Blood glucose prediction for diabetes therapy using a recurrent artificial neural network	
	3	Sparacino et al., 2007, IEEE Transactions on Biomedical Engineering 54(5):931-937. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sen	

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

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1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	5	(US-20110193704-$ or US-20090160656-$ or US-20110225112-$ or US-20110106011-$ or US-20110184267-$).did.	US-PGPUB	OR	OFF	2014/09/25 13:45
L2	4	l1 and pump	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 13:45
L3	107	("6287765" "6312907" "20140118138" "20140118166" "6380398" "6441015" "20140100279" "6302838" "6317700" "6448043" "20080015422" "5531991" "7399277" "7824333" "20050038332" "20080255438" "20090036753" "20100324401" "6358678" "6436705" "8275438" "8287453" "8290559" "8298142" "8369919" "8417312" "8423113" "8447376" "8449464" "8478377" "8562528" "8626257" "8778168" "20090084687" "20090131768" "20090131769" "20090131776" "20090131777" "20090137886" "20090137887" "20090143659" "20090156924" "20090178459" "20090182217" "20090192366" "20090192380" "20090192722" "20090192745" "20090192751" "20110004085").pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 14:03
S1	1	(hampapuram.in.) and transition$4.clm. and state.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/16 14:37
S2	1	(bhavaraju.in.) and transition$4.clm. and state.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/16 14:37
S3	4	(kamath.in.) and transition$4.clm. and state.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	OR	OFF	2014/09/16 14:37

Abbott Ex. 1002 - 1286/1438

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S6	2	"20110193704".pn. and alarm$3 with user	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/16 16:21
S7	0	"20110193704".pn. and (alert$3 alarm$3) with normal$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 09:43
S8	0	"20110193704".pn. and (alert$3 alarm$3) with normal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 09:43
S9	1	"20110193704".pn. and (alert$3 alarm$3) same normal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 09:43
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S14	0	"20110193704".pn. and (ceas$4 stop$4) same (insulin meal food)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 10:09
S15	1	"20110193704".pn. and (insulin meal food)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 10:09
S16	1	"20110193704".pn. and (insulin meal food)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 12:58
S17	0	"20110193704".pn. and (implant$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 13:22
S18	1	"20110193704".pn. and (immediat$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 14:21
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S21	1262	"340".clas. and glucose	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 16:34
S22	223	"340".clas. and glucose and acknowledg$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 16:39
S23	85	"340".clas. and glucose and acknowledg$4 and transition	US-PGPUB; USPAT; USOCR;	OR	ON	2014/09/17 16:40

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S24	102	"340".clas. and glucose and transition$3 near3 stat$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 16:41
S25	15	"340".clas. and glucose and monitor$4 near3 after near3 (alert$3 alarm$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 16:42
S26	166	"340".clas. and glucose with continuous$4 near2 monitor$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/17 16:43
S27	6362	340/573.1.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/17 16:46
S28	2551	(g08B21/00.cpc. g08B23/00.cpc.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/18 08:30
S29	11	(g08B21/00.cpc. g08B23/00.cpc.) and glucose	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/18 08:37
S30	10	(g08B21/00.cpc. g08B23/00.cpc.) and analyte	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/18 08:40
S31	376	(glucose) with trend$3 with (alarm$3 alert$3 warn$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/18 08:43
S32	376	(glucose) with trend$3 with (alarm$3	US-PGPUB;	OR	ON	2014/09/18

		alert$3 warn$3)	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			08:43
S33	2	(glucose) with trend$3 near2 toward same trend$3 near3 away same (alarm$3 alert$3 warn$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/18 08:56
S34	2	(glucose) with trend$3 near2 toward same trend$3 near3 away	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/18 08:58
S35	522811	(glucose) near4trend$3 with (alarm$3 alert$3 warn$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/18 08:58
S36	213	(glucose) near4 trend$3 with (alarm$3 alert$3 warn$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/18 08:58
S37	1534	340/539.12.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 12:52
S38	1	Bhavaraju.in. and glucose.clm. and predict$3.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 13:06
S39	53	kamath.in. and glucose.clm. and predict$3.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 13:06
S40	53	kamath.in. and apurv.in. and glucose.clm. and predict$3.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	OR	OFF	2014/09/24 13:06

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S42	2	"20110193704".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 13:40
S43	2	"20110193704".pn. and rate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 15:32
S44	2	"20110193704".pn. and rate same alarm$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 15:33
S45	2	"13742694" and static	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 15:50
S46	0	"20110193704".pn. and (artifical neural)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 15:54
S47	0	"20110193704".pn. and (autoregressive)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 15:54
S48	0	"20110193704".pn. and (regressive)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 15:54
S49	1	"20110193704".pn. and number near3 (alert$3 alarm$3)	US-PGPUB; USPAT; USOCR; FPRS;	OR	OFF	2014/09/24 15:56

			EPO; JPO; DERWENT; IBM_TDB			
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S51	1	"20110193704".pn. and acceptable near3 rate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:06
S52	1	"20110193704".pn. and horizon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:16
S53	1	"20110193704".pn. and pump	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:30
S54	1	"20110193704".pn. and insulin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:35
S55	1	"20110193704".pn. and (delivery pump$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:37
S56	0	"20110193704".pn. and (implant$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:40
S57	1	"20110193704".pn. and (skin)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/24 16:40
S58	24	(predict$3 project$3) near2 glucose same (artificial adj neural)	US-PGPUB; USPAT;	OR	OFF	2014/09/25 08:33

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S60	1	"20110225112".pn. and (exercise stress illness surgery)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 08:36
S61	0	"20110225112".pn. and (autoregressive)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 08:47
S62	10	(predict$3 project$3) near2 glucose same (autoregressive)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/25 08:47
S63	1	"20110106011".pn. and autoregressive	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 09:04
S64	1	"20110106011".pn. and order	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 09:19
S65	2	(predict$3 project$3) near2 glucose same first adj order same (autoregressive)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/25 09:21
S66	0	"20110106011".pn. and alpha	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 09:30

S67	2	"13742694" and alpha	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 09:30
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S70	0	"20110106011".pn. and week	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 09:47
S71	1	"20110106011".pn. and threshold	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 10:04
S72	4	(US-20110193704-$ or US-20090160656-$ or US-20110225112-$ or US-20110106011-$).did.	US-PGPUB	OR	OFF	2014/09/25 10:05
S73	0	S72 and kalman	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 10:05
S74	21	(predict$3 project$3) near2 glucose same Kalman	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/25 10:06
S75	5	(predict$3 project$3) near2 glucose same Kalman same rate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/09/25 10:11
S76	2	"20110193704".pn. and threshold	US-PGPUB; USPAT;	OR	OFF	2014/09/25 10:38

			USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S77	1	"20110193704".pn. and threshold same project$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 10:41
S78	5	(US-20110193704-$ or US-20090160656-$ or US-20110225112-$ or US-20110106011-$ or US-20110184267-$).did.	US-PGPUB	OR	OFF	2014/09/25 10:44
S79	4	S78 and (predict$3 project$3) same threshold	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 10:44
S80	0	S78 and (predict$3 project$3) with threshold near4 (calculat$$ determin$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 10:45
S81	3	S78 and threshold near4 (calculat$$ determin$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/09/25 10:45

EAST Search History (Interference)

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9/ 25/ 2014 2:24:27 PM
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13742694
Filing Date	2013-01-16
First Named Inventor	Cobelli, Claudio
Art Unit	~~2684~~ 2682
Examiner Name	~~LEE, Benjamin C.~~ Kerri McNally
Attorney Docket Number	DEXCOM.217A

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	Bremer et al., Diabetes 48:445-451 (March 1999): Is Blood Glucose Predictable From Previous Values? A Solicitation for Data	

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.M./

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	Claudio Cobelli
App. No.	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	McNally, Kerri L
Art Unit	:	2682
Conf. No.	:	6142

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated October 2, 2014, Applicants respectfully request that the Examiner enter the following amendments and consider the following remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

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AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

2. (Currently Amended) The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

3. (Currently Amended) The method of Claim 2, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

4. (Currently Amended) The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value.

5. (Original) The method of Claim 1, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value.

6. (Original) The method of Claim 1, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

7. (Original) The method of Claim 1, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

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8. (Original) The method of Claim 7, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

9. (Currently Amended) ~~The method of Claim 7~~ A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

10. (Original) The method of Claim 1, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

11. (Original) The method of Claim 1, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

12. (Currently Amended) The method of Claim 1, wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable.

13. (Currently Amended) The method of Claim 12, wherein the one or more non user settable second criteria comprises a second threshold that is not user settable.

14. (Currently Amended) The method of Claim ~~12~~ 1, wherein the one or more non user settable second ~~function~~ criteria comprises a prediction horizon ~~that is not user settable~~.

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15. (Currently Amended) The method of Claim ~~12~~ 1, wherein the one or more non user settable second criteria comprises a second threshold that is adaptively set by ~~the~~ a processor module based on the one or more user settable first ~~threshold~~ criteria.

16. (Currently Amended) The method of Claim ~~12~~ 1, wherein the one or more non user settable second ~~function~~ criteria comprises a prediction horizon that is adaptively set by ~~the~~ a processor module based on the first ~~threshold~~ user settable criteria.

17. (Currently Amended) The method of Claim 1, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

18. (Currently Amended) The method of Claim 1, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

19. (Original) The method of Claim 1, wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

20. (Currently Amended) A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria;

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activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

21. (Currently Amended) The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

22. (Currently Amended) The system of Claim 21, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

23. (Currently Amended) The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value.

24. (Currently Amended) The system of Claim 20, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more non user settable second criteria comprises evaluating a dynamic risk of the predicted glucose value.

25. (Original) The system of Claim 20, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

26. (Original) The system of Claim 20, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

27. (Original) The system of Claim 26, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

28. (Currently Amended) ~~The system of Claim 26~~ A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

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evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone;

activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

29. (Original) The system of Claim 20, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

30. (Original) The system of Claim 20, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

31. (Currently Amended) The system of Claim 20, wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable.

32. (Currently Amended) The system of Claim 31, wherein the one or more non user settable second criteria comprises a second threshold that is not user settable.

33. (Currently Amended) The system of Claim ~~31~~ 20, wherein the one or more non user settable second ~~function~~ criteria comprises a prediction horizon that is not user settable.

34. (Currently Amended) The system of Claim ~~31~~ 20, wherein the one or more non user settable second criteria comprises a second threshold that is adaptively set by ~~the~~ a processor module based on the one or more user settable first ~~threshold~~ criteria.

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35. (Currently Amended) The system of Claim ~~31~~ 20, wherein the one or more non user settable second ~~function~~ criteria comprises a prediction horizon that is adaptively set by the processor module based on the one or more user settable first ~~threshold~~ criteria.

36. (Currently Amended) The system of Claim 20, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

37. (Currently Amended) The system of Claim 20, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

38. (Original) The system of Claim 20, wherein providing output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

39. (New) The method of Claim 1, wherein the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the second criteria.

40. (New) The system of Claim 20, wherein the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the non user settable second criteria.

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REMARKS

Claims 1-38 are currently pending in this application. By this amendment, Claims 1-4, 9, 12-18, 20-24, 28, and 31-37 have been amended and new Claims 39 and 40 have been added. Support for the amendments and new claims is found in the specification and claims as filed. Upon entry of the amendment, Claims 1-40 will be pending and under consideration. Cancellation and/or amendment of certain claims in this response or any other response is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented, and Applicants reserve the ability to pursue the amended claims as filed, the canceled claims or similar claims in one or more continuing applications, e.g., continuation, divisional, or continuation-in-part applications.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 15 and 16 have been rejected as indefinite for lack of antecedent basis of the limitation "the processor module". Claims 15 and 16 have been amended to provide proper antecedent basis all limitations. In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Claim Rejection - 35 U.S.C. § 102(b) - Harper

Claims 1-5, 10, 12, 17, 18, 20-24, 29, 31, 36, and 37 have been rejected under 35 U.S.C. §102(b) as anticipated by US 2011/0193704 ("Harper"). "A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." *See, e.g., In re Paulsen*, 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994).

Claim 1 as amended recites "[a] method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising: evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria; evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria; activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and providing an output based on the activated hypoglycemic indicator." Claim 20 as amended recites "[a] system for processing data, the system comprising: a continuous analyte sensor configured to be implanted within a body; and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor

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configured to: evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria; evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria; activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and provide an output based on the activated hypoglycemic indicator." The remaining rejected claims variously depend from Claim 1 or Claim 20.

