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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/438,144	**02/09/2024 05:29:40 PM Z ET**	**OMNI0101PUSA10**

Title of Invention

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6361	FILED BY	Sharon Kaiser
PATENT CENTER #	64273927	FILING DATE	-
CUSTOMER #	109543	FIRST NAMED INVENTOR	Mohammed N. ISLAM
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kevin Heinl

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
ADS-aia0014_OMNI0101PUSA10.pdf	12	Application Data Sheet	1229 KB
OMNI0101PUSA10_Application-APP.TEXT.docx	133	Application body structured text document	263 KB
OMNI0101PUSA10_Application.pdf	133	Auxiliary PDF of Application	1429 KB
Drawings_OMNI0101PUSA10.pdf	100	Drawings-only black and white line drawings	14443 KB
Declaration-Assignment_OMNI0101PUSA10.pdf	1	Oath or Declaration filed	276 KB

POA-OMNI0101PUSA10.pdf	2	Power of Attorney	709 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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ELECTRONIC PAYMENT RECEIPT

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18/438,144	**02/09/2024 05:29:40 PM Z ET**	**OMNI0101PUSA10**

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CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Mohammed N. ISLAM

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PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
023978	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2111	UTILITY PATENT APPL. SEARCH FEE	280.00	1	280.00
4011	BASIC FILING FEE- UTILITY	64.00	1	64.00
2311	EXAMINATION OF ORIGINAL PATENT APPLICATION	320.00	1	320.00
2081	UTILITY APPL. SIZE FEE > THAN 100 PAGES (FEE X PAGES >= 101 IN 50 PAGE INCREMENTS)	168.00	2	336.00
			TOTAL	**$1,000.00**

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WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Serial No. 18/103,408 filed January 30, 2023, now U.S. Patent No. 11,896,346, which is a continuation of U.S. application Serial No. 17/514,778 filed October 29, 2021, now U.S. Patent No. 11,564,577, which is a continuation of U.S. application Serial No. 17/078,771 filed October 23, 2020, now U.S. Patent No. 11,160,455, which is a continuation of U.S. application Serial No. 16/722188 filed December 20, 2019, now U.S. Patent No. 10,820,807, which is a continuation of U.S. application Serial No. 16/506,885 filed July 9, 2019, now U.S. Patent No. 10,517,484, which is a continuation of U.S. application Serial No. 16/272,069 filed February 11, 2019, now abandoned, which is a continuation of U.S. application Serial No. 16/029,611 filed July 8, 2018, now U.S. Patent No. 10,201,283, which is a continuation of U.S. application Serial No. 15/888,052 filed February 4, 2018 (U.S. Patent No. 10,136,819), now abandoned, which is a continuation of U.S. application Serial No. 15/212,549 filed July 18, 2016 (U.S. Patent No. 9,885,698), now abandoned, which is a continuation of U.S. application Serial No. 14/650,897 filed June 10, 2015, now U.S. Patent No. 9,494,567, which is a U.S. National Phase of PCT/US2013/075700 filed December 17, 2013, which claims the benefit of U.S. provisional application Serial No. 61/747,472 filed December 31, 2012, the disclosures of all of which are hereby incorporated in their entirety by reference herein.

[0002] U.S. application Serial No. 16/506,885, now U.S. Patent No. 10,517,484, is also a continuation of U.S. application Serial No. 16/004,359 filed June 9, 2018, now U.S. Patent No. 11,109,761, which is a continuation of U.S. application Serial No. 14/109,007 filed December 17, 2013 (now U.S. Patent No. 9,993,159), which claims the benefit of U.S. provisional application Serial No. 61/747,553 filed December 31, 2012, the disclosures of all of which are hereby incorporated in their entirety by reference herein.

[0003] U.S. application Serial No. 16/506,885, now U.S. Patent No. 10,517,484, is also a continuation of U.S. application Serial No.16/188,194 filed November 12, 2018 (U.S. Patent No. 10,386,230), now abandoned, which is a continuation of U.S. Application No. 16/004,154 filed June 8, 2018 (now U.S. Patent No. 10,126,283), which is a continuation of U.S. Application No.

15/855,201 filed December 27, 2017 (U.S. Patent No. 9,995,722), now abandoned, which is a continuation of U.S. Application No. 15/711,907 filed September 21, 2017 (U.S. Patent No. 9,897,584), now abandoned, which is a divisional of U.S. Application No. 15/357,225 filed November 21, 2016 (U.S. Patent No. 9,797,876), now abandoned, which is a continuation of U.S. Application No. 14/650,981 filed June 10, 2015 (now U.S. Patent No. 9,500,634), which is the U.S. national phase of PCT Application No. PCT/US2013/075767 filed December 17, 2013, which claims the benefit of U.S. provisional application Ser. No. 61/747,485 filed Dec. 31, 2012, the disclosures of all of which are hereby incorporated by reference in their entirety.

[0004] U.S. application Serial No. 16/506,885, now U.S. Patent No. 10,517,484, is also a continuation of U.S. application Serial No. 16/241,628 filed January 7, 2019, now U.S. Patent No. 10,441,176, which is a continuation of U.S. Serial No. 16/015,737 filed June 22, 2018 (U.S. Patent No. 10,172,523), now abandoned, which is a continuation of U.S. Serial No. 15/594,053 filed May 12, 2017 (U.S. Patent No. 10,188,299), now abandoned, which is a continuation of U.S. application Serial No. 14/875,709 filed October 6, 2015 (now U.S. Patent No. 9,651,533), which is a continuation of U.S. application Serial No. 14/108,986 filed December 17, 2013 (U.S. Patent No. 9,164,032), now abandoned, which claims the benefit of U.S. provisional application Serial No. 61/747,487 filed December 31, 2012, the disclosures of all of which are hereby incorporated in their entirety by reference herein.

[0005] U.S. application Serial No. 16/506,885, now U.S. Patent No. 10,517,484, is also a continuation of U.S. Application Ser. No. 16/284,514 filed February 25, 2019, now abandoned, which is a continuation of U.S. Application Ser. No. 16/016,649 filed June 24, 2018 (U.S. Patent No. 10,213,113), now abandoned, which is a continuation of U.S. Application Ser. No. 15/860,065 filed January 2, 2018 (U.S. Patent No. 10,098,546), now abandoned, which is a continuation of U.S. Application Ser. No. 15/686,198 filed August 25, 2017 (U.S. Patent No. 9,861,286), now abandoned, which is a continuation of U.S. Application Ser. No. 15/357,136 filed November 21, 2016 (U.S. Patent. No. 9,757,040), now abandoned, which is a continuation of U.S. Application Ser. No. 14/651,367 filed June 11, 2015 (now U.S. Patent No. 9,500,635), which is the U.S. national phase of PCT Application No. PCT/US2013/075736 filed December 17, 2013, which claims the benefit of U.S. provisional application Ser. No. 61/747,477 filed Dec. 31, 2012 and U.S.

provisional application Ser. No. 61/754,698 filed Jan. 21, 2013, the disclosures of all of which are hereby incorporated by reference in their entirety.

[0006] This application is related to U.S. provisional application Serial Nos. 61/747,477 filed Dec. 31, 2012; Ser. No. 61/747,481 filed Dec. 31, 2012; Ser. No. 61/747,485 filed Dec. 31, 2012; Ser. No. 61/747,487 filed Dec. 31, 2012; Ser. No. 61/747,492 filed Dec. 31, 2012; Ser. No. 61/747,553 filed Dec. 31, 2012; and Ser. No. 61/754,698 filed Jan. 21, 2013, the disclosures of all of which are hereby incorporated in their entirety by reference herein.