Harper does not teach all elements of Applicants' claims, namely, that one or more first criteria are user settable while one or more second criteria are not user settable.

Because Harper does not disclose every element of Applicants' claims, it therefore cannot be considered as an anticipating reference under 35 U.S.C. § 102(b). Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) - Harper, Cameron

Claims 6 and 25 have been rejected under 35 U.S.C. §103(a) as obvious over Harper in view of US 2011/0225112 ("Cameron"). It is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability..." *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the Examiner has established a *prima facie* case of obviousness, the Applicant need not present arguments or evidence of non-obviousness. To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Merely establishing that the claimed elements can be found in the prior art is not sufficient to establish a *prima facie* case of obviousness:

> As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added).

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Instead, the Court has made clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007).

Applicants respectfully submit that the pending claims as amended are not obvious under 35 U.S.C. § 103(a) for the reasons detailed below.

The limitations of Claims 1 and 20, from which the rejected claims depend, are set forth above. As also noted above, Claims 1 and 20 have each been amended to recite the feature that the one or more first criteria are user settable while the one or more second criteria are not user settable. This configuration solves a specific problem in the prior art. For example, the text associated with Figs. 6 and 7 in the specification as filed describes the problem with over alerting in the prior art. Namely, that while the prior art may attempt to provide many options to a user (e.g., a patient or care taker) to allow for alerting at many potentially risky situations (e.g., real time threshold alerts, rate of change alerts and predictive alerts), unfortunately, that same flexibility can easily create nuisance alarms, ultimately causing the user to turn off the alarms (or worse, the entire device) and lose the benefit that they would otherwise gain. The method and system of the present claims address this issue by providing user settable alarms for certain hypoglycemia criteria, but fixed non-user settable alarms for certain other (different) hypoglycemia criteria that provides for greater safety (more true positive alerts) without significantly increasing false alerts that could otherwise cause a user to turn the device or device alerts off altogether.

It is particularly notable that the Office Action (on pages 14-15) asserts an idea that an alarm settable only by a health care provider (if disclosed in the prior art) would not be "user

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settable." However, Applicants respectfully disagree and point to paragraph [0072] of the specification as filed, "… can be configured or customized by ***a user, such as the host or a care provider***…" (emphasis added). Namely, in the specification as filed, the term "user" is broadly construed to include both the host (patient) and care provider (health care provider). Accordingly, even if, assuming arguendo, it were obvious to limit the setting configurability to the health care provider, the claim would still differentiate from such a teaching. Indeed, the idea of the one or more second criteria being "non-user settable" suggests that the criteria may not be determined by anyone other than the manufacturer or programmer of the manufacturer, e.g., at the factory.

Cameron includes no teachings overcoming the deficiencies of Harper.

Because Harper and Cameron in combination do not teach or suggest all limitations as recited in the rejected claims, a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper, Cinar

Claims 7, 8, 19, 26, 27, and 38 have been rejected under 35 U.S.C. §103(a) as obvious over Harper in view of US 2011/0106011 ("Cinar"). The requirements for establishing a *prima facie* case of obviousness are set forth above, as are the limitations of Claims 1 and 20, from which the rejected claims depend, and deficiencies in the teachings of Harper.

As discussed above, Harper fails to teach or suggest each limitation of the pending claims, including but not limited to the feature that the one or more first criteria are user settable while the one or more second criteria are not user settable. Cinar includes no teaching overcoming these deficiencies of Harper.

Because Harper and Cinar in combination do not teach or suggest all limitations as recited in the rejected claims, a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper, Duke

Claims 11, 15, 16, 30, 34, and 35 have been rejected under 35 U.S.C. §103(a) as obvious over Harper in view of US 2011/0184267 ("Duke"). The requirements for establishing a *prima*

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facie case of obviousness are set forth above, as are the limitations of Claims 1 and 20, from which the rejected claims depend, and deficiencies in the teachings of Harper.

As discussed above, Harper fails to teach or suggest each limitation of the pending claims, including but not limited to the feature that the one or more first criteria are user settable while the one or more second criteria are not user settable. Duke includes no teaching overcoming these deficiencies of Harper.

Because Harper and Duke in combination do not teach or suggest all limitations as recited in the rejected claims, a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper

Claims 13, 14, 32, and 33 have been rejected under 35 U.S.C. §103(a) as obvious over Harper. The requirements for establishing a *prima facie* case of obviousness are set forth above, as are the limitations of Claims 1 and 20, from which the rejected claims depend, and deficiencies in the teachings of Harper.

As discussed above, Harper fails to teach or suggest each limitation of the pending claims, including but not limited to the feature that the one or more first criteria are user settable while the one or more second criteria are not user settable.

Because Harper does not teach or suggest all limitations as recited in the rejected claims, a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Allowable Subject Matter

Claims 9 and 28 have been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 9 and 8 have been rewritten in independent form to include some, but not all, limitations of the intervening claims; but are, however, believed to be allowable as amended. Accordingly, Applicant respectfully requests that the objection be withdrawn. Applicants respectfully disagree with the Examiner's statement of reasons for the indication of allowable subject matter to the extent that some claims may not include all of the elements mentioned by the Examiner, and other claims may include elements not mentioned by the Examiner. Also, to the extent that there is any implication that the patentability of the claims

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rests on the recitation of the particular combination of features as stated by the Examiner, Applicants respectfully disagree with the Examiner's Statement because, for each claim, it is the combination of features recited in the claim that makes it patentable. All claims of the present application are patentable because they each recite a combination of features that are not taught or suggested by the prior art.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

Should the Examiner have any concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 2, 2015

By: /Rose M. Thiessen/
Rose M. Thiessen
Registration No. 40,202
Attorney of Record
Customer No. 68851
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19642569 010215

Abbott Ex. 1002 - 1310/1438

Electronic Patent Application Fee Transmittal

Application Number:	13742694
Filing Date:	16-Jan-2013
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	2	80	160
Independent claims in excess of 3	1201	1	420	420
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**580**

Electronic Acknowledgement Receipt

EFS ID:	21110260
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Rose M. Thiessen/Kealani Aguon
Filer Authorized By:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	02-JAN-2015
Filing Date:	16-JAN-2013
Time Stamp:	20:13:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	2975
Deposit Account	111410
Authorized User	KNOBBE MARTENS OLSON AND BEAR

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		DEXCOM217AAMEND.pdf	77122 a7bb2c5d39d206ad7d70bed589b047fbefc7f3b3	yes	13

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	7
	Applicant Arguments/Remarks Made in an Amendment	8	13

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30653 c8d62bf4d13ba01ef9dd8378732b0a5db8511781	no	2

Warnings:

Information:

Total Files Size (in bytes):	107775

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/742,694	Filing Date 01/16/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

01/02/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 40	Minus	** 38	= 2	X $80 =	160
Independent (37 CFR 1.16(h))	* 4	Minus	***3	= 1	X $420 =	420
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**580**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/ERIC DANTZLER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 20090160656	6/25/2009	Seetharaman et al.	
		US-			
		US-			
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		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	13742694
Filing Date:	16-Jan-2013
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Laura Jeanette Johnson/Renee Zavala
Attorney Docket Number:	DEXCOM.217A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	21122194
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Laura Jeanette Johnson/Renee Zavala
Filer Authorized By:	Laura Jeanette Johnson
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	05-JAN-2015
Filing Date:	16-JAN-2013
Time Stamp:	17:24:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	4095
Deposit Account	506176
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2015-0105-SupplDS-217A.pdf	178433 05193e53bae8934932c4f30d63c685765d89f0e6	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	3

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30743 396ce5f99d57b1e80c5d9e6daf315be24ae6807d	no	2

Warnings:

Information:

Total Files Size (in bytes):	209176

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. DEXCOM.217A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Claudio Cobelli et al.
App. No	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	McNALLY, Kerri L.
Art Unit	:	2682
Conf #	:	6142

CERTIFICATE OF TRANSMITTAL UNDER 37 C.F.R. 1.8

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being filed electronically via EFS-Web at the United States Patent and Trademark Office on the date indicated.

By: Renee Zavala

Date: January 05, 2015

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Submitted herewith in the above-identified application is an Information Disclosure Statement listing references for consideration. In accordance with 37 C.F.R. §1.98(a)(2)(ii), Applicant submits herewith copies of all cited references, other than copies of U.S. patents or U.S. patent publications.

It is respectfully requested that the Examiner initial and return a copy of the enclosed Form PTO/SB/08, and indicate in the official file wrapper oaf this patent application that the documents listed therein have been considered.

This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance.

Applicant believes a fee of $180.00 is due under 37 C.F.R. §1.17(p), and the Commissioner is hereby authorized to charge that amount to Deposit Account No. 506176, referencing Applicant Docket No. DEXCOM. 217A. Further, the Commissioner is hereby

authorized to charge all fees and credit all overpayments to Deposit Account No. 506176 during the pendency of this application

Respectfully submitted,
DEXCOM, INC.

Dated: 1/5/15

By: _____
Laura J. Johnson, PTO Reg. No. 48,208

Customer Number 68851
DEXCOM, INC.
6340 Sequence Drive
San Diego, CA 92121
Telephone: 858.875.9786

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	Claudio Cobelli
App. No.	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	McNally, Kerri L.
Art Unit	:	2682
Conf. No.	:	6142

SUPPLEMENTAL AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated October 2, 2014, and supplemental to the Amendment filed January 2, 2015, Applicants respectfully request that the Examiner enter the following amendments and consider the following remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Summary of Interview begins on page 9 of this paper.

Remarks/Arguments begin on page 10 of this paper.

Abbott Ex. 1002 - 1323/1438

AMENDMENTS TO THE CLAIMS

1. (Previously Presented) A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

2. (Previously Presented) The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

3. (Previously Presented) The method of Claim 2, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

4. (Previously Presented) The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value.

5. (Original) The method of Claim 1, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value.

6. (Original) The method of Claim 1, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

7. (Original) The method of Claim 1, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

Abbott Ex. 1002 - 1324/1438

8. (Original) The method of Claim 7, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

9. (Previously Presented) A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

10. (Original) The method of Claim 1, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

11. (Original) The method of Claim 1, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

12. (Previously Presented) The method of Claim 1, wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable.

13. (Previously Presented) The method of Claim 12, wherein the one or more non user settable second criteria comprises a second threshold that is not user settable.

14. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria comprises a prediction horizon.

Abbott Ex. 1002 - 1325/1438

15. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria comprises a second threshold that is adaptively set by a processor module based on the one or more user settable first criteria.

16. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria comprises a prediction horizon that is adaptively set by a processor module based on the first user settable criteria.

17. (Previously Presented) The method of Claim 1, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

18. (Previously Presented) The method of Claim 1, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

19. (Original) The method of Claim 1, wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

20. (Previously Presented) A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

Abbott Ex. 1002 - 1326/1438

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria;

activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

21. (Previously Presented) The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

22. (Previously Presented) The system of Claim 21, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

23. (Previously Presented) The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value.

24. (Previously Presented) The system of Claim 20, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more non user settable second criteria comprises evaluating a dynamic risk of the predicted glucose value.

25. (Original) The system of Claim 20, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

26. (Original) The system of Claim 20, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

27. (Original) The system of Claim 26, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

Abbott Ex. 1002 - 1327/1438

28. (Previously Presented) A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone;

activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

29. (Original) The system of Claim 20, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

30. (Original) The system of Claim 20, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

31. (Previously Presented) The system of Claim 20, wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable.

32. (Previously Presented) The system of Claim 31, wherein the one or more non user settable second criteria comprises a second threshold that is not user settable.

Abbott Ex. 1002 - 1328/1438

33. (Previously Presented) The system of Claim 20, wherein the one or more non user settable second criteria comprises a prediction horizon that is not user settable.

34. (Previously Presented) The system of Claim 20, wherein the one or non user settable second criteria comprises a second threshold that is adaptively set by a processor module based on the one or more user settable first criteria.

35. (Previously Presented) The system of Claim 20, wherein the one or more non user settable second criteria comprises a prediction horizon that is adaptively set by the processor module based on the one or more user settable first criteria.

36. (Previously Presented) The system of Claim 20, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

37. (Previously Presented) The system of Claim 20, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

38. (Original) The system of Claim 20, wherein providing output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

39. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the second criteria.

40. (Previously Presented) The system of Claim 20, wherein the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the non user settable second criteria.

Abbott Ex. 1002 - 1329/1438

41. (New) The method of claim 1, wherein the user is a host or a healthcare provider.

42. (New) The system of claim 20, wherein the user is a host or a healthcare provider.

43. (New) The method of claim 1, wherein the second function provides no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone.

44. (New) The system of 20, wherein the second function provides no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone.

45. (New) The method of claim 1, wherein evaluating the sensor data using the first function and the second function provides increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

46. (New) The system of claim 20, wherein the evaluation of the sensor data using the first function and the second function provides increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluation of the sensor data using the first function without evaluation of the sensor data using the second function.

Abbott Ex. 1002 - 1330/1438

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

The telephonic interview was conducted on January 8, 2015 and attended by Examiner Kerri L. McNally and Applicants' representative Laura Johnson.

Exhibits and/or Demonstrations

None.

Identification of Claims Discussed

Claims 1, 9, and 39.

Identification of Prior Art Discussed

US 2011/0193704 ("Harper"); US 2011/0225112 ("Cameron"); US 2011/0106011 ("Cinar"); US 2011/0184267 ("Duke").

Proposed Amendments, Principal Arguments and Other Matters

The differences between the claims as presented in the January 2, 2015 amendment and the prior art of record were discussed.

Results of Interview

Agreement was not reached.

Abbott Ex. 1002 - 1331/1438

REMARKS

Claims 1-40 are currently pending in this application. By this amendment, new Claims 41-46 have been added. Support for the new claims is found in the specification and claims as filed. Upon entry of the amendment, Claims 1-46 will be pending and under consideration. Cancellation and/or amendment of certain claims in this response or any other response is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented, and Applicants reserve the ability to pursue the amended claims as filed, the canceled claims or similar claims in one or more continuing applications, e.g., continuation, divisional, or continuation-in-part applications.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

Should the Examiner have any concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Abbott Ex. 1002 - 1332/1438

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 9, 2015

By: /Rose M. Thiessen/
Rose M. Thiessen
Registration No. 40,202
Attorney of Record
Customer No. 68851
(858) 707-4000

19699264
010915

Abbott Ex. 1002 - 1333/1438

Electronic Patent Application Fee Transmittal

Application Number:	13742694
Filing Date:	16-Jan-2013
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	6	80	480
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	21176056
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Rose M. Thiessen/Daniela Lopez
Filer Authorized By:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	09-JAN-2015
Filing Date:	16-JAN-2013
Time Stamp:	20:43:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$480
RAM confirmation Number	6068
Deposit Account	111410
Authorized User	KNOBBE MARTENS OLSON AND BEAR

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		217a.pdf	53098 1f6b89d5a307524a960331764000222967971d39	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	8
	Applicant summary of interview with examiner	9	9
	Applicant Arguments/Remarks Made in an Amendment	10	11

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30749 35ed7a12c1bbc8748b0c4385d471386ec536ecc5	no	2

Warnings:

Information:

Total Files Size (in bytes):	83847

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/742,694	Filing Date 01/16/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)		
	01/09/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 46	Minus	** 40	= 6	X $80 =	480
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**480**

		(Column 1)		(Column 2)	(Column 3)		
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/LASHAWN MARKS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

68851 7590 01/13/2015

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
MCNALLY, KERRI L	

ART UNIT	PAPER NUMBER
2682	

NOTIFICATION DATE	DELIVERY MODE
01/13/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jayna.cartee@knobbe.com
efiling@knobbe.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/742,694	COBELLI ET AL.	
	Examiner	Art Unit	
	KERRI MCNALLY	2682	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KERRI MCNALLY*. (3)_____.

(2) *LAURA JOHNSON*. (4)_____.

Date of Interview: *08 January 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☒102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1, 9, and 39*.

Identification of prior art discussed: *Harper (2011/0193704)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Claim amendments made to claims 1, 9, and 39 were discussed. In claim 1, the term "user" was discussed on how it should be interpreted. No agreement was reached as to whether claim 1 as amended would overcome Harper because further consideration is needed. Claim 9 appears to be rewritten to take the allowable subject matter. Claim 39 is a new claim that requires search and/or consideration before a determination can be made about it. Examiner said an updated search would be required. No agreements as to the claims were made..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/KERRI MCNALLY/ Primary Examiner, Art Unit 2682	

Abbott Ex. 1002 - 1340/1438

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

68851 7590 01/28/2015

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
MCNALLY, KERRI L

ART UNIT	PAPER NUMBER
2682	

NOTIFICATION DATE	DELIVERY MODE
01/28/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jayna.cartee@knobbe.com
efiling@knobbe.com

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/742,694	COBELLI ET AL.	
	Examiner	Art Unit	
	KERRI MCNALLY	2682	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KERRI MCNALLY*. (3)_____.

(2) *LAURA JOHNSON*. (4)_____.

Date of Interview: *16 January 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☒102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-46*.

Identification of prior art discussed: *US 2014/0012511 Mensinger*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

After reviewing the amendment filed 1/9/15 and doing an updated search, Examiner telephoned Ms. Johnson to discuss her finding of new prior art (Mensinger) and indicate which claims were allowable. Exmainer suggested moving the allowable subject matter into the independent claims in order to expedite prosecution of the case to allowance. Ms. Johnson thanked Examiner for the telephone call, but could not agree to said changes and instead asked Examiner to send the Office action. The telephone call ended with no agreement reached as to the claims .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/KERRI MCNALLY/ Primary Examiner, Art Unit 2682	

Abbott Ex. 1002 - 1343/1438

Office Action Summary	Application No. 13/742,694	Applicant(s) COBELLI ET AL.	
	Examiner KERRI MCNALLY	Art Unit 2682	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/9/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-46* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☒ Claim(s) *9 and 28* is/are allowed.

7)☒ Claim(s) *1-8, 10-27, 29-42, 45, 46* is/are rejected.

8)☒ Claim(s) *43 and 44* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

Abbott Ex. 1002 - 1344/1438

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of the Claims

1. Claims 1-46 are currently pending.

Examiner's Note

2. Examiner telephoned Applicant's representative, Laura Johnson, on 1/16/15 in order to try to expedite prosecution in the case, including indicating allowable subject matter in the case. However, no agreement was reached.

Response to Arguments

3. Applicant's arguments, see page 8, filed 1/2/15, with respect to 112, second paragraph rejections have been fully considered and are persuasive. The previous rejections of claims 15 and 16 under 112 second paragraph have been withdrawn.

4. Applicant's arguments, see pages 8 and 9, filed 1/2/15, with respect to the rejection(s) of claim(s) 1-5, 10, 12, 17, 18, 20-24, 29, 31, 36, 37 under 102(b) Harper have been fully considered and are persuasive due to Applicant's amendment of the claims. Therefore, the rejection has been withdrawn. However, upon further

consideration, a new ground(s) of rejection is made in view of 102(e) Mensinger, and also 103(a) Harper in view of Botvinick.

5. Applicant's arguments, see pages 9-11, filed 1/2/15, with respect to the rejection(s) of claim(s) 6 and 25 under 103(a) have been fully considered and are persuasive due to Applicant's amendment of the claims. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 103(a) Mensinger in view of Cameron; and also 103(a) Harper in view of Botvinick and Cameron.

6. Applicant's arguments, see page 11, filed 1/2/15, with respect to the rejection(s) of claim(s) 7, 8, 19, 26, 27, 38 under 103(a) have been fully considered and are persuasive due to Applicant's amendment of the claims. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 103(a) Mensinger in view of Cinar; and also 103(a) Harper in view of Botvinick and Cinar.

7. Applicant's arguments, see pages 11 and 12, filed 1/2/15, with respect to the rejection(s) of claim(s) 11, 15, 16, 30, 34, and 35 under 103(a) have been fully considered and are persuasive due to Applicant's amendment of the claims. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 103(a) Mensinger in view of Duke; and also 103(a) Harper in view of Botvinick and Duke.

8. Applicant's arguments, see page 12, filed 1/2/15, with respect to the rejection(s) of claim(s) 13, 14, 32, and 33 under 103(a) have been fully considered and are persuasive due to Applicant's amendment of the claims. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 102(e) Mensinger; and also 103(a) Harper in view of Botvinick.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. **Claims 1-5, 10, 12-14, 17-24, 29, 31-33, 36-38, 41, 42, 45, and 46** are rejected under pre-AIA 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 2014/0012511 (Mensinger et al.) (priority to Provisional application No. 61/669,574, filed on Jul. 9, 2012).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under pre-AIA 35 U.S.C. 102(e). This rejection under pre-AIA 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not

claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131(a).

Regarding claim 1, Mensinger discloses a method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

Evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria (threshold alert; see [0170]; [0177]; PROVISIONAL [0172] and [0179]);

Evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria (predictive algorithm to predict future glucose values; [0170]; PROVISIONAL [0172]);

Activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met (alerts for a threshold alert or a predictive alert, including hypoglycemia; [0170; 0177]; PROVISIONAL [0172] and [0179]); and

Providing an output based on the activated hypoglycemic indicator (such as an alert to a smart phone display; ([0177]; PROVISIONAL [0179]).

Regarding claim 2, Mensinger further discloses wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold ([0177]; PROVISIONAL [0179]).

Regarding claim 3, Mensinger further discloses wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion (rate of change is calculated and sent to the CGM module for display – if the user's blood glucose is dropping, the CGM module outputs this information by orienting the arrow downward; [0190]; PROVISIONAL [0192]).

Regarding claim 4, Mensinger further discloses wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value ([0160]; [0177]; [0178]; PROVISIONAL [0162]; [0179]; [0180]).

Regarding claim 5, Mensinger further discloses wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value (predictive algorithm determines severity (risk) of the predicted glucose value and alerts based on it, i.e. the more severe the predicted glucose value, the higher the risk and thus the alert is emphasized to accentuate the seriousness of the predicted glucose state; [0174]; PROVISINAL [0176]).

Regarding claim 10, Mensinger further discloses wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function ([0170]; PROVISIONAL [0172]).

Regarding claim 12, Mensinger further discloses wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable ([0170]; [0177]; PROVISIONAL [0172] and [0179]).

Regarding claim 13, Mensinger further discloses wherein the one or more non user settable second criteria comprises a second threshold that is not user settable (([0170]; [0177]; PROVISIONAL [0172] and [0179]).

Regarding claim 14, Mensinger further discloses wherein the one or more non user settable second criteria comprises a prediction horizon ([0170]; [0177]; PROVISIONAL [0172] and [0179]).

Regarding claim 17, Mensinger further discloses wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was

activated based on the second function meeting the one or more non user settable second criteria (the display alert generated is different based on whether the real time glucose threshold is exceeded versus the predicted threshold; and thus there are different instructions depending on whether the first criteria or the second criteria were met; [0174]; [0178]; PROVISIONAL [0176]; [0178]).

Regarding claim 18, Mensinger further discloses wherein the output comprises at least one of an audible, tactile, or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria (outputs are on the display (visual); and the display alert generated is different based on whether the real time glucose threshold is exceeded versus the predicted threshold; [0174]; [0178]; PROVISIONAL [0176]; [0178]).

Regarding claim 19, Mensinger further discloses wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: suspending insulin delivery, initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, controlling insulin delivery or information associated with the hypoglycemia indicator (a low glucose suspend feature suspending insulin

delivery responsive to sensor data meeting a predetermined criterion; [0085]; PROVISIONAL [0085]).

Regarding claim 20, Mensinger discloses a system for processing data, the system comprising:

A continuous analyte sensor configured to be implanted within a body [0145] PROVISIONAL [0147]); and

Sensor electronics configured to receive and process sensor data output by the sensor (Fig. 1; PROVISIONAL Fig. 1), the sensor electronics including a processor configured to:

Evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria (threshold alert; see [0170]; [0177]; PROVISIONAL [0172] and [0179]);

Evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria (predictive algorithm to predict future glucose values; [0170]; PROVISIONAL [0172]);

Activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non settable second criteria are met (alerts for a threshold alert or a predictive alert, including hypoglycemia; [0170; 0177]; PROVISIONAL [0172] and [0179]); and

Provide an output based on the activated hypoglycemic indicator (such as an alert to a smart phone display; ([0177]; PROVISIONAL [0179]).

Regarding claim 21, see above discussion for claim 2.

Regarding claim 22, see above discussion for claim 3.

Regarding claim 23, see above discussion for claim 4.

Regarding claim 24, see above discussion for claim 5.

Regarding claim 29, see above discussion for claim 10.

Regarding claim 31, see above discussion for claim 12.

Regarding claim 32, see above discussion for claim 13.