[0007] This application is also related to International Application PCT/US2013/075736 entitled Short-Wave Infrared Super-Continuum Lasers For Early Detection Of Dental Caries; U.S. Application 14/108,995 filed December 17, 2013 entitled Focused Near-Infrared Lasers For Non-Invasive Vasectomy And Other Thermal Coagulation Or Occlusion Procedures (U.S. Pat. App. Pub. No. US2014/0188092A1); International Application PCT/US2013/075767 entitled Short-Wave Infrared Super-Continuum Lasers For Natural Gas Leak Detection, Exploration, And Other Active Remote Sensing Applications; U.S. Application 14/108,986 filed December 17, 2013 (U.S. Patent No. 9,164,032) entitled Short-Wave Infrared Super-Continuum Lasers For Detecting Counterfeit Or Illicit Drugs And Pharmaceutical Process Control; U.S. Application 14/108,974 filed December 17, 2013 entitled Non-Invasive Treatment Of Varicose Veins (U.S. Pat. App. Pub. No. US2014/018894A1); and U.S. Application 14/109,007 filed December 17, 2013 entitled Near-Infrared Super-Continuum Lasers For Early Detection Of Breast And Other Cancers (now U.S. Patent No. 9,993,159), the disclosures of all of which are hereby incorporated in their entirety by reference herein.

BACKGROUND

[0008] With the growing obesity epidemic, the number of individuals with diabetes is also increasing dramatically. For example, there are over 200 million people who have diabetes. Diabetes control requires monitoring of the glucose level, and most glucose measuring systems available commercially require drawing of blood. Depending on the severity of the diabetes, a patient may have to draw blood and measure glucose four to six times a day. This may be extremely painful and inconvenient for many people. In addition, for some groups, such as soldiers

in the battlefield, it may be dangerous to have to measure periodically their glucose level with finger pricks.

[0009] Thus, there is an unmet need for non-invasive glucose monitoring (e.g., monitoring glucose without drawing blood). The challenge has been that a non-invasive system requires adequate sensitivity and selectivity, along with repeatability of the results. Yet, this is a very large market, with an estimated annual market of over $10B in 2011 for self-monitoring of glucose levels.

[0010] One approach to non-invasive monitoring of blood constituents or blood analytes is to use near-infrared spectroscopy, such as absorption spectroscopy or near-infrared diffuse reflection or transmission spectroscopy. Some attempts have been made to use broadband light sources, such as tungsten lamps, to perform the spectroscopy. However, several challenges have arisen in these efforts. First, many other constituents in the blood also have signatures in the near-infrared, so spectroscopy and pattern matching, often called spectral fingerprinting, is required to distinguish the glucose with sufficient confidence. Second, the non-invasive procedures have often transmitted or reflected light through the skin, but skin has many spectral artifacts in the near-infrared that may mask the glucose signatures. Moreover, the skin may have significant water and blood content. These difficulties become particularly complicated when a weak light source is used, such as a lamp. More light intensity can help to increase the signal levels, and, hence, the signal-to-noise ratio.

[0011] As described in this disclosure, by using brighter light sources, such as fiber-based supercontinuum lasers, super-luminescent laser diodes, light-emitting diodes or a number of laser diodes, the near-infrared signal level from blood constituents may be increased. By shining light through the teeth, which have fewer spectral artifacts than skin in the near-infrared, the blood constituents may be measured with less interfering artifacts. Also, by using pattern matching in spectral fingerprinting and various software techniques, the signatures from different constituents in the blood may be identified. Moreover, value-add services may be provided by wirelessly communicating the monitored data to a handheld device such as a smart phone, and then wirelessly communicating the processed data to the cloud for storing, processing, and transmitting to several locations.

[0012] Dental care and the prevention of dental decay or dental caries has changed in the United States over the past several decades, due to the introduction of fluoride to drinking water, the use of fluoride dentifrices and rinses, application of topical fluoride in the dental office, and improved dental hygiene. Despite these advances, dental decay continues to be the leading cause of tooth loss. With the improvements over the past several decades, the majority of newly discovered carious lesions tend to be localized to the occlusal pits and fissures of the posterior dentition and the proximal contact sites. These early carious lesions may be often obscured in the complex and convoluted topography of the pits and fissures or may be concealed by debris that frequently accumulates in those regions of the posterior teeth. Moreover, such lesions are difficult to detect in the early stages of development.

[0013] Dental caries may be a dynamic disease that is characterized by tooth demineralization leading to an increase in the porosity of the enamel surface. Leaving these lesions untreated may potentially lead to cavities reaching the dentine and pulp and perhaps eventually causing tooth loss. Occlusal surfaces (bite surfaces) and approximal surfaces (between the teeth) are among the most susceptible sites of demineralization due to acid attack from bacterial by-products in the biofilm. Therefore, there is a need for detection of lesions at an early stage, so that preventive agents may be used to inhibit or reverse the demineralization.

[0014] Traditional methods for caries detection include visual examination and tactile probing with a sharp dental exploration tool, often assisted by radiographic (x-ray) imaging. However, detection using these methods may be somewhat subjective; and, by the time that caries are evident under visual and tactile examination, the disease may have already progressed to an advanced stage. Also, because of the ionizing nature of x-rays, they are dangerous to use (limited use with adults, and even less used with children). Although x-ray methods are suitable for approximal surface lesion detection, they offer reduced utility for screening early caries in occlusal surfaces due to their lack of sensitivity at very early stages of the disease.

[0015] Some of the current imaging methods are based on the observation of the changes of the light transport within the tooth, namely absorption, scattering, transmission, reflection and/or fluorescence of light. Porous media may scatter light more than uniform media. Taking advantage of this effect, the Fiber-optic trans-illumination is a qualitative method used to highlight

the lesions within teeth by observing the patterns formed when white light, pumped from one side of the tooth, is scattered away and/or absorbed by the lesion. This technique may be difficult to quantify due to an uneven light distribution inside the tooth.

[0016] Another method called quantitative light-induced fluorescence – QLF – relies on different fluorescence from solid teeth and caries regions when excited with bright light in the visible. For example, when excited by relatively high intensity blue light, healthy tooth enamel yields a higher intensity of fluorescence than does demineralized enamel that has been damaged by caries infection or any other cause. On the other hand, for excitation by relatively high intensity of red light, the opposite magnitude change occurs, since this is the region of the spectrum for which bacteria and bacterial by-products in carious regions absorb and fluoresce more pronouncedly than do healthy areas. However, the image provided by QLF may be difficult to assess due to relatively poor contrast between healthy and infected areas. Moreover, QLF may have difficulty discriminating between white spots and stains because both produce similar effects. Stains on teeth are commonly observed in the occlusal sites of teeth, and this obscures the detection of caries using visible light.

[0017] As described in this disclosure, the near-infrared region of the spectrum offers a novel approach to imaging carious regions because scattering is reduced and absorption by stains is low. For example, it has been demonstrated that the scattering by enamel tissues reduces in the form of $1/(\text{wavelength})^3$, e.g., inversely as the cube of wavelength. By using a broadband light source in the short-wave infrared (SWIR) part of the spectrum, which corresponds approximately to 1400nm to 2500nm, lesions in the enamel and dentine may be observed. In one embodiment, intact teeth have low reflection over the SWIR wavelength range. In the presence of caries, the scattering increases, and the scattering is a function of wavelength; hence, the reflected signal decreases with increasing wavelength. Moreover, particularly when caries exist in the dentine region, water build up may occur, and dips in the SWIR spectrum corresponding to the water absorption lines may be observed. The scattering and water absorption as a function of wavelength may thus be used for early detection of caries and for quantifying the degree of demineralization.

[0018] SWIR light may be generated by light sources such as lamps, light emitting diodes, one or more laser diodes, super-luminescent laser diodes, and fiber-based super-continuum

sources. The SWIR super-continuum light sources advantageously may produce high intensity and power, as well as being a nearly transform-limited beam that may also be modulated. Also, apparatuses for caries detection may include C-clamps over teeth, a handheld device with light input and light detection, which may also be attached to other dental equipment such as drills. Alternatively, a mouth-guard type apparatus may be used to simultaneously illuminate one or more teeth. Fiber optics may be conveniently used to guide the light to the patient as well as to transport the signal back to one or more detectors and receivers.

[0019] Remote sensing or hyper-spectral imaging often uses the sun for illumination, and the short-wave infrared (SWIR) windows of about 1.5-1.8 microns and about 2-2.5 microns may be attractive because the atmosphere transmits in these wavelength ranges. Although the sun can be a bright and stable light source, its illumination may be affected by the time-of-day variations in the sun angle as well as weather conditions. For example, the sun may be advantageously used for applications such as hyper-spectral imaging only between about 9am to 3pm, and it may be difficult to use the sun during cloudy days or during inclement weather. In one embodiment, the hyper-spectral sensors measure the reflected solar signal at hundreds (e.g., 100 to 200+) contiguous and narrow wavelength bands (e.g., bandwidth between 5nm and 10nm). Hyper-spectral images may provide spectral information to identify and distinguish between spectrally similar materials, providing the ability to make proper distinctions among materials with only subtle signature differences. In the SWIR wavelength range, numerous gases, liquids and solids have unique chemical signatures, particularly materials comprising hydro-carbon bonds, O-H bonds, N-H bonds, etc. Therefore, spectroscopy in the SWIR may be attractive for stand-off or remote sensing of materials based on their chemical signature, which may complement other imaging information.

[0020] A SWIR super-continuum (SC) source may be able to replace at least in part the sun as an illumination source for active remote sensing, spectroscopy, or hyper-spectral imaging. In one embodiment, reflected light spectroscopy may be implemented using the SWIR light source, where the spectral reflectance can be the ratio of reflected energy to incident energy as a function of wavelength. Reflectance varies with wavelength for most materials because energy at certain wavelengths may be scattered or absorbed to different degrees. Using a SWIR light source may permit 24/7 detection of solids, liquids, or gases based on their chemical signatures. As an example, natural gas leak detection and exploration may require the detection of methane and

ethane, whose primary constituents include hydro-carbons. In the SWIR, for instance, methane and ethane exhibit various overtone and combination bands for vibrational and rotational resonances of hydro-carbons. In one embodiment, diffuse reflection spectroscopy or absorption spectroscopy may be used to detect the presence of natural gas. The detection system may include a gas filter correlation radiometer, in a particular embodiment. Also, one embodiment of the SWIR light source may be an all-fiber integrated SWIR SC source, which leverages the mature technologies from the telecommunications and fiber optics industry. Beyond natural gas, active remote sensing in the SWIR may also be used to identify other materials such as vegetation, greenhouse gases or environmental pollutants, soils and rocks, plastics, illicit drugs, counterfeit drugs, firearms and explosives, paints, and various building materials.

[0021] Counterfeiting of pharmaceuticals is a significant issue in the healthcare community as well as for the pharmaceutical industry worldwide. For example, according to the World Health Organization, in 2006 the market for counterfeit drugs worldwide was estimated at around $43 Billion. Moreover, the use of counterfeit medicines may result in treatment failure or even death. For instance, in 1995 dozens of children in Haiti and Nigeria died after taking counterfeit medicinal syrups that contained diethylene glycol, an industrial solvent. As another example, in Asia one report estimated that 90% of Viagra sold in Shanghai, China, was counterfeit. With more pharmaceuticals being purchased through the internet, the problem of counterfeit drugs coming from across the borders into the United States has been growing rapidly.

[0022] A rapid, non-destructive, non-contact optical method for screening or identification of counterfeit pharmaceuticals is needed. Spectroscopy using near-infrared or short-wave infrared (SWIR) light may provide such a method, because most pharmaceuticals comprise organic compounds that have overtone or combination absorption bands in this wavelength range (e.g., between approximately 1-2.5 microns). Moreover, most drug packaging materials are at least partially transparent in the near-infrared or SWIR, so that drug compositions may be detected and identified through the packaging non-destructively. Also, using a near-infrared or SWIR light source with a spatially coherent beam permits screening at stand-off or remote distances. Beyond identifying counterfeit drugs, the near-infrared or SWIR spectroscopy may have many other beneficial applications. For example, spectroscopy may be used for rapid screening of illicit drugs or to implement process analytical technology in pharmaceutical manufacturing. There are also a

wide array of applications in assessment of quality in the food industry, including screening of fruit, vegetables, grains and meats.

[0023] In one embodiment, a near-infrared or SWIR super-continuum (SC) source may be used as the light source for spectroscopy, active remote sensing, or hyper-spectral imaging. One embodiment of the SWIR light source may be an all-fiber integrated SWIR SC source, which leverages the mature technologies from the telecommunications and fiber optics industry. Exemplary fiber-based super-continuum sources may emit light in the near-infrared or SWIR between approximately 1.4-1.8 microns, 2-2.5 microns, 1.4-2.4 microns, 1-1.8 microns, or any number of other bands. In particular embodiments, the detection system may be a dispersive spectrometer, a Fourier transform infrared spectrometer, or a hyper-spectral imaging detector or camera. In addition, reflection or diffuse reflection light spectroscopy may be implemented using the SWIR light source, where the spectral reflectance can be the ratio of reflected energy to incident energy as a function of wavelength.

[0024] Breast cancer is considered to be the most common cancer among women in industrialized countries. It is believed that early diagnosis and consequent therapy could significantly reduce mortality. Mammography is considered the gold standard among imaging techniques in diagnosing breast pathologies. However, the use of ionizing radiation in mammography may have adverse effects and lead to other complications. Moreover, screening x-ray mammography may be limited by false positives and negatives, leading to unnecessary physical and psychological morbidity. Although breast cancer is one of the focuses of this disclosure, the same techniques may also be applied to other cancer types, including, for example, skin, prostate, brain, pancreatic, and colorectal cancer.

[0025] Diagnostic methods for assessment and therapy follow-up of breast cancer include mammography, ultrasound, and magnetic resonance imaging. The most effective screening technique at this time is x-ray mammography, with an overall sensitivity for breast cancer detection around 75%, which is even further reduced in women with dense breasts to around 62%. Moreover, x-ray mammography has a 22% false positive rate in women under 50, and the method cannot accurately distinguish between benign and malignant tumors. Magnetic resonance imaging and ultrasound are sometimes used to augment x-ray mammography, but they have limitations

such as high cost, low throughput, limited specificity and low sensitivity. Thus, there is a continued need to detect cancers earlier for treatment, missed by mammography, and to add specificity to the procedures.

[0026] Optical breast imaging may be an attractive technique for breast cancer to screen early, augment with mammography, or use in follow-on treatments. Also, optical breast imaging may be performed by intrinsic tissue contrast alone (e.g., hemoglobin, water, collagen, and lipid content), or with the use of exogenous fluorescent probes that target specific molecules. For example, near-infrared (NIR) light may be used to assess optical properties, where the absorption and scattering by the tissue components may change with carcinoma. For most of the studies conducted to date, NIR light in the wavelength range of 600-1000nm has been used for sufficient tissue penetration; these wavelengths have permitted imaging up to several centimeters deep in soft tissue. Optical breast imaging using fluorescent contrast agents may improve lesion contrast and may potentially permit detection of changes in breast tissue earlier. In one embodiment, the fluorescent probes may either bind specifically to certain targets associated with cancer or may non-specifically accumulate at the tumor site.