Regarding claim 33, see above discussion for claim 14.

Regarding claim 36, see above discussion for claim 17.

Regarding claim 37, see above discussion for claim 18.

Regarding claim 38, see above discussion for claim 19.

Regarding claims 41 and 42, Mensinger further discloses the user is a host or a healthcare provider (user can be a host (host's the CGM; Fig 1); PROVISIONAL FIG. 1).

Regarding claim 45 and 46, see above discussion for claim 10.

Claim Rejections - 35 USC § 103

11. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. **Claims 6 and 25** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2014/0012511 (Mensinger et al.) (priority to Provisional application No. 61/669,574, filed on Jul. 9, 2012) in view of US Patent Application Publication No. 2011/0225112 (Cameron et al.).

Regarding claims 6 and 25, Mensinger discloses the method and system of claims 1 and 20 as discussed above. Mensinger fails to expressly disclose the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness, or surgery to determine the predicted glucose value.

However, Cameron discusses using a neural network to predict glucose values ([0247] - [0257]) and analyzing data such as stress levels and activity when determining the future predicted glucose values [0300] and [0301]. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Mensginer and utilize a neural network with as much data as possible when predicting future glucose levels in order to get a more accurate result for the patient. Furthermore, the use of neural networks to determine a predicted future value is old and well known in the prior art, as evidenced by Cameron.

13. **Claims 7, 8, 26, and 27** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2014/0012511 (Mensinger et al.) (priority to Provisional application No. 61/669,574, filed on Jul. 9, 2012) in view of US Patent Application Publication No. 2011/0106011 (Cinar et al.).

Regarding claims 7 and 26, Mensinger discloses the method and system of claims 1 and 20 as discussed above. Mensinger fails to expressly disclose the second function utilizes a first order autoregressive model to determine the predicted glucose value.

However, Cinar discloses an automatic insulin pump system using autoregressive moving-average models, including low order and first order autoregressive models [0079] and [0097]. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Mensinger and utilize a first order autoregressive model to better predict glucose levels and to get a more accurate result for the patient. Furthermore, as evidenced by Cinar, the use of autoregressive models is old and well known in the prior art for predicting future values and the selection of which order of autoregressive model could be easily selected or chosen by one of ordinary skill in the art depending on the specific purpose or desired result.

Regarding claims 8 and 27, Mensinger and Cinar disclose the method and system of claims 7 and 26 as discussed above.

Cinar further discloses wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received (Lambda is estimated recursively when data is received; [0086] and [0087]). Therefore, it would have been obvious to one of ordinary skill in the art at the

time the invention was made to modify Mensinger and utilize the autoregressive scheme as described in Cinar including estimating lambda recursively "in order to capture unpredicted glycemic disturbances rapidly and to provide quick response to such conditions" [0087] and thus better predict glucose levels to get a more accurate result for the patient.

14. **Claims 11, 15, 16, 30, 34, and 35** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2014/0012511 (Mensinger et al.) (priority to Provisional application No. 61/669,574, filed on Jul. 9, 2012) in view of US Patent Application Publication No. 2011/0184267 (Duke et al.).

Regarding claims 11 and 30, Mensinger discloses the method and system of claims 1 and 20 as discussed above. Mensinger fails to expressly disclose the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

However, Duke discloses methods and systems for processing glucose measurements from a person having diabetes wherein a Kalman filter is used to predict future glucose levels over future time based on past sensed data [0048]). Thus the Kalman filter inherently has an at least one input of an estimated rate of change (based on past readings), otherwise future predictions would not be able to be calculated. Therefore, it would have been obvious to one of ordinary skill in the art at the time the

invention was made to modify Mensinger and utilize a Kalman filter to better predict future glucose levels and thus give the patient better and more accurate treatment.

Regarding claims 15, 16, 34, and 35, Mensinger discloses the method and system of claims 1 and 20 as discussed above. Mensinger fails to expressly disclose wherein the one or more second criteria comprises a second threshold that is adaptively set by the processor module based on the one or more user settable first criteria or wherein the second function comprises a prediction horizon that is adaptively set by the processor module based on the first user settable criteria.

Duke discloses methods and systems for processing glucose measurements from a person having diabetes wherein a second (critieria), ie. threshold, ie. prediction hypoglycemic threshold, is set based on the first threshold (hypoglycemic threshold) and that is used when determining the prediction horizon (future values over time) [0048]). The thresholds are uniquely determined for each person based on activity. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to set the prediction threshold based on the first or hypoglycemic threshold and wherein the second function comprises a prediction horizon based on the first threshold in order to keep the alarms consistent for the patient.

15. **Claims 39 and 40** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2014/0012511 (Mensinger et

al.) (priority to Provisional application No. 61/669,574, filed on Jul. 9, 2012) in view of US Patent Application Publication No. 2005/0177035 (Botvinick et al.).

Regarding claims 39 and 40, Mensinger discloses the method and system of claims 1 and 20 as discussed above. Mensinger discloses above that the second criteria are fixed and thus no user is able to modify the non user settable second criteria. Mensinger fails to expressly disclose the one or more non user settable second criteria are programmed at the factory.

However, Botvinick discloses an implantable biosensor wherein glucose concentration rates can be factory set [0060]). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Mensinger with this feature of Botvinick such that the second criteria and threshold are programmed at the factory such that all devices coming out of the factory are consistent for the second threshold in order to better serve all patients and have a uniform criteria for predicting glucose values.

16. **Claims 1-5, 10, 12-14, 17, 18, 20-24, 29, 31-33, 36, 37, 39-42, 45, and 46** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper) in view of US Patent Application Publication No. 2005/0177035 (Botvinick et al.).

Regarding claims 1, 13, 32, and 39, Harper discloses a method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first user settable criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more second criteria are met; and

providing an output based on the activated hypoglycemic indicator

(display for an analyte monitoring device wherein user may select varying glucose threshold levels at which various alarms will sound for low glucose levels or projected low glucose levels [0201] - [0203]).

Harper fails to disclose that the second criteria is non user settable and that the second criteria comprises a second threshold that is not user settable.

Furthermore, Harper fails to expressly disclose the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the second criteria.

However, Botvinick discloses an implantable biosensor wherein glucose concentration rates can be factory set (threshold) (and thus are not set by user) [0060]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper with this feature of Botvinick such that the second criteria and threshold are programmed at the factory such that all devices coming out of the factory are consistent for the second threshold in order to better serve all patients safety and have a uniform criteria for predicting glucose values, while at the same time allowing the user some flexibility still with the first criteria and threshold.

Regarding claims 2 and 21, Harper further discloses the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria comprises determining whether the real-time glucose value passes a glucose threshold (Abstract; [0201] - [0203]).

Regarding claims 3 and 22, Harper further discloses wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion (amplitude of rate of change and direction of rate of change [0134]).

Regarding claims 4 and 23, Harper further discloses wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more first criteria comprises evaluating a static risk of a substantially real time glucose value (current glucose measurement is compared to a threshold level in order to

determine if glucose is low or not - low glucose threshold level a static or fixed number [0201] – [0203]).

Regarding claims 5 and 24, Harper further discloses wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value (historical values or moving average, for example; [0134]; [0201] – [0203]).

Regarding claims 10, 45, and 46, Harper further discloses wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function (harper discloses not only detected low glucose but projected low glucose, which allows for increased warning time before low glucose; [0201] - [0203]; furthermore the user can customize the alerts, including the timing and frequency [0201]).

Regarding claims 12 and 31, Harper further discloses wherein the one or more first criteria comprises a first threshold that is configured to be user settable [0202]).

Regarding claims 14 and 33, Harper in combination with Botvinick above in claim 1 discloses the second criteria is non user settable (see above discussion for claim 1).

Harper further discloses the second function comprises a prediction horizon (projected alarm with time horizon for the alarm projection; [0253]),

Regarding claims 17 and 36, Harper further discloses wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria (each of the specific thresholds or alarms can be customized with different alarm settings, for example, low glucose can be customized with a different tone, timing, volume, vibration, than a projected low glucose alarm; [0198] - [0203]).

Regarding claims 18 and 37, Harper further discloses wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more second criteria (each of the specific thresholds or alarms can be customized with different alarm settings, for example, low glucose can be customized with a different tone, timing, volume, vibration, than a projected low glucose alarm; [0198] - [0203]). Please note that the user settable and non user settable limitations were addressed with regards to claim 1.

Regarding claim 20, Harper discloses a system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body (Abstract; [0052]); and sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more second criteria;

activate a hypoglycemic indicator if either the one or more first criteria or the one or more second criteria are met; and

provide an output based on the activated hypoglycemic indicator (display for an analyte monitoring device wherein user may select varying glucose threshold levels at which various alarms will sound for low glucose levels or projected low glucose levels [0201] - [0203]).

Harper fails to disclose that the second criteria is non user settable and that the second criteria comprises a second threshold that is not user settable.

However, Botvinick discloses an implantable biosensor wherein glucose concentration rates can be factory set (threshold) [0060]). Therefore, it would have

been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper with this feature of Botvinick such that the second criteria and threshold are programmed at the factory such that all devices coming out of the factory are consistent for the second threshold in order to better serve all patients safety and have a uniform criteria for predicting glucose values, while at the same time allowing the user some flexibility still with the first criteria and threshold.

Regarding claim 29, Harper further discloses wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function (Harper discloses not only detected low glucose but projected low glucose, which allows for increased warning time before low glucose; [0201] - [0203]; furthermore the user can customize the alerts, including the timing and frequency [0201]).

Regarding claim 40, see above discussion for claim 39.

Regarding claims 41 and 42, Harper further discloses the user is a host or a healthcare provider (user is a host of the analyte sensor; [0052]).

17. **Claims 6 and 25** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper et al.) as modified by US Patent Application Publication No. 2005/0177035 (Botvinick et al.) and further in view of US Patent Application Publication No. 2011/0225112 (Cameron et al.).

Regarding claims 6 and 25, Harper and Botvinick disclose the system and method of claims 1 and 20, respectively, as discussed above. Harper fails to expressly disclose wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness, or surgery to determine the predicted glucose value.

However, Cameron discusses using a neural network to predict glucose values ([0247] - [0257]) and analyzing data such as stress levels and activity when determining the future predicted glucose values [0300] and [0301]. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper as combined with Botvinick and utilize a neural network with as much data as possible when predicting future glucose levels in order to get a more accurate result for the patient. Furthermore, the use of neural networks to determine a predicted future value is old and well known in the prior art, as evidenced by Cameron.

18. **Claims 7, 8, 19, 26, 27, and 38** are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper

et al.) as modified by US Patent Application Publication No. 2005/0177035 (Botvinick et al.) and further in view of US Patent Application Publication No. 2011/0106011 (Cinar et al.).

Regarding claims 7 and 26, Harper and Botvinick disclose the method and system of claims 1 and 20, respectively, as discussed above. Harper fails to expressly disclose the second function utilizes a first order autoregressive model to determine the predicted glucose value.

However, Cinar discloses an automatic insulin pump system using autoregressive moving-average models, including low order and first order autoregressive models [0079] and [0097]. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper as combined with Botvinick and utilize a first order autoregressive model to better predict glucose levels and to get a more accurate result for the patient. Furthermore, as evidenced by Cinar, the use of autoregressive models is old and well known in the prior art for predicting future values and the selection of which order of autoregressive model could be easily selected or chosen by one of ordinary skill in the art depending on the specific purpose or desired result.

Regarding claims 8 and 27, Harper, Botvinick, and Cinar disclose the method and system of claims 7 and 26 as discussed above.

Cinar further discloses wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received (Lambda is estimated recursively when data is received; [0086] and [0087]). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper as combined with Botvinick and utilize the autoregressive scheme as described in Cinar including estimating lambda recursively "in order to capture unpredicted glycemic disturbances rapidly and to provide quick response to such conditions" [0087] and thus better predict glucose levels to get a more accurate result for the patient.

Regarding claims 19 and 38, Harper and Botvinick disclose the method and system of claims 1 and 20 as discussed above. Harper fails to expressly disclose wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of suspending insulin delivery, initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, controlling insulin delivery or information associated with the hypoglycemia indicator.
However, Cinar discloses an insulin pump system with added hypoglycemia warning that stops insulin infusion when measured glucose values drop below specified limits [0005]). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper as combined with Botvinick with a pump system like Cinar such that when glucose drops too low, the pump can stop insulin infusion to try to stabilize the patient's glucose better.

19. **Claims 11, 15, 16, 30, 34, and 35 a**re rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2011/0193704 (Harper et al.) as modified by US Patent Application Publication No. 2005/0177035 (Botvinick et al.) and further in view of US Patent Application Publication No. 2011/0184267 (Duke et al.).

Regarding claims 11 and 30, Harper and Botvinick disclose the method and system of claims 1 and 20 as discussed above. Harper fails to expressly disclose wherein the second function comprises a Kalman filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.
However, Duke discloses methods and systems for processing glucose measurements from a person having diabetes wherein a Kalman filter is used to predict future glucose levels over future time based on past sensed data [0048]). Thus the Kalman filter inherently has an at least one input of an estimated rate of change (based on past readings), otherwise future predictions would not be able to be calculated. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Harper as combined with Botvinick and utilize a Kalman filter to better predict future glucose levels and thus give the patient better and more accurate treatment.

Regarding claims 15, 16, 34, and 35, Harper and Botvinick disclose the method and system of claim 1 as discussed above. Harper fails to expressly disclose wherein the one or more second criteria comprises a second threshold that is adaptively set by the processor module based on the first threshold or wherein the second function comprises a prediction horizon that is adaptively set by the processor module based on the first threshold.

Duke discloses methods and systems for processing glucose measurements from a person having diabetes wherein a second (critieria), ie. threshold, ie. prediction hypoglycemic threshold, is set based on the first threshold (hypoglycemic threshold) and that is used when determining the prediction horizon (future values over time) [0048]). The thresholds are uniquely determined for each person based on activity. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to set the prediction threshold based on the first or hypoglycemic threshold and wherein the second function comprises a prediction horizon based on the first threshold in order to keep the alarms consistent for the patient.

Allowable Subject Matter

20. **Claims 9 and 28** are allowed.

21. **Claims 43 and 44** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

22. This Office action is NON-FINAL.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KERRI MCNALLY whose telephone number is (571)270-1840. The examiner can normally be reached on Mon-Fri 6 am - 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Bugg can be reached on 571-272-2998. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KERRI MCNALLY/
Primary Examiner, Art Unit 2682

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/742,694	COBELLI ET AL.	
	Examiner	Art Unit	
	KERRI MCNALLY	2682	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KERRI MCNALLY*. (3)_____.

(2) *LAURA JOHNSON*. (4)_____.

Date of Interview: *16 January 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☒102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-46*.

Identification of prior art discussed: *US 2014/0012511 Mensinger*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

After reviewing the amendment filed 1/9/15 and doing an updated search, Examiner telephoned Ms. Johnson to discuss her finding of new prior art (Mensinger) and indicate which claims were allowable. Exmainer suggested moving the allowable subject matter into the independent claims in order to expedite prosecution of the case to allowance. Ms. Johnson thanked Examiner for the telephone call, but could not agree to said changes and instead asked Examiner to send the Office action. The telephone call ended with no agreement reached as to the claims .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/KERRI MCNALLY/ Primary Examiner, Art Unit 2682	

Abbott Ex. 1002 - 1372/1438

Notice of References Cited	Application/Control No. 13/742,694	Applicant(s)/Patent Under Reexamination COBELLI ET AL.	
	Examiner KERRI MCNALLY	Art Unit 2682	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2014/0012511	01-2014	Mensinger et al.	702/19
*	B	US-2005/0177035	08-2005	Botvinick et al.	600/347
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Abbott Ex. 1002 - 1373/1438

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	**Art Unit**
	KERRI MCNALLY	2682

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/25/2014	01/21/2015							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	O	=							
	10	✓	✓							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							
	15	✓	✓							
	16	✓	✓							
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	24	✓	✓							
	25	✓	✓							
	26	✓	✓							
	27	✓	✓							
	28	O	=							
	29	✓	✓							
	30	✓	✓							
	31	✓	✓							
	32	✓	✓							
	33	✓	✓							
	34	✓	✓							
	35	✓	✓							
	36	✓	✓							

Abbott Ex. 1002 - 1374/1438

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	**Art Unit**
	KERRI MCNALLY	2682

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/25/2014	01/21/2015							
	37	✓	✓							
	38	✓	✓							
	39		✓							
	40		✓							
	41		✓							
	42		✓							
	43		O							
	44		O							
	45		✓							
	46		✓							

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1010	A61B5/0004.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/21 16:31
S85	2	"20110193704".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:27
S86	0	"20110193704".pn. and factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:33
S87	5	(US-20110193704-$ or US-20090160656-$ or US-20110225112-$ or US-20110106011-$ or US-20110184267-$).did.	US-PGPUB	OR	OFF	2015/01/15 08:33
S88	0	S87 and non adj (set settable setting programmable)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:34
S89	5	340/539.12.ccls. and non adj (set settable setting programmable)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:34
S90	0	340/539.12.ccls. and non adj (set settable setting)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:35
S91	50	glucose and non adj (set settable setting)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:37
S92	0	"340".clas. and glucose and non adj (set settable setting)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:38
S93	23	"340".clas. and glucose and non adj (chang$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:38

Abbott Ex. 1002 - 1376/1438

S94	23	"340".clas. and glucose and non adj (chang$4 changeable)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:38
S95	0	"340".clas. and glucose and threshold with non adj (chang$4 changeable)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:39
S96	0	"340".clas. and glucose and threshold with non adj (settable set$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 08:46
S97	2	"20090160656".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:50
S98	1	"20090160656".pn. and (set settable)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:51
S99	0	"20090160656".pn. and (factory)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:53
S100	1	"20090160656".pn. and (second)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:54
S101	1	"20090160656".pn. and (set settable) same (range threshold)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 08:54
S102	0	"340".clas. and analyte and threshold with non adj (settable set$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 08:57
S103	0	"340".clas. and analyte and threshold with non adj (chang$4 changeable)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 08:57
S104	0	"13742694" and non adj user	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 09:03
S105	2	"13742694"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 09:03

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S106	2	"13742694" and set$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 09:03
S107	42	"340".clas. and (glucose analyte) and threshold near5 (fixed factory)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:05
S108	0	"340".clas. and predict$3 near3 glucose near5 (fixed factory)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:11
S109	5	predict$3 near3 glucose near5 (fixed factory)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:11
S110	1	"20140012511".pn. and threshold with alert	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 09:26
S111	1	"20140012511".pn. and threshold with alert	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:26
S112	0	"20140012511".pn. and autoregressive	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:29
S113	1	"20140012511".pn. and week	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:29
S114	0	"20140012511".pn. and factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:34
S115	1	"20140012511".pn. and fixed	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:34
S116	4	"13801445"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 09:36
S117	0	"20140012511".pn. and increas$4 near3 warn$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:37

Abbott Ex. 1002 - 1378/1438

S118	1	"20140012511".pn. and increas$4 near3 time	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/15 09:37
S119	3	"20140012511"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/15 12:50
S120	3	"20140012511".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/20 06:50
S121	1	"20140012511".pn. and static	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/20 14:28
S122	1	"20140012511".pn. and real	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/20 14:31
S123	0	"20140012511".pn. and neural	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/20 14:36
S124	0	"20140012511".pn. and artificial	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/20 14:36
S125	0	"20140012511".pn. and artificial	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:36
S126	1	"20140012511".pn. and model	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:36
S127	1	"20140012511".pn. and dynamic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:37
S128	1	"20140012511".pn. and predict$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:40
S129	0	"20140012511".pn. and autoregressive	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:46

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S130	0	"20140012511".pn. and Kalman	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:50
S131	1	"20140012511".pn. and filter	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 14:50
S132	1	"20140012511".pn. and threshold with (adapt$4 adaptively adjust$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 15:06
S133	1	"20140012511".pn. and horizon with (adapt$4 adaptively adjust$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 15:09
S134	0	"20140012511".pn. and flag	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 15:11
S135	3	"20140012511".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 15:27
S136	24644	"20140012511".pn. insulin with (delivery pump)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 15:51
S137	1	"20140012511".pn. and insulin with (delivery pump)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 15:52
S138	0	"20140012511".pn. and suspending$3 near3 insulin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 16:01
S139	0	"20140012511".pn. and suspending$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 16:01
S140	1	"20140012511".pn. and minimiz$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 16:02
S141	1	"20140012511".pn. and control$4 near3 insulin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 16:03

S142	1	"20140012511".pn. and hypoglycem$3 with (insulin pump)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/20 16:03
S143	3	"20140012511".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/21 07:45
S144	2	"20140012511".pn. and (hypoglycem$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/21 07:47
S145	1	"20140012511".pn. and (implant$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:00
S146	3	"20140012511".pn. and (output$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:09
S147	0	"20140012511".pn. and (factory)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:26
S148	3	"20140012511".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:26
S149	2	"20140012511".pn. and (host healthcare provider)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:28
S150	1	"20140012511".pn. and (user)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:33
S151	1	"20140012511".pn. and (user) with (host doctor healthcare)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 08:35
S152	2	"20110184627".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/21 09:12
S153	2	"20110184267".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/21 09:13

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S154	799	"340".clas. and program$4 near3 factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 09:35
S155	28	"340".clas. and threshold with program$4 near3 factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 09:35
S156	0	(glucose analyte) with threshold with program$4 near3 factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 09:38
S157	0	(glucose analyte) with threshold with set$4 near5 factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 09:38
S158	24	(glucose analyte) with (program$4 set$4) near5 factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/01/21 09:38
S159	2	"20050177035".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/01/21 10:45

EAST Search History (Interference)

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1/21/2015 4:40:08 PM
C:\Users\kmcnally\Documents\EAST\Workspaces\13742694.wsp

Abbott Ex. 1002 - 1382/1438

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	~~2684~~ 2682
Examiner Name	~~LEE, Benjamin C.~~ Kerri McNally
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 20090160656	6/25/2009	Seetharaman et al.	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/Kerri Mcnally/	Date Considered	01/15/2015

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.M./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	Art Unit
	KERRI MCNALLY	2682

CPC- SEARCHED		
Symbol	Date	Examiner
A61B 5/0004	1/21/15	KLM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
340	539.12	9/24/14	KLM

SEARCH NOTES		
Search Notes	Date	Examiner
PLUS Search	9/25/14	KLM
Inventor name search	9/24/14	KLM
Keyword search - see attached EAST history	9/24/14	KLM
Inventor name search	1/16/15	KLM
Keyword search - see attached EAST history	1/16/15	KLM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/KERRI MCNALLY/ Primary Examiner.Art Unit 2682

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	Claudio Cobelli
App. No.	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	McNally, Kerri L.
Art Unit	:	2682
Conf. No.	:	6142

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated January 28, 2015, Applicants respectfully request that the Examiner enter the following amendments and consider the following remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Summary of Interview begins on page 9 of this paper.

Remarks/Arguments begin on page 10 of this paper.

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AMENDMENTS TO THE CLAIMS

1. (Previously Presented) A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

2. (Previously Presented) The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

3. (Previously Presented) The method of Claim 2, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

4. (Previously Presented) The method of Claim 1, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value.

5. (Original) The method of Claim 1, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more second criteria comprises evaluating a dynamic risk of the predicted glucose value.

6. (Original) The method of Claim 1, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

7. (Original) The method of Claim 1, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

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8. (Original) The method of Claim 7, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

9. (Previously Presented) A method of activating a hypoglycemic indicator based on continuous glucose sensor data, the method comprising:

evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluating sensor data using a second function to determine whether a predicted glucose value meets one or more non user settable second criteria, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone;

activating a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

providing an output based on the activated hypoglycemic indicator.

10. (Original) The method of Claim 1, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

11. (Original) The method of Claim 1, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

12. (Previously Presented) The method of Claim 1, wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable.

13. (Previously Presented) The method of Claim 12, wherein the one or more non user settable second criteria comprises a second threshold that is not user settable.

14. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria comprises a prediction horizon.

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15. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria comprises a second threshold that is adaptively set by a processor module based on the one or more user settable first criteria.

16. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria comprises a prediction horizon that is adaptively set by a processor module based on the first user settable criteria.

17. (Previously Presented) The method of Claim 1, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

18. (Previously Presented) The method of Claim 1, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

19. (Original) The method of Claim 1, wherein providing an output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

20. (Previously Presented) A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

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evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria;

activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

21. (Previously Presented) The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria comprises determining whether the real-time glucose value passes a glucose threshold.

22. (Previously Presented) The system of Claim 21, wherein the evaluating sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria further comprises determining whether an amplitude of rate of change or direction of rate of change meets a rate of change criterion.