[0027] Optical methods of imaging and spectroscopy can be non-invasive using non-ionizing electromagnetic radiation, and these techniques could be exploited for screening of wide populations and for therapy monitoring. "Optical mammography" may be a diffuse optical imaging technique that aims at detecting breast cancer, characterizing its physiological and pathological state, and possibly monitoring the efficacy of the therapeutic treatment. The main constituents of breast tissue may be lipid, collagen, water, blood, and other structural proteins. These constituents may exhibit marked and characteristic absorption features in the NIR wavelength range. Thus, diffuse optical imaging and spectroscopy in the NIR may be helpful for diagnosing and monitoring breast cancer. Another advantage of such imaging is that optical instruments tend to be portable and more cost effective as compared to other instrumentation that is conventionally used for medical diagnosis. This can be particularly true, if the mature technologies for telecommunications and fiber optics are exploited.

[0028] Spectroscopy using NIR or short-wave infrared (SWIR) light may be beneficial, because most tissue has organic compounds that have overtone or combination absorption bands

in this wavelength range (e.g., between approximately 0.8-2.5 microns). In one embodiment, a NIR or SWIR super-continuum (SC) laser that is an all-fiber integrated source may be used as the light source for diagnosing cancerous tissue. Exemplary fiber-based super-continuum sources may emit light in the NIR or SWIR between approximately 1.4-1.8 microns, 2-2.5 microns, 1.4-2.4 microns, 1-1.8 microns, or any number of other bands. In particular embodiments, the detection system may be one or more photo-detectors, a dispersive spectrometer, a Fourier transform infrared spectrometer, or a hyper-spectral imaging detector or camera. In addition, reflection or diffuse reflection light spectroscopy may be implemented using the SWIR light source, where the spectral reflectance can be the ratio of reflected energy to incident energy as a function of wavelength.

[0029] For breast cancer, experiments have shown that with growing cancer the collagen content increases while the lipid content decreases. Therefore, early breast cancer detection may involve the monitoring of absorption or scattering features from collagen and lipids. In addition, NIR spectroscopy may be used to determine the concentrations of hemoglobin, water, as well as oxygen saturation of hemoglobin and optical scattering properties in normal and cancerous breast tissue. For optical imaging to be effective, it may also be desirable to select the wavelength range that leads to relatively high penetration depths into the tissue. In one embodiment, it may be advantageous to use optical wavelengths in the range of about 1000-1400nm. In another embodiment, it may be advantageous to use optical wavelengths in the range of about 1600-1800nm. Higher optical power densities may be used to increase the signal-to-noise ratio of the detected light through the diffuse scattering tissue, and surface cooling or focused light may be beneficial for preventing pain or damage to the skin and outer layer surrounding the breast tissue. Since optical energy may be non-ionizing, different exposure times may be used without danger or harmful radiation.

SUMMARY

[0030] In one embodiment, an optical system is provided. The optical system comprises a wearable device for measuring one or more physiological parameters, and the wearable device is adapted to be placed on a wrist or a hand dorsal of a user. The measuring of the one or more physiological parameters is configured to change in response to stretching of the hand or

movement of fingers or thumb of the user. The wearable device includes a light source comprising a plurality of light emitting diodes that are configured to generate an output optical light having one or more optical wavelengths. Then, one or more lenses are configured to receive at least a portion of the output optical light and to deliver a lens output light to tissue comprising skin. The wearable device further comprises a detection system configured to receive at least a portion of the lens output light reflected from the tissue and to generate an output signal having a signal-to-noise ratio, wherein the detection system is configured to be synchronized to the light source. The detection system also comprises a plurality of detectors that are spatially separated from each other, and wherein at least one analog to digital converter is coupled to at least one of the spatially separated detectors. The output signal is indicative of the one or more of the physiological parameters configured to change in response to the stretching of the hand or movement of fingers or thumb of the user. The wearable device is also configured to increase the signal-to-noise ratio by increasing light intensity of at least one of the plurality of light emitting diodes from an initial light intensity. Moreover, the detection system is further configured to generate a first signal responsive to light received while the light emitting diodes are off, generate a second signal responsive to light received while at least one of the light emitting diodes is on, and increase the signal-to-noise ratio by comparing the first signal and the second signal. In addition, the wearable device is at least in part configured to identify an object.

[0031] In another embodiment, an optical system is provided that comprises a wearable device for measuring one or more physiological parameters, the wearable device adapted to be placed on a wrist of a user. The wearable device includes a light source comprising a plurality of semiconductor diodes that are configured to generate an output optical light having one or more optical wavelengths, wherein at least a portion of the one or more optical wavelengths is a near-infrared wavelength between 700 nanometers and 2500 nanometers. The wearable device also comprises one or more lenses configured to receive at least a portion of the output optical light and to deliver a lens output light to tissue comprising skin. The wearable device further comprises a detection system configured to receive at least a portion of the lens output light reflected from the tissue and to generate an output signal having a signal-to-noise ratio, wherein the detection system is configured to be synchronized to the light source. In addition, the detection system comprises a plurality of detectors that are spatially separated from each other, and wherein at least one analog

to digital converter is coupled to at least one of the spatially separated detectors. The output signal is indicative of the one or more of the physiological parameters. Furthermore, the wearable device is configured to increase the signal-to-noise ratio by increasing light intensity of at least one of the plurality of semiconductor diodes from an initial light intensity. Also, the detection system is further configured to generate a first signal responsive to light received while the semiconductor diodes are off, generate a second signal responsive to light received while at least one of the semiconductor diodes is on, and increase the signal-to-noise ratio by comparing the first signal and the second signal. Moreover, the wearable device is at least in part configured to identify an object.

[0032] In yet another embodiment, a remote sensing system is provided that comprises an array of laser diodes to generate light having one or more optical wavelengths that includes at least one near-infrared wavelength between 600 nanometers and 1000 nanometers. At least one laser diode of the array comprises one or more Bragg reflectors, and at least one of the laser diodes is configured to pulse at a modulation frequency between 10 Megahertz and 1 Gigahertz and configured to have a phase associated with the modulation frequency. Also, at least a portion of the light generated by the array is configured to be directed to an object. A detection system comprises at least one photo-detector, a lens and a spectral filter at an input to the at least one photo-detector, and a processor to process digitized signals received from the at least one photo-detector. The detection system is configured to (i) measure a phase shift of at least a portion of the light from the array of laser diodes reflected from the object relative to the at least a portion of the light generated by the array configured to be directed to the object, (ii) measure time-of-flight of the at least a portion of the light from the array of laser diodes reflected from the object relative to the at least a portion of the light generated by the array configured to be directed to the object, and (iii) generate one or more images of the object based at least in part on an amplitude of the at least a portion of the light from the array of laser diodes reflected from the object. Moreover, the detection system is further configured to use a lock-in technique and configured to synchronize to pulsing of the at least one of the laser diodes, and wherein the processor is configured to generate a time-of-flight measurement. In addition, a camera system is coupled to a lens system and the processor, the camera system configured to capture a second image including at least a part of the object. The remote sensing system including the processor is configured to combine at least a portion of the second image and at least a portion of the time-of-flight measurement to create a

combined portion. Furthermore, the remote sensing system including the processor is configured to communicate with a wearable device, a smart phone or a tablet that is further configured to process or display some of the combined portion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] For a more complete understanding of the present disclosure, and for further features and advantages thereof, reference is now made to the following description taken in conjunction with the accompanying drawings, in which:

[0034] FIGURE 1 plots the transmittance versus wavenumber for glucose in the mid-wave and long-wave infrared wavelengths between approximately 2.7 to 12 microns.

[0035] FIGURE 2 illustrates measurements of the absorbance of different blood constituents, such as glucose, hemoglobin, and hemoglobin A1c. The measurements are done using an FTIR spectrometer in samples with a 1mm path length.

[0036] FIGURE 3A shows the normalized absorbance of water and glucose (not drawn to scale). Water shows transmission windows between about 1500-1850nm and 2050-2500nm.