23. (Previously Presented) The system of Claim 20, wherein the evaluating sensor data using a first function to determine whether the real time glucose value meets one or more user settable first criteria comprises evaluating a static risk of a substantially real time glucose value.

24. (Previously Presented) The system of Claim 20, wherein the evaluating sensor data using a second function to determine whether the predicted glucose value meets one or more non user settable second criteria comprises evaluating a dynamic risk of the predicted glucose value.

25. (Original) The system of Claim 20, wherein the second function comprises an artificial neural network model that uses at least one of exercise, stress, illness or surgery to determine the predicted glucose value.

26. (Original) The system of Claim 20, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value.

27. (Original) The system of Claim 26, wherein the first order autoregressive model comprises a parameter alpha, and wherein alpha is estimated recursively each time a sensor data points is received.

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28. (Previously Presented) A system for processing data, the system comprising:

a continuous analyte sensor configured to be implanted within a body; and

sensor electronics configured to receive and process sensor data output by the sensor, the sensor electronics including a processor configured to:

evaluate sensor data using a first function to determine whether a real time glucose value meets one or more user settable first criteria;

evaluate sensor data using a second function to determine whether a predicted glucose value meets one or more non-user settable second criteria, wherein the second function utilizes a first order autoregressive model to determine the predicted glucose value, wherein the first order autoregressive model comprises a forgetting factor, a prediction horizon and a prediction threshold tuned to provide no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone;

activate a hypoglycemic indicator if either the one or more user settable first criteria or the one or more non user settable second criteria are met; and

provide an output based on the activated hypoglycemic indicator.

29. (Original) The system of Claim 20, wherein evaluating the sensor data using the first function and the second function allows for increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

30. (Original) The system of Claim 20, wherein the second function comprises a Kalman Filter to determine the predicted glucose value using as an input an estimate of the rate of change of the blood glucose.

31. (Previously Presented) The system of Claim 20, wherein the one or more user settable first criteria comprises a first threshold that is configured to be user settable.

32. (Previously Presented) The system of Claim 31, wherein the one or more non user settable second criteria comprises a second threshold that is not user settable.

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33. (Previously Presented) The system of Claim 20, wherein the one or more non user settable second criteria comprises a prediction horizon that is not user settable.

34. (Previously Presented) The system of Claim 20, wherein the one or non user settable second criteria comprises a second threshold that is adaptively set by a processor module based on the one or more user settable first criteria.

35. (Previously Presented) The system of Claim 20, wherein the one or more non user settable second criteria comprises a prediction horizon that is adaptively set by the processor module based on the one or more user settable first criteria.

36. (Previously Presented) The system of Claim 20, wherein the hypoglycemic indicator comprises a flag that has a particular set of instructions associated with it depending on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

37. (Previously Presented) The system of Claim 20, wherein the output comprises at least one of an audible, tactile or visual output, and wherein the output is differentiated and/or provides information selectively based on whether the hypoglycemic indicator was activated based on the first function meeting the one or more user settable first criteria or whether the hypoglycemic indicator was activated based on the second function meeting the one or more non user settable second criteria.

38. (Original) The system of Claim 20, wherein providing output comprises transmitting a message to an insulin delivery device including instructions associated with at least one of: a) suspending insulin delivery, b) initiating a hypoglycemia and/or hyperglycemia minimizer algorithm, c) controlling insulin delivery or d) information associated with the hypoglycemia indicator.

39. (Previously Presented) The method of Claim 1, wherein the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the second criteria.

40. (Previously Presented) The system of Claim 20, wherein the one or more non user settable second criteria are programmed at the factory in such a way that no user is able to modify the non user settable second criteria.

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41. (Previously Presented) The method of claim 1, wherein the user is a host or a healthcare provider.

42. (Previously Presented) The system of claim 20, wherein the user is a host or a healthcare provider.

43. (Previously Presented) The method of claim 1, wherein the second function provides no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone.

44. (Previously Presented) The system of 20, wherein the second function provides no more than one additional alarm per week based on a retrospective analysis comparing the use of the first function and the second function together as compared to the first function alone.

45. (Previously Presented) The method of claim 1, wherein evaluating the sensor data using the first function and the second function provides increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluating the sensor data using the first function without evaluating the sensor data using the second function.

46. (Previously Presented) The system of claim 20, wherein the evaluation of the sensor data using the first function and the second function provides increased warning time of hypoglycemic alerts without substantially increasing the number of alerts as compared to evaluation of the sensor data using the first function without evaluation of the sensor data using the second function.

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SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

The telephonic interview was conducted on January 16, 2015 and attended by Examiner Kerri L. McNally and Applicants' representative Laura Johnson.

Exhibits and/or Demonstrations

None.

Identification of Claims Discussed

Claims 1-46.

Identification of Prior Art Discussed

US 2014/0012511 ("Mensinger '511").

Proposed Amendments, Principal Arguments and Other Matters

After reviewing the amendment filed January 9, 2015 and doing an updated search, Examiner telephoned Ms. Johnson to discuss her finding of new prior art (Mensinger) and indicate which claims were allowable. Examiner suggested moving the allowable subject matter into the independent claims in order to expedite prosecution of the case to allowance. Ms. Johnson thanked Examiner for the telephone call, but could not agree to the changes and instead asked Examiner to send the Office Action.

Results of Interview

Agreement was not reached.

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REMARKS

Claims 1-46 are currently pending in this application.

Claim Rejection - 35 U.S.C. § 102(e) - Mensinger

Claims 1-5, 10, 12-14, 17-24, 29, 31-33, 36-38, 41, 42, 45, and 46 have been rejected under pre-AIA 35 U.S.C. §102(e) as anticipated by US 2014/0012511 ("Mensinger '511").

As discussed below, Applicants' declaration establishes that Mensinger '511 is not prior art to the present application.

Enclosed herein is the Declaration under 37 CFR §1.132 of Anna Leigh Rack-Gomer and Apurv Ullas Kamath. The disclosure in paragraph [0170] of Mensinger '511 (and in paragraph [0177] of U.S. Provisional Application No. 61/669574 filed July 9, 2012, to which Mensinger '511 claims priority) is clearly taken directly from the Information Disclosure Form IDF581 dated October 31, 2011 as referred to in the Declaration. The Information Disclosure Form IDF581 names Anna Leigh Rack-Gomer and Apurv Kamath as inventors of the disclosed subject matter. Anna Leigh Rack-Gomer and Apurv Kamath contributed to the overlapping subject matter of both Mensinger '511 and the instant patent application. The derivation of the disclosure of paragraph [0170] of Mensinger '511 from the disclosure in IDF581 is clearly seen.

The inventorship of the present application as filed is correct in that the overlapping subject matter was derived from Anna Leigh Rack-Gomer and Apurv Ullas Kamath, rather than invented by the other inventors on Mensinger '511. The inventorship of Mensinger '511 as filed is correct in that the overlapping subject matter derived from Anna Leigh Rack-Gomer and Apurv Ullas Kamath was not claimed in Mensinger '511. Anna Leigh Rack-Gomer contributed to other subject matter as claimed in Mensinger '511, and is properly named as co-inventor of that Mensinger '511.

Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Mensinger '511 and Cameron

Claims 6 and 25 have been rejected under 35 U.S.C. §103(a) as obvious over Mensinger '511 in view of US 2011/0225112 ("Cameron"). To articulate a *prima facie* case of obviousness under 35 U.S.C. §103(a), the PTO must, *inter alia*, cite prior art that teaches or suggests all the claimed limitations. *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974).

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As discussed above, submitted herewith is the Declaration under 37 CFR §1.132 of Anna Leigh Rack-Gomer and Apurv Ullas Kamath, which removes Mensinger '511 as prior art from the present application. The remaining reference, Cameron, alone fails to teach or suggest all limitations of the pending claims, such that a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Mensinger '511 and Cinar

Claims 7, 8, 26, and 27 have been rejected under 35 U.S.C. §103(a) as obvious over Mensinger '511 in view of US 2011/0106011 ("Cinar"). To articulate a *prima facie* case of obviousness under 35 U.S.C. §103(a), the PTO must, *inter alia*, cite prior art that teaches or suggests all the claimed limitations. *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974).

As discussed above, submitted herewith is the Declaration under 37 CFR §1.132 of Anna Leigh Rack-Gomer and Apurv Ullas Kamath, which removes Mensinger '511 as prior art from the present application. The remaining reference, Cinar, alone fails to teach or suggest all limitations of the pending claims, such that a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Mensinger '511 and Duke

Claims 11, 15, 16, 30, 34, and 35 have been rejected under 35 U.S.C. §103(a) as obvious over Mensinger '511 in view of US 2011/0184267 ("Duke"). To articulate a *prima facie* case of obviousness under 35 U.S.C. §103(a), the PTO must, *inter alia*, cite prior art that teaches or suggests all the claimed limitations. *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974).

As discussed above, submitted herewith is the Declaration under 37 CFR §1.132 of Anna Leigh Rack-Gomer and Apurv Ullas Kamath, which removes Mensinger '511 as prior art from the present application. The remaining reference, Duke, alone fails to teach or suggest all limitations of the pending claims, such that a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Mensinger '511 and Botvinick

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Claims 39 and 40 have been rejected under 35 U.S.C. §103(a) as obvious over Mensinger '511 in view of US 2005/0177035 ("Botvinick"). To articulate a *prima facie* case of obviousness under 35 U.S.C. §103(a), the PTO must, *inter alia*, cite prior art that teaches or suggests all the claimed limitations. *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974).

As discussed above, submitted herewith is the Declaration under 37 CFR §1.132 of Anna Leigh Rack-Gomer and Apurv Ullas Kamath, which removes Mensinger '511 as prior art from the present application. The remaining reference, Botvinick, alone fails to teach or suggest all limitations of the pending claims, such that a *prima facie* case of obviousness cannot be established. Accordingly, and for at least this reason, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper and Botvinick

Claims 1-5, 10, 12-14, 17, 18, 20-24, 29, 31-33, 36, 37, 39-42, 45, and 46 have been rejected under 35 U.S.C. §103(a) as obvious over US 2011/0193704 ("Harper") in view of Botvinick. It is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability…" *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the Examiner has established a *prima facie* case of obviousness, the Applicant need not present arguments or evidence of non-obviousness. To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Merely establishing that the claimed elements can be found in the prior art is not sufficient to establish a *prima facie* case of obviousness:

> As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added).

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Instead, the Court has made clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007).

Applicants respectfully submit that the pending claims as amended are not obvious under 35 U.S.C. § 103(a) for the reasons detailed below.

The limitations of the pending claims are set forth above. Harper discloses glucose alarms with user settable criteria, and neither discloses nor suggests an evaluation of whether a predicted glucose value meets one or more non user settable criteria. Botvinick et al teach that patients can be alerted by the sensor if their blood glucose falls below factory or user set concentrations. Unfortunately, Botvinick lacks: 1) a teaching of an evaluation of whether a predicted glucose value meets one or more non user settable criteria; and 2) a teaching that factory set concentrations are non user settable. For example, many devices come with factory settings, or defaults, but that does not necessary disclose, suggest or fairly imply the non-user settable feature as claimed.

Additionally, Applicants respectfully submit that the combination of Harper in view of Botvinick is improper because the Office Action relies on information gleaned solely from Applicant's specification. MPEP § 2142 states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art". "'Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only

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from applicant's disclosure, such a reconstruction is proper'" (MPEP § 2145(X)(A), quoting *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

In the present case, the Office Action relies on the reasoning that "the second criteria and threshold are programmed at the factory are consistent for the second threshold in order to better serve all patients safety and have a uniform criteria for predicting glucose values, while at the same time allowing the user some flexibility still with the first criteria and threshold" to allegedly support the combination of Harper in view of Botvinick. This reasoning is not only inconsistent with the teachings of Harper, which is replete with discussion of the apparent value of user settable criteria, but any such reasoning is absent from the cited art and is only present throughout Applicant's specification in paragraphs, for example, paragraphs [0006], [0090], [0097], and [0109]. Due to the lack of consistency with teachings in the cited art and the fact that reasoning for the non-user settable feature as claimed is only present on the record in Applicant's specification, it logically follows that Examiner's reasoning has been improperly gleaned from Applicants' own specification and that the combination of Harper in view of Botvinick is an exercise of impermissible hindsight. It is therefore respectfully submitted that the combination is improper.