[0037] FIGURE 3B illustrates the absorbance of hemoglobin and oxygenated hemoglobin overlapped with water.

[0038] FIGURE 4A shows measured absorbance in different concentrations of glucose solution over the wavelength range of about 2000 to 2400nm. This data is collected using a SWIR super-continuum laser with the sample path length of about 1.1mm.

[0039] FIGURE 4B illustrates measured absorbance in different concentrations of glucose solution over the wavelength range of about 1550 to 1800nm. The data is collected using a SWIR super-continuum laser with a sample path length of about 10mm.

[0040] FIGURE 5 illustrates the spectrum for different blood constituents in the wavelength range of about 2 to 2.45 microns (2000 to 2450nm).

[0041] FIGURE 6 shows the transmittance versus wavelength in microns for the ketone 3-hydroxybutyrate. The wavelength range is approximately 2 to 16 microns.

[0042] FIGURE 7 illustrates the optical absorbance for ketones as well as some other blood constituents in the wavelength range of about 2100 to 2400nm.

[0043] FIGURE 8A shows the first derivative spectra of ketone and protein at concentrations of 10g/L (left). In addition, the first derivative spectra of urea, creatinine, and glucose are shown on the right at concentrations of 10g/L.

[0044] FIGURE 8B illustrates the near infrared absorbance for triglyceride.

[0045] FIGURE 8C shows the near-infrared reflectance spectrum for cholesterol.

[0046] FIGURE 8D illustrates the near-infrared reflectance versus wavelength for various blood constituents, including cholesterol, glucose, albumin, uric acid, and urea.

[0047] FIGURE 9 shows a schematic of the human skin. In particular, the dermis may comprise significant amounts of collagen, elastin, lipids, and water.

[0048] FIGURE 10 illustrates the absorption coefficients for water (including scattering), adipose, collagen, and elastin.

[0049] FIGURE 11 shows the dorsal of the hand, where a differential measurement may be made to at least partially compensate for or subtract out the skin interference.

[0050] FIGURE 12 shows the dorsal of the foot, where a differential measurement may be made to at least partially compensate for or subtract out the skin interference.

[0051] FIGURE 13 illustrates a typical human nail tissue structure and the capillary vessels below it.

[0052] FIGURE 14 shows the attenuation coefficient for seven nail samples that are allowed to stand in an environment with a humidity level of 14%. These coefficients are measured using an FTIR spectrometer over the near-infrared wavelength range of approximately 1 to 2.5 microns. Below is also included the spectrum of glucose.

[0053] FIGURE 15 illustrates the structure of a tooth.

[0054] FIGURE 16A shows the attenuation coefficient for dental enamel and water versus wavelength from approximately 600nm to 2600nm.

[0055] FIGURE 16B illustrates the absorption spectrum of intact enamel and dentine in the wavelength range of approximately 1.2 to 2.4 microns.

[0056] FIGURE 17 shows the near infrared spectral reflectance over the wavelength range of approximately 800nm to 2500nm from an occlusal tooth surface. The black diamonds correspond to the reflectance from a sound, intact tooth section. The asterisks correspond to a tooth section with an enamel lesion. The circles correspond to a tooth section with a dentine lesion.

[0057] FIGURE 18A illustrates a clamp design of a human interface to cap over one or more teeth and perform a non-invasive measurement of blood constituents.

[0058] FIGURE 18B shows a mouth guard design of a human interface to perform a non-invasive measurement of blood constituents.

[0059] FIGURE 19 illustrates a block diagram or building blocks for constructing high power laser diode assemblies.

[0060] FIGURE 20 shows a platform architecture for different wavelength ranges for an all-fiber-integrated, high powered, super-continuum light source.

[0061] FIGURE 21 illustrates one embodiment of a short-wave infrared (SWIR) super-continuum (SC) light source.

[0062] FIGURE 22 shows the output spectrum from the SWIR SC laser of FIGURE 21 when ~10m length of fiber for SC generation is used. This fiber is a single-mode, non-dispersion shifted fiber that is optimized for operation near 1550nm.

[0063] FIGURE 23 illustrates high power SWIR-SC lasers that may generate light between approximately 1.4-1.8 microns (top) or approximately 2-2.5 microns (bottom).

[0064] FIGURE 24 schematically shows that the medical measurement device can be part of a personal or body area network that communicates with another device (e.g., smart phone or tablet) that communicates with the cloud. The cloud may in turn communicate information with the user, healthcare providers, or other designated recipients.

[0065] FIGURE 25 illustrates the structure of a tooth.

[0066] FIGURE 26A shows the attenuation coefficient for dental enamel and water versus wavelength from approximately 600nm to 2600nm.

[0067] FIGURE 26B illustrates the absorption spectrum of intact enamel and dentine in the wavelength range of approximately 1.2 to 2.4 microns.

[0068] FIGURE 27 shows the near infrared spectral reflectance over the wavelength range of approximately 800nm to 2500nm from an occlusal tooth surface. The black diamonds correspond to the reflectance from a sound, intact tooth section. The asterisks correspond to a tooth section with an enamel lesion. The circles correspond to a tooth section with a dentine lesion.

[0069] FIGURE 28 illustrates a hand-held dental tool design of a human interface that may also be coupled with other dental tools.

[0070] FIGURE 29 illustrates a clamp design of a human interface to cap over one or more teeth and perform a non-invasive measurement for dental caries.

[0071] FIGURE 30 shows a mouth guard design of a human interface to perform a non-invasive measurement for dental caries.

[0072] FIGURE 31 schematically shows that the medical measurement device can be part of a personal or body area network that communicates with another device (e.g., smart phone or tablet) that communicates with the cloud. The cloud may in turn communicate information with the user, dental or healthcare providers, or other designated recipients.

[0073] FIGURE 32 illustrates wavelength bands for different chemical compounds over the SWIR wavelength range of approximately 1400nm to 2500nm. Also indicated are whether the bands are overtone or combination bands.

[0074] FIGURE 33A shows the absorption spectra for methane.

[0075] FIGURE 33B shows the absorption spectra for ethane.

[0076] FIGURE 34 illustrates the reflectance spectra for some members of the alkane family plus paraffin.

[0077] FIGURE 35A depicts that micro-seepages may result from the vertical movement of hydro-carbons from their respective reservoirs to the surface. It is assumed that the rock column, including the seal rock, comprises interconnected fractures or micro-fracture systems.

[0078] FIGURE 35B illustrates that surface alterations may occur because leaking hydro-carbons set up near-surface oxidation and/or reduction zones that favor the development of a diverse array of chemical and mineralogical changes.

[0079] FIGURE 36A shows the reflectance spectra for locations with natural gas fields (3601) and locations without natural gas fields (3602).

[0080] FIGURE 36B illustrates spectra from field tests over regions with natural gas, which show two spectral features: one near 1.725 microns and another doublet between about 2.311 microns and 2.36 microns.

[0081] FIGURE 37 shows the reflectance spectra of a sample of oil emulsion from the Gulf of Mexico 2010 oil spill (different thicknesses of oil).

[0082] FIGURE 38 illustrates the reflectance spectra of some representative minerals that may be major components of rocks and soils.

[0083] FIGURE 39 shows the reflectance spectra of different types of green vegetation compared with dry, yellowed grass.

[0084] FIGURE 40 illustrates the atmospheric absorption and scattering of greenhouse gases at different wavelengths.

[0085] FIGURE 41 overlays the reflectance for different building materials from the ASTER spectra library.

[0086] FIGURE 42 shows the absorbance for two common plastics, polyethylene and polystyrene.

[0087] FIGURE 43 shows the experimental set-up for a reflection-spectroscopy based stand-off detection system.

[0088] FIGURE 44 illustrates the chemical structure and molecular formula for various explosives, along with the absorbance spectra obtained using a super-continuum source.

[0089] FIGURE 45A shows the reflection spectra for gypsum, pine wood, ammonium nitrate and urea.

[0090] FIGURE 45B illustrates the reflection spectra for three commercial automotive paints and military grade CARC paint (chemical agent resistant coating) (reflectance in this case are in arbitrary units).

[0091] FIGURE 46 shows the mid-wave infrared and long-wave infrared absorption spectra for various illicit drugs. It is expected that overtone and combination bands should be evident in the SWIR and near-infrared wavelength bands.

[0092] FIGURE 47A is a schematic diagram of the basic elements of an imaging spectrometer.

[0093] FIGURE 47B illustrates one example of a typical imaging spectrometer used in hyper-spectral imaging systems.

[0094] FIGURE 48 shows one example of a gas-filter correlation radiometer, which is a detection system that uses a sample of the gas of interest as a spectral filter for the gas.

[0095] FIGURE 49 exemplifies a dual-beam experimental set-up that may be used to subtract out (or at least minimize the adverse effects of) light source fluctuations.

[0096] FIGURE 50 shows the absorbance for two common plastics, polyethylene and polystyrene.

[0097] FIGURE 51 illustrates one example of the difference in near-infrared spectrum between an authentic tablet and a counterfeit tablet.

[0098] FIGURE 52 shows the second derivative of the spectral comparison of Prozac and a similarly formulated generic.

[0099] FIGURE 53 illustrates an example of the near infrared spectra for different pure components of a studied drug.

[0100] FIGURE 54 shows the mid-wave infrared and long-wave infrared absorption spectra for various illicit drugs.

[0101] FIGURE 55 shows the absorbance versus wavelength in the near-infrared region for four classes of illegal drugs.

[0102] FIGURE 56 illustrates the diffuse reflectance near-infrared spectrum of heroin samples.

[0103] FIGURE 57 illustrates the diffuse reflectance near-infrared spectra of different seized illicit drugs containing heroin of different concentrations, along with the spectrum for pure heroin.

[0104] FIGURE 58A lists possible band assignments for the various spectral features in pure heroin.

[0105] FIGURES 58B also lists possible band assignments for the various spectral features in pure heroin.

[0106] FIGURE 59 shows the diffuse reflectance near-infrared spectra of different compounds that may be frequently employed as cutting agents.

[0107] FIGURE 60 provides one example of a flow-chart in the process analytical technology for the pharmaceutical industry.

[0108] FIGURE 61 illustrates the typical near-infrared spectra of a variety of excipients.

[0109] FIGURE 62 exemplifies the absorbance from the blending process of a pharmaceutical compound.

[0110] FIGURE 63 shows what might be an eventual flow-chart of a smart manufacturing process.

[0111] FIGURE 64A illustrates the near-infrared reflectance spectrum of wheat flour.

[0112] FIGURE 64B shows the near-infrared absorbance spectra obtained in diffusion reflectance mode for a series of whole 'Hass' avocado fruit.

[0113] FIGURE 65A is a schematic diagram of the basic elements of an imaging spectrometer.

[0114] FIGURE 65B illustrates one example of a typical imaging spectrometer used in hyper-spectral imaging systems.

[0115] FIGURE 66 shows one example of the Fourier transform infrared spectrometer.

[0116] FIGURE 67 exemplifies a dual-beam experimental set-up that may be used to subtract out (or at least minimize the adverse effects of) light source fluctuations.

[0117] FIGURE 68 illustrates the optical absorption of pure water, hemoglobin without oxygen, and hemoglobin saturated with oxygen.

[0118] FIGURE 69 shows examples of various absorption bands of chemical species in the wavelength range between about 1200-2200nm.

[0119] FIGURE 70 depicts the structure of a female breast.

[0120] FIGURE 71 illustrates particular embodiments of imaging systems for optically scanning a breast.

[0121] FIGURE 72 shows the normalized absorption spectra of main tissue absorbers in the NIR for breast cancer, between about 600-1100nm.

[0122] FIGURE 73 illustrates the normalized absorption coefficient in the wavelength range between about 500-1600nm for many of the components of breast tissue.

[0123] FIGURE 74A shows the typical spectra of the cancerous site of a treated rat and the corresponding site of a normal rat and illustrates the logarithm of the inverse of reflection spectra.

[0124] FIGURES 74B shows the typical spectra of the cancerous site of a treated rat and the corresponding site of a normal rat and illustrates second derivative spectra.

[0125] FIGURE 75 shows the second derivative of spectral changes over several weeks between about 1600-1800nm in rats with breast cancer.

[0126] FIGURE 76 illustrates the second derivative spectra for cholesterol, collagen and elastin.

[0127] FIGURE 77 shows the absorption coefficient as a function of wavelength between about 1000nm and 2600nm for water, adipose and collagen.

[0128] FIGURE 78 illustrates the absorbance for four types of collagen: collagen I, collagen II, collagen III, and collagen IV.

[0129] FIGURE 79 shows an experimental set-up for testing chicken breast samples using collimated light. In this experiment, the collimated light has a beam diameter of about 3mm.

[0130] FIGURE 80 plots the measured depth of damage (in millimeters) versus the time-averaged incident power (in Watts). Data is presented for laser wavelengths near 980nm, 1210nm and 1700nm, and lines are drawn corresponding to penetration depths of approximately 2mm, 3mm, and 4mm.

[0131] FIGURE 81 illustrates the optical absorption or density as a function of wavelength between approximately 700nm and 1300nm for water, hemoglobin and oxygenated hemoglobin.

[0132] FIGURE 82 shows a set-up used for in vitro damage experiments using focused infrared light. After a lens system, the tissue is placed between two microscope slides.

[0133] FIGURE 83A presents histology of renal arteries comprising endothelium, media and adventitia layers and some renal nerves in or below the adventitia and illustrates renal arteries with no laser exposure.

[0134] FIGURE 83B presents histology of renal arteries comprising endothelium, media and adventitia layers and some renal nerves in or below the adventitia and illustrates renal arteries after focused laser exposure, with the laser light near 1708nm.

[0135] FIGURE 84 illustrates the experimental set-up for ex vivo skin laser treatment with surface cooling to protect the epidermis and top layer of the dermis.

[0136] FIGURE 85A shows MTT histo-chemistry of ex vivo human skin treated with ~1708nm laser and cold window (5 seconds precool; 2mm diameter spot exposure for 3 seconds) at 725mW corresponding to ~70 J/cm2 average fluence.

[0137] FIGURE 85B also shows MTT histo-chemistry of ex vivo human skin treated with ~1708nm laser and cold window (5 seconds precool; 2mm diameter spot exposure for 3 seconds) at 725mW corresponding to ~70 J/cm2 average fluence.

[0138] FIGURE 85C shows MTT histo-chemistry of ex vivo human skin treated with ~1708nm laser and cold window (5 seconds precool; 2mm diameter spot exposure for 3 seconds) at 830mW corresponding to ~80 J/cm2 average fluence.

[0139] FIGURE 85D also shows MTT histo-chemistry of ex vivo human skin treated with ~1708nm laser and cold window (5 seconds precool; 2mm diameter spot exposure for 3 seconds) at 830mW corresponding to ~80 J/cm2 average fluence.

DETAILED DESCRIPTION

[0140] SECTION 1: NEAR-INFRARED LASERS FOR NON-INVASIVE MONITORING OF GLUCOSE, KETONES, HBA1C, AND OTHER BLOOD CONSTITUENTS

[0141] As required, detailed embodiments of the present disclosure are described herein; however, it is to be understood that the disclosed embodiments are merely exemplary of the disclosure that may be embodied in various and alternative forms. The figures are not necessarily

to scale; some features may be exaggerated or minimized to show details of particular components. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present disclosure.