Accordingly, and for at least these reasons, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper, Botvinick, and Cameron

Claims 6 and 25 have been rejected under 35 U.S.C. §103(a) as obvious over Harper and Botvinick in view of US 2011/0225112 ("Cameron"). The criteria for establishing a prima facie case of obviousness are set forth above, as are the limitations of the rejected claims and certain deficiencies in the teachings of Harper and Botvinick. Cameron includes no teachings overcoming these deficiencies. Cameron is cited merely for teachings related to neural networks. Accordingly, a *prima facie* case of obviousness cannot be established, and Applicants therefore respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper, Botvinick, and Cinar

Claims 7, 8, 26, and 27 have been rejected under 35 U.S.C. §103(a) as obvious over Mensinger '511 in view of US 2011/0106011 ("Cinar"). The criteria for establishing a prima facie case of obviousness are set forth above, as are the limitations of the rejected claims and certain

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deficiencies in the teachings of Harper and Botvinick. Cinar includes no teachings overcoming these deficiencies. Cinar is cited merely for teachings related to automatic insulin pumps. Accordingly, a *prima facie* case of obviousness cannot be established, and Applicants therefore respectfully request that the rejection be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) – Harper, Botvinick, and Duke

Claims 11, 15, 16, 30, 34, and 35 have been rejected under 35 U.S.C. §103(a) as obvious over Mensinger '511 in view of US 2011/0184267 ("Duke"). The criteria for establishing a prima facie case of obviousness are set forth above, as are the limitations of the rejected claims and certain deficiencies in the teachings of Harper and Botvinick. Duke includes no teachings overcoming these deficiencies. Duke is cited merely for teachings related to Kalman filters. Accordingly, a *prima facie* case of obviousness cannot be established, and Applicants therefore respectfully request that the rejection be withdrawn.

Allowed or Allowable Subject Matter

Claims 9 and 28 have been allowed. Claims 43 and 44 have been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

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Should the Examiner have any concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 23, 2015

By: /Rose M. Thiessen/
Rose M. Thiessen
Registration No. 40,202
Attorney of Record
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	Claudio Cobelli
App. No.	:	13/742694
Filed	:	January 16, 2013
For	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Examiner	:	McNally, Kerri L.
Art Unit	:	2682
Conf. No.	:	6142

DECLARATION UNDER 37 CFR §1.132 OF

ANNA LEIGH RACK-GOMER AND APURV ULLAS KAMATH

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Anna Leigh Rack-Gomer and Apurv Ullas Kamath declare as follows:

1. We, Anna Leigh Rack-Gomer and Apurv Ullas Kamath, are citizens of the United States residing in San Diego, CA.

2. We believe that we are the original, first and joint inventors with Naresh C. Bhavaraju, Hari Hampapuram, Claudio Cobelli, Andrea Facchinetti, Giovanni Sparacino, and Chiara Zecchin, of the subject matter which is claimed and for which a patent is sought on the invention entitled "SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS"; the specification of which was filed on January 16, 2013 as Application Serial No. 13/742694.

Abbott Ex. 1002 - 1401/1438

3. I, Anna Leigh Rack-Gomer, am a co-inventor on U. S. Appl. No. 13/802424 filed March 13, 2013 entitled "SYSTEMS AND METHODS FOR LEVERAGING SMARTPHONE FEATURES IN CONTINUOUS GLUCOSE MONITORING", which published as US 2014/0012511 ("Mensinger '511").

4. The disclosure in paragraph [0170] of Mensinger '511 (and in paragraph [0177] of U.S. Provisional Application No. 61/669574 filed July 9, 2012, to which Mensinger '511 claims priority) is clearly taken directly from the Information Disclosure Form IDF581 dated October 31, 2011, a copy of which is attached hereto. The Information Disclosure Form IDF581 names Anna Leigh Rack-Gomer and Apurv Kamath as inventors of the disclosed subject matter. We, Anna Leigh Rack-Gomer and Apurv Kamath, contributed to the overlapping subject matter of Mensinger '511 and the instant patent application. The derivation of the disclosure of paragraph [0170] of Mensinger '511 from the disclosure in IDF581 is clearly seen. Accordingly, we hereby state that the portions of Mensinger '511 relevant to the present application originated with or were obtained from us and not from any other inventor on Mensinger '511.

5. The inventorship of the present application as filed is correct in that the overlapping subject matter was derived from us, Anna Leigh Rack-Gomer and Apurv Ullas Kamath, rather than invented by the other inventors on Mensinger '511.

6. The inventorship of Mensinger '511 as filed is correct in that the overlapping subject matter derived from us, Anna Leigh Rack-Gomer and Apurv Ullas Kamath, was not claimed in Mensinger '511. I, Anna Leigh Rack-Gomer, contributed to other subject matter as claimed in Mensinger '511.

7. We acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

Abbott Ex. 1002 - 1402/1438

8. The undersigned Applicants declare further that all the statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 4/23/15

Anna Leigh Rack-Gomer

Dated: 4/23/15

Apurv Ullas Kamath

Abbott Ex. 1002 - 1403/1438

DEXCOM, INC.

INVENTION DISCLOSURE FORM
(FOR PATENT PURPOSES ONLY)
Attach Additional Sheets as Necessary

Disclosure No.: 581
Date: [redacted]

1. **INVENTOR NAME(S):**
Anna Leigh Rack-Gomer
Apurv Kamath

2. **DESCRIPTIVE TITLE OF THE INVENTION**:
Fixed Parameter Predictive Alerts

3. **KEY WORDS:**
Hypoglycemia, prediction, alerts, hyperglycemia, low glucose suspend, fixed parameters

4. **DETAILED DESCRIPTION AND OPERATION OF THE INVENTION**:
In this invention, a prediction algorithm will be used to predict future glucose values. The parameters of the prediction algorithm, such as prediction horizon and alert threshold, will be fixed rather than user settable options. This predictive alert will be used in conjunction with a threshold alert (user can still set the threshold value for this alert) with the goal of providing patients with sufficient warning time (>10 min) to avoid a hypo event (defined as a glucose value below 55 mg/dl) without generating an excessive number of additional alarms. This prediction scheme can also be used to generate alerts for hyperglycemia and determine when to shut off insulin in a low glucose suspend type of device.

5. **WHAT ADVANTAGES ARE GAINED OR PROBLEMS SOLVED BY USE OF THE INVENTION?**
Threshold alerts are useful in shortening the duration of hypoglycemia and if set high enough they can also help prevent the occurrence of hypoglycemia as well. However, there are some instances when glucose is dropping rapidly that a threshold alert will give patients very little or no warming time at all before they drop below 55 mg/dl. Using a predictive alert will give patients more time to deal with the impending hypo event in these cases. The advantage of using fixed parameters for predictive alerts is that it makes the feature very easy to use, as patients have only to turn it off or on. In addition, we can define the parameters in a way that leads to very few additional nuisance alarms, which can cause the patient to not want to use the feature.

[redacted]

Disclosure No.: _____

[redacted]

Insert Inventor Name [redacted] Date

Insert Inventor Name [redacted] Date

Insert Inventor Name Date

Insert Inventor Name Date

Read, Witnessed and Understood by:

Insert Witness Signature [redacted] Date

Insert Witness Signature [redacted] Date

Electronic Acknowledgement Receipt

EFS ID:	22154989
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Rose M. Thiessen/Tony Do
Filer Authorized By:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	23-APR-2015
Filing Date:	16-JAN-2013
Time Stamp:	20:01:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		DEXCOM_217A_Amend.pdf	724512 97a90153c5fc3f1c1ee309d119a53558d42785c3	yes	16

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	8
	Applicant summary of interview with examiner	9	9
	Applicant Arguments/Remarks Made in an Amendment	10	16

Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	DEXCOM_217A_Declaration.pdf	346569 e9b0a339c5a8ff2b8b506387248bf52e598d62a7	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	1071081		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/742,694	Filing Date 01/16/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT	04/23/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 46	Minus	** 46	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/NICOLE NICHOLSON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

68851 7590 05/04/2015

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
MCNALLY, KERRI L

ART UNIT	PAPER NUMBER
2682	

DATE MAILED: 05/04/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

TITLE OF INVENTION: SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	08/04/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Abbott Ex. 1002 - 1409/1438

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

68851 7590 05/04/2015

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

TITLE OF INVENTION: SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	08/04/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
MCNALLY, KERRI L	2682	340-539120

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Abbott Ex. 1002 - 1410/1438

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

68851 7590 05/04/2015

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
MCNALLY, KERRI L	

ART UNIT	PAPER NUMBER
2682	

DATE MAILED: 05/04/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Abbott Ex. 1002 - 1411/1438

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/742,694	Applicant(s) COBELLI ET AL.	
	Examiner KERRI MCNALLY	Art Unit 2682	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *4/23/15*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-46*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KERRI MCNALLY/
Primary Examiner, Art Unit 2682

The present application is being examined under the pre-AIA first to invent provisions.

REASONS FOR ALLOWANCE

1. The declaration under 37 CFR 1.132 filed 4/23/15 is sufficient to overcome the rejection of claims 1-8, 10-27, 29-42, 45, and 46 based upon US 2014/0012511 (Mensinger et al.).

2. Applicants' arguments filed 4/23/15 that Botvinick fails to disclose “non-user settable” criteria is persuasive and therefore, the previous rejection of claims 1-8, 10-27, 29-42, 45, and 46 that utilize the Botvinick reference are withdrawn.

3. None of the prior art teaches, alone or in reasonable combination with other references, the claimed limitations as discussed in claims 1-46.

4. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KERRI MCNALLY whose telephone number is (571)270-1840. The examiner can normally be reached on Mon-Thurs 6 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Bugg can be reached on 571-272-2998. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KERRI MCNALLY/
Primary Examiner, Art Unit 2682

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	**Art Unit**
	KERRI MCNALLY	2682

CPC							
Symbol						**Type**	**Version**
A61B		5	/	0004		F	2013-01-01
A61B		5	/	746		I	2013-01-01
A61B		5	/	14532		I	2013-01-01
A61B		5	/	7275		I	2013-01-01
A61B		5	/	002		A	2013-01-01
A61B		5	/	0022		A	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 46	
/KERRI MCNALLY/ Primary Examiner.Art Unit 2682	04/28/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	3B

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	**Art Unit**
	KERRI MCNALLY	2682

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
340	539.12	G	0	8	B	1 / 08 (2006.01.01)	G	0	8	B	1 / 08 (2006.01.01)

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
340	573.1				

NONE		Total Claims Allowed: 46	
(Assistant Examiner)	(Date)		
/KERRI MCNALLY/ Primary Examiner.Art Unit 2682	04/28/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	3B

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	**Art Unit**
	KERRI MCNALLY	2682

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	16	17	36	33										
2	2	17	18	37	34										
3	3	18	19	38	35										
4	4	24	20	39	36										
5	5	25	21	40	37										
6	6	26	22	41	38										
7	7	27	23	19	39										
8	8	28	24	42	40										
23	9	29	25	20	41										
9	10	30	26	43	42										
10	11	31	27	21	43										
11	12	46	28	44	44										
12	13	32	29	22	45										
13	14	33	30	45	46										
14	15	34	31												
15	16	35	32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 46	
/KERRI MCNALLY/ Primary Examiner.Art Unit 2682 (Primary Examiner)	04/28/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 3B

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3	"20140012511".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/04/28 11:41
L2	2	"20050177035".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/04/28 12:43
L3	6859	340/573.1.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/04/28 13:18
L5	13	(g08B21/00.cpc. g08B23/00.cpc.) and glucose	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/04/28 14:05
L9	1758	340/539.12.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/04/28 14:28
L10	24	(glucose analyte) with (program$4 set$4) near5 factory	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/04/28 14:30
L11	55	(glucose analyte) with (program$4 set$4) near5 non near2 sett$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/04/28 14:31

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	3515	340/573.1.ccls.	USPAT; UPAD	OR	OFF	2015/04/28 13:18
L6	3	(g08B21/00.cpc. g08B23/00.cpc.) and glucose	USPAT; UPAD	OR	OFF	2015/04/28 14:05
L7	126	A61B5/0004.cpc.	USPAT; UPAD	OR	OFF	2015/04/28 14:13
L8	830	340/539.12.ccls.	USPAT; UPAD	OR	OFF	2015/04/28 14:14

4/28/2015 2:32:21 PM
C:\Users\kmcnally\Documents\EAST\Workspaces\13742694.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13742694	COBELLI ET AL.
	Examiner	Art Unit
	KERRI MCNALLY	2682

CPC- SEARCHED		
Symbol	Date	Examiner
A61B 5/0004	1/21/15	KLM
A61B 5/0004	4/28/15	KLM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
340	539.12	9/24/14	KLM
340	573.1, 539.12	4/28/15	KLM

SEARCH NOTES		
Search Notes	Date	Examiner
PLUS Search	9/25/14	KLM
Inventor name search	9/24/14	KLM
Keyword search - see attached EAST history	9/24/14	KLM
Inventor name search	1/16/15	KLM
Keyword search - see attached EAST history	1/16/15	KLM
Inventor name search	4/28/15	KLM
Keyword search - see attached EAST history	4/28/15	KLM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
340	573.1,539.12	4/28/15	KLM
PG PUB	Text Search	4/28/15	KLM
A61B	5/0004	4/28/15	KLM

	/KERRI MCNALLY/ Primary Examiner.Art Unit 2682

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

68851 7590 05/04/2015
KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	01/16/2013	Claudio Cobelli	DEXCOM.217A	6142

TITLE OF INVENTION: SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	08/04/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
MCNALLY, KERRI L	2682	340-539120

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Knobbe Martens
2 Olson & Bear, LLP
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: DexCom, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Diego, California

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge ~~the required fee(s),~~ any deficiency, or credits any overpayment, to Deposit Account Number 11-1410 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date July 29, 2015

Typed or printed name Rose M. Thiessen Registration No. 40,202

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Abbott Ex. 1002 - 1421/1438

Electronic Patent Application Fee Transmittal

Application Number:	13742694
Filing Date:	16-Jan-2013
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Rose M. Thiessen/Gisele Metcalf
Attorney Docket Number:	DEXCOM.217A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	23060720
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Rose M. Thiessen/Melanie Neat
Filer Authorized By:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	29-JUL-2015
Filing Date:	16-JAN-2013
Time Stamp:	18:10:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	4810
Deposit Account	111410
Authorized User	KNOBBE MARTENS OLSON AND BEAR

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	DEXCOM_217A_IssueFee.pdf	98763 48887d04268f17f84e37619193fb5e9bee69d26d	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30732 3a8f1a767d0322352cfca6400ba838f50233dc37	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	129495		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	~~2684~~ 2682
Examiner Name	~~LEE, Benjamin C.~~ Kerri McNally
Attorney Docket Number	DEXCOM.217A

Change(s) applied to document.
/B.H.H./
5/20/2015

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
2008	1	US- ~~2005~~0033254	2/7/2008	Kamath et al.	
	2	US- 20110193704	8/11/2011	Harper, Wesley Scott	
		US-			
		US-			
		US-			
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		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.M./

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	2684
Examiner Name	LEE, Benjamin C.
Attorney Docket Number	DEXCOM.217A

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	20	US- 6553244	4/22/2003	Lesho et al.	
	21	US- 6558351	5/6/2003	Steil et al.	
	22	US- 6560471	5/6/2003	Heller et al.	
	23	US- 6572545	6/3/2003	Knobbe et al.	
	24	US- 6574490	6/3/2003	Abbink et al.	
	25	US- 6575905	6/10/2003	Knobbe et al.	
	26	US- 6577899	6/10/2003	Lebel et al.	
	27	US- ~~6470600~~ 6,579,690	6/17/2003	Bonnecaze et al.	
	28	US- 6607509	8/19/2003	Bobroff et al.	
	29	US- 6653091	11/25/2003	Dunn et al.	
	30	US- 6656114	12/2/2003	Poulsen et al.	
	31	US- 6695860	2/24/2004	Ward et al.	
	32	US- 6740518	5/25/2004	Duong et al.	
	33	US- 6882940	4/19/2005	Potts et al.	
	34	US- 6895263	5/17/2005	Shin et al.	
	35	US- 6990366	1/24/2006	Say et al.	
	36	US- 6991619	1/31/2006	Marano-Ford et al.	
	37	US- 6991620	1/31/2006	Marano-Ford et al.	
	38	US- 6997907	2/14/2006	Safabash et al.	

Change(s) applied to document,
/B.H.H/
5/20/2015

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	7	EP 1473050-B1	2009-12-09	Medtronic MiniMed, Inc.		
	8	EP 1503660-B1	2007-01-17	Medtronic Minimed, Inc.		
	9	EP 1518495-B1	2010-03-31	Roche Diagnostics GmbH		
	10	EP 1703839-B1	2012-02-08	Medtronic MiniMed, Inc.		
	11	EP 1706022-B1	2008-10-29	Medtronic MiniMed, Inc.		
	12	EP 1759201-B1	2010-10-13	Medtronic Minimed, Inc.		

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.M./

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	13/742694
Filing Date	01/16/2013
First Named Inventor	Cobelli, Claudio
Art Unit	~~2684~~ 2682
Examiner Name	~~LEE, Benjamin C.~~ Kerri McNally
Attorney Docket Number	DEXCOM.217A

Change(s) applied to document, /B.H.H/ 5/20/2015

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 5299571	4/5/1994	Mastrototaro, John J.	
	2	US- 5390671	2/21/1995	Lord et al.	
	3	US- 5568806	10/29/1996	Cheney et al.	
	4	US- 5586553	12/24/1996	Halili et al.	
	5	US- 5680858	10/28/1997	~~Hanrik Egeeberg~~ et al. Hansen	
	6	US- 5851197	12/22/1998	Marano et al.	
	7	US- 5971922	10/26/1999	Arita et al.	
	8	US- 5993411	11/30/1999	Choi, Soo Bong	
	9	US- 6093172	7/25/2000	Funderburk et al.	
	10	US- 6180416	1/30/2001	Kurnik et al.	
	11	US- 6197001	3/6/2001	Wilson et al.	
	12	US- 6212424	4/3/2001	Robinson, Mak Ries	
	13	US- 6236872	5/22/2001	Diab et al.	
	14	US- 6254586	7/3/2001	Mann et al.	
	15	US- 6272364	8/7/2001	Kurnik, Ronald T.	
	16	US- 6293925	9/25/2001	Safabash et al.	
	17	US- 6424847	7/23/2002	Mastrototaro et al.	
	18	US- 6544212	4/8/2003	Galley et al.	
	19	US- 6546269	4/8/2003	Kurnik, Ronald T.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	1	EP 1077634-B1	2003-07-30	Cygnus, Inc.		
	2	EP 1078258-B1	2003-07-30	Cygnus, Inc.		
	3	EP 1102559-B1	2003-06-04	Cygnus, Inc.		
	4	EP 1119637-B1	2004-03-24	Therasense, Inc.		
	5	EP 1144028-B1	2004-06-23	Novo Nordisk A/S		
	6	EP 1437674-B1	2008-08-13	Novo Nordisk A/S		

Examiner Signature	/Kerri Mcnally/	Date Considered	09/24/2014

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/742,694	09/01/2015	9119528	DEXCOM.217A	6142

68851 7590 08/12/2015

KNOBBE, MARTENS, OLSEN & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 193 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Claudio Cobelli, Padova, ITALY;
Giovanni Sparacino, Padova, ITALY;
Andrea Facchinetti, Padova, ITALY;
Hari Hampapuram, San Diego, CA;
Anna Leigh Rack-Gomer, San Diego, CA;
Chiara Zecchin, Pernumia, ITALY;
Naresh C. Bhavaraju, San Diego, CA;
Apurv Ullas Kamath, San Diego, CA;
DEXCOM, INC., San Diego, CA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,119,528
APPLICATION NO. : 13/742,694
ISSUE DATE : September 1, 2015
INVENTOR(S) : Claudio Cobelli

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1 (item 72, Inventors) at line 6, Change "Pernumla" for Chiara Zecchin to --Pernumia--.

In column 2 (page 1, item 56) at line 11, Under Other Publications, change "Transacrtions" to --Transactions--.

In column 1 (page 3, item 56) at line 13, Under Other Publications, change "AUtomatic" to --Automatic--.

In column 1 (page 3, item 56) at line 17, Under Other Publications, change "Predicition" to --Prediction--.

In column 1 (page 3, item 56) at line 23, Under Other Publications, change "Glujcose" to --Glucose--.

In column 1 (page 3, item 56) at line 26, Under Other Publications, change "Predition" to --Prediction--.

In column 1 (page 3, item 56) at line 42, Under Other Publications, change "Concentrati." to --Concentration.--.

In column 1 (page 3, item 56) at line 43, Under Other Publications, change "Therapetucics" to --Therapeutics--.

In column 1 (page 3, item 56) at line 44, Under Other Publications, change "Rish Meausre" to --Risk Measure--.

In column 1 (page 3, item 56) at line 48, Under Other Publications, change "devconvolution" to --deconvolution--.

In column 2 (page 3, item 56) at lines 2-3, Under Other Publications, change "evaulation" to --evaluation--.

In column 2 (page 3, item 56) at line 3, Under Other Publications, change "insuling" to --insulin--.

MAILING ADDRESS OF SENDER:

Rose M. Thiessen
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street, 14th Floor
Irvine, California 92614

DOCKET NO. DEXCOM.217A

PTO/SB/44 Equivalent

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,119,528
APPLICATION NO. : 13/742,694
ISSUE DATE : September 1, 2015
INVENTOR(S) : Claudio Cobelli

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In column 5 at line 2, Change "the a" to --a--.

In column 6 at line 6, Change "the a" to --a--.

In column 22 at line 63, Change "nighttime)," to --night time),--.

In column 24 at line 18, Change "gylcemia)" to --glycemia)--.

In column 24 at line 66, Change "voL" to --vol--.

In column 29 at line 50, Change "TV_L," to --TV_1,--.

In column 35 at line 34, Change "the a" to --the--.

In column 50 at line 53, In Claim 44, after "system of" insert --claim--.

22717754
021816

MAILING ADDRESS OF SENDER:

Rose M. Thiessen
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street, 14th Floor
Irvine, California 92614

DOCKET NO. DEXCOM.217A

PTO/SB/44 Equivalent

Electronic Patent Application Fee Transmittal

Application Number:	13742694
Filing Date:	16-Jan-2013
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Filer:	Rose M. Thiessen/Edgar Compton
Attorney Docket Number:	DEXCOM.217A

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of Correction	1811	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	24963915
Application Number:	13742694
International Application Number:	
Confirmation Number:	6142
Title of Invention:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
First Named Inventor/Applicant Name:	Claudio Cobelli
Customer Number:	68851
Filer:	Rose M. Thiessen/Anthony Bonilla
Filer Authorized By:	Rose M. Thiessen
Attorney Docket Number:	DEXCOM.217A
Receipt Date:	19-FEB-2016
Filing Date:	16-JAN-2013
Time Stamp:	14:37:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$100
RAM confirmation Number	993
Deposit Account	111410
Authorized User	KNOBBE MARTENS OLSON AND BEAR

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	217A_COC_TRANS.pdf	139236 cde2caf63b4d185d7e3383bedaaf8e9b7e0a7e4d	no	1
Warnings:					
Information:					
2	Request for Certificate of Correction	217A_COC.pdf	268340 c4a47950302c262a6db872f6d57b7a8dba2ae9bf	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30593 54c6659d1fb58f9d1ccc7e55d637a47aeceb43a5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	438169		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Please Direct All Correspondence to Customer Number 68851

REQUEST FOR CERTIFICATE OF CORRECTION

Inventor	:	Claudio Cobelli
App. No.	:	13/742694
Filed	:	January 16, 2013
Patent No.	:	9,119,528
Issue Date	:	September 1, 2015
Title	:	SYSTEMS AND METHODS FOR PROVIDING SENSITIVE AND SPECIFIC ALARMS
Conf No.	:	6142

Commissioner for Patents
Office of Data Management Attention: Certificates of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed for filing is a Certificate of Correction in connection with the above-identified patent.

Some of the errors cited in the Certificate of Correction appear to have been incurred through the fault of the PTO (see 35 USC § 254, 37 CFR § 1.322, and MPEP § 1480). However, because this may not apply to each item in the Certificate of Correction, the $100 fee under 37 CFR § 1.20(a) is submitted herewith. Please charge any additional fees to our Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: February 18, 2016

By: /Rose M. Thiessen/
Rose M. Thiessen
Registration No. 40,202
Attorney of Record
Customer No. 68851
(858) 707-4000

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,119,528 B2
APPLICATION NO. : 13/742694
DATED : September 1, 2015
INVENTOR(S) : Cobelli et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page

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In column 2 (page 3, item 56) at line 3, Under Other Publications, change "insuling" to

Signed and Sealed this
Nineteenth Day of April, 2016



Michelle K. Lee
Director of the United States Patent and Trademark Office

--insulin--.

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In the Claims

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