[0142] Various ailments or diseases may require measurement of the concentration of one or more blood constituents. For example, diabetes may require measurement of the blood glucose and HbA1c levels. On the other hand, diseases or disorders characterized by impaired glucose metabolism may require the measurement of ketone bodies in the blood. Examples of impaired glucose metabolism diseases include Alzheimer's, Parkinson's, Huntington's, and Lou Gehrig's or amyotrophic lateral sclerosis (ALS). Techniques related to near-infrared spectroscopy or hyper-spectral imaging may be particularly advantageous for non-invasive monitoring of some of these blood constituents.

[0143] As used throughout this document, the term "couple" and or "coupled" refers to any direct or indirect communication between two or more elements, whether or not those elements are physically connected to one another. As used throughout this disclosure, the term "spectroscopy" means that a tissue or sample is inspected by comparing different features, such as wavelength (or frequency), spatial location, transmission, absorption, reflectivity, scattering, refractive index, or opacity. In one embodiment, "spectroscopy" may mean that the wavelength of the light source is varied, and the transmission, absorption or reflectivity of the tissue or sample is measured as a function of wavelength. In another embodiment, "spectroscopy" may mean that the wavelength dependence of the transmission, absorption or reflectivity is compared between different spatial locations on a tissue or sample. As an illustration, the "spectroscopy" may be performed by varying the wavelength of the light source, or by using a broadband light source and analyzing the signal using a spectrometer, wavemeter, or optical spectrum analyzer.

[0144] As used throughout this document, the term "fiber laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein at least a part of the laser comprises an optical fiber. For instance, the fiber in the "fiber laser" may comprise one of or a combination of a single mode fiber, a multi-mode fiber, a mid-infrared fiber, a photonic crystal fiber, a doped fiber, a gain fiber, or, more generally, an approximately cylindrically shaped waveguide or light-

pipe. In one embodiment, the gain fiber may be doped with rare earth material, such as ytterbium, erbium, and/or thulium. In another embodiment, the mid-infrared fiber may comprise one or a combination of fluoride fiber, ZBLAN fiber, chalcogenide fiber, tellurite fiber, or germanium doped fiber. In yet another embodiment, the single mode fiber may include standard single-mode fiber, dispersion shifted fiber, non-zero dispersion shifted fiber, high-nonlinearity fiber, and small core size fibers.

[0145] As used throughout this disclosure, the term "pump laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein the output light or optical beam is coupled to a gain medium to excite the gain medium, which in turn may amplify another input optical signal or beam. In one particular example, the gain medium may be a doped fiber, such as a fiber doped with ytterbium, erbium or thulium. In one embodiment, the "pump laser" may be a fiber laser, a solid state laser, a laser involving a nonlinear crystal, an optical parametric oscillator, a semiconductor laser, or a plurality of semiconductor lasers that may be multiplexed together. In another embodiment, the "pump laser" may be coupled to the gain medium by using a fiber coupler, a dichroic mirror, a multiplexer, a wavelength division multiplexer, a grating, or a fused fiber coupler.

[0146] As used throughout this document, the term "super-continuum" and or "supercontinuum" and or "SC" refers to a broadband light beam or output that comprises a plurality of wavelengths. In a particular example, the plurality of wavelengths may be adjacent to one-another, so that the spectrum of the light beam or output appears as a continuous band when measured with a spectrometer. In one embodiment, the broadband light beam may have a bandwidth of at least 10nm. In another embodiment, the "super-continuum" may be generated through nonlinear optical interactions in a medium, such as an optical fiber or nonlinear crystal. For example, the "super-continuum" may be generated through one or a combination of nonlinear activities such as four-wave mixing, the Raman effect, modulational instability, and self-phase modulation.

[0147] As used throughout this disclosure, the terms "optical light" and or "optical beam" and or "light beam" refer to photons or light transmitted to a particular location in space. The "optical light" and or "optical beam" and or "light beam" may be modulated or unmodulated,

which also means that they may or may not contain information. In one embodiment, the "optical light" and or "optical beam" and or "light beam" may originate from a fiber, a fiber laser, a laser, a light emitting diode, a lamp, a pump laser, or a light source.

[0148] SPECTRUM FOR GLUCOSE

[0149] One molecule of interest is glucose. The glucose molecule has the chemical formula C6H12O6, so it has a number of hydro-carbon bonds. An example of the infrared transmittance of glucose 100 is illustrated in FIGURE 1. The vibrational spectroscopy shows that the strongest lines for bending and stretching modes of C-H and O-H bonds lie in the wavelength range of approximately 6-12 microns. However, light sources and detectors are more difficult in the mid-wave infrared and long-wave infrared, and there is also strongly increasing water absorption in the human body beyond about 2.5 microns. Although weaker, there are also non-linear combinations of stretching and bending modes between about 2 to 2.5 microns, and first overtone of C-H stretching modes between approximately 1.5-1.8 microns. These signatures may fall in valleys of water absorption, permitting non-invasive detection through the body. In addition, there are yet weaker features from the second overtones and higher-order combinations between about 0.8-1.2 microns; in addition to being weaker, these features may also be masked by absorption in the hemoglobin. Hence, the short-wave infrared (SWIR) wavelength range of approximately 1.4 to 2.5 microns may be an attractive window for near-infrared spectroscopy of blood constituents.

[0150] As an example, measurements of the optical absorbance 200 of hemoglobin, glucose and HbA1c have been performed using a Fourier-Transform Infrared Spectrometer – FTIR. As FIGURE 2 shows, in the SWIR wavelength range hemoglobin is nearly flat in spectrum 201 (the noise at the edges is due to the weaker light signal in the measurements). On the other hand, the glucose absorbance 202 has at least five distinct peaks near 1587nm, 1750nm, 2120nm, 2270nm and 2320nm.

[0151] FIGURE 3A overlaps 300 the normalized absorbance of glucose 301 with the absorbance of water 302 (not drawn to scale). It may be seen that water has an absorbance feature between approximately 1850nm and 2050nm, but water 302 also has a nice transmission window between approximately 1500-1850nm and 2050 to 2500nm. For wavelengths less than about

1100nm, the absorption of hemoglobin 351 and oxygenated hemoglobin 352 in FIGURE 3B has a number of features 350, which may make it more difficult to measure blood constituents. Also, beyond 2500nm the water absorption becomes considerably stronger over a wide wavelength range. Therefore, an advantageous window for measuring glucose and other blood constituents may be in the SWIR between 1500 and 1850nm and 2050 to 2500nm. These are exemplary wavelength ranges, and other ranges can be used that would still fall within the scope of this disclosure.

[0152] One further consideration in choosing the laser wavelength is known as the "eye safe" window for wavelengths longer than about 1400nm. In particular, wavelengths in the eye safe window may not transmit down to the retina of the eye, and therefore, these wavelengths may be less likely to create permanent eye damage. The near-infrared wavelengths have the potential to be dangerous, because the eye cannot see the wavelengths (as it can in the visible), yet they can penetrate and cause damage to the eye. Even if a practitioner is not looking directly at the laser beam, the practitioner's eyes may receive stray light from a reflection or scattering from some surface. Hence, it can always be a good practice to use eye protection when working around lasers. Since wavelengths longer than about 1400nm are substantially not transmitted to the retina or substantially absorbed in the retina, this wavelength range is known as the eye safe window. For wavelengths longer than 1400nm, in general only the cornea of the eye may receive or absorb the light radiation.

[0153] Beyond measuring blood constituents such as glucose using FTIR spectrometers, measurements have also been conducted in another embodiment using super-continuum lasers, which will be described later in this disclosure. In this particular embodiment, some of the exemplary preliminary data for glucose absorbance are illustrated in FIGURES 4A and 4B. The optical spectra 401 in FIGURE 4A for different levels of glucose concentration in the wavelength range between 2000 and 2400nm show the three absorption peaks near 2120nm (2.12μm), 2270nm (2.27μm) and 2320nm (2.32μm). Moreover, the optical spectra 402 in FIGURE 4B for different levels of glucose concentration in the wavelength range between 1500 and 1800nm show the two broader absorption peaks near 1587nm and 1750nm. It should be appreciated that although data measured with FTIR spectrometers or super-continuum lasers have been illustrated, other light sources can also be used to obtain the data, such as super-luminescent laser diodes, light emitting

diodes, a plurality of laser diodes, or even bright lamp sources that generate adequate light in the SWIR.

[0154] Although glucose has a distinctive signature in the SWIR wavelength range, one problem of non-invasive glucose monitoring is that many other blood constituents also have hydrocarbon bonds. Consequently, there can be interfering signals from other constituents in the blood. As an example, FIGURE 5 illustrates the spectrum 500 for different blood constituents in the wavelength range of 2 to 2.45 microns. The glucose absorption spectrum 501 can be unique with its three peaks in this wavelength range. However, other blood constituents such as triacetin 502, ascorbate 503, lactate 504, alanine 505, urea 506, and BSA 507 also have spectral features in this wavelength range. To distinguish the glucose 501 from these overlapping spectra, it may be advantageous to have information at multiple wavelengths. In addition, it may be advantageous to use pattern matching algorithms and other software and mathematical methods to identify the blood constituents of interest. In one embodiment, the spectrum may be correlated with a library of known spectra to determine the overlap integrals, and a threshold function may be used to quantify the concentration of different constituents. This is just one way to perform the signal processing, and many other techniques, algorithms, and software may be used and would fall within the scope of this disclosure.

[0155] KETONE BODIES MONITORING

[0156] Beyond glucose, there are many other blood constituents that may also be of interest for health or disease monitoring. In another embodiment, it may be desirous to monitor the level of ketone bodies in the blood stream. Ketone bodies are three water-soluble compounds that are produced as by-products when fatty acids are broken down for energy in the liver. Two of the three are used as a source of energy in the heart and brain, while the third is a waste product excreted from the body. In particular, the three endogenous ketone bodies are acetone, acetoacetic acid, and beta-hydroxybutyrate or 3-hydroxybutyrate, and the waste product ketone body is acetone.

[0157] Ketone bodies may be used for energy, where they are transported from the liver to other tissues. The brain may utilize ketone bodies when sufficient glucose is not available for energy. For instance, this may occur during fasting, strenuous exercise, low carbohydrate,

ketogenic diet and in neonates. Unlike most other tissues that have additional energy sources such as fatty acids during periods of low blood glucose, the brain cannot break down fatty acids and relies instead on ketones. In one embodiment, these ketone bodies are detected.

[0158] Ketone bodies may also be used for reducing or eliminating symptoms of diseases or disorders characterized by impaired glucose metabolism. For example, diseases associated with reduced neuronal metabolism of glucose include Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease), Huntington's disease and epilepsy. In one embodiment, monitoring of alternate sources of ketone bodies that may be administered orally as a dietary supplement or in a nutritional composition to counteract some of the glucose metabolism impairments is performed. However, if ketone bodies supplements are provided, there is also a need to monitor the ketone level in the blood stream. For instance, if elevated levels of ketone bodies are present in the body, this may lead to ketosis; hyperketonemia is also an elevated level of ketone bodies in the blood. In addition, both acetoacetic acid and beta-hydroxybutyric acid are acidic, and, if levels of these ketone bodies are too high, the pH of the blood may drop, resulting in ketoacidosis.

[0159] The general formula for ketones is CnH2n0. In organic chemistry, a ketone is an organic compound with the structure RC(=O)R', where R and R' can be a variety of carbon-containing substituents. It features a carbonyl group (C=O) bonded to two other carbon atoms. Because the ketones contain the hydrocarbon bonds, there might be expected to be features in the SWIR, similar in structure to those found for glucose.

[0160] The infrared spectrum 600 for the ketone 3-hydroxybutyrate is illustrated in FIGURE 6. Just as in glucose, there are significant features in the mid- and long-wave infrared between 6 to 12 microns, but these may be difficult to observe non-invasively. On the other hand, there are some features in the SWIR that may be weaker, but they could potentially be observed non-invasively, perhaps through blood and water.

[0161] The optical spectra 700 for ketones as well as some other blood constituents are exemplified in FIGURE 7 in the wavelength range of 2100nm to 2400nm. In this embodiment, the absorbance for ketones is 701, while the absorbance for glucose is 702. However, there are also features in this wavelength range for other blood constituents, such as urea 703, albumin or

blood protein 704, creatinine 705, and nitrite 706. In this wavelength range of 2100 to 2400nm, the features for ketone 701 seem more spectrally pronounced than even glucose.

[0162] Different signal processing techniques can be used to enhance the spectral differences between different constituents. In one embodiment, the first or second derivatives of the spectra may enable better discrimination between substances. The first derivative may help remove any flat offset or background, while the second derivative may help to remove any sloped offset or background. In some instances, the first or second derivative may be applied after curve fitting or smoothing the reflectance, transmittance, or absorbance. For example, FIGURE 8A illustrates the derivative spectra for ketone 801 and glucose 802, which can be distinguished from the derivative spectra for protein 803, urea 804 and creatinine 805. Based on FIGURE 8A, it appears that ketones 801 may have a more pronounced difference than even glucose 802 in the wavelength range between 2100 and 2400nm. Therefore, ketone bodies should also be capable of being monitored using a non-invasive optical technique in the SWIR, and a different pattern matching library could be used for glucose and ketones.

[0163] HEMOGLOBIN A1C MONITORING

[0164] Another blood constituent that may be of interest for monitoring of health or diseases is hemoglobin A1c, also known as HbA1c or glycated hemoglobin (glycol-hemoglobin or glycosylated hemoglobin). HbA1c is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. Thus, HbA1c may serve as a marker for average blood glucose levels over the previous months prior to the measurements.

[0165] In one embodiment, when a physician suspects that a patient may be diabetic, the measurement of HbA1c may be one of the first tests that are conducted. An HbA1c level less than approximately 6% may be considered normal. On the other hand, an HbA1c level greater than approximately 6.5% may be considered to be diabetic. In diabetes mellitus, higher amounts of HbA1c indicate poorer control of blood glucose levels. Thus, monitoring the HbA1c in diabetic patients may improve treatment. Current techniques for measuring HbA1c require drawing blood, which may be inconvenient and painful. The point-of-care devices use immunoassay or boronate

affinity chromatography, as an example. Thus, there is also an unmet need for non-invasive monitoring of HbA1c.

[0166] FIGURE 2 illustrates the FTIR measurements of HbA1c absorbance 203 over the wavelength range between 1500 and 2400nm for a concentration of approximately 1mg/ml. Whereas the absorbance of hemoglobin 201 over this wavelength range is approximately flat, the HbA1c absorbance 203 shows broad features and distinct curvature. Although the HbA1c absorbance 203 does not appear to exhibit as pronounced features as glucose 202, the non-invasive SWIR measurement should be able to detect HbA1c with appropriate pattern matching algorithms. Moreover, the spectrum for HbA1c may be further enhanced by using first or second derivative data, as seen for ketones in FIGURE 8A. Beyond absorption, reflectance, or transmission spectroscopy, it may also be possible to detect blood constituents such as HbA1c using Raman spectroscopy or surface-enhanced Raman spectroscopy. In general, Raman spectroscopy may require higher optical power levels.

[0167] As an illustration, non-invasive measurement of blood constituents such as glucose, ketone bodies, and HbA1c has been discussed thus far. However, other blood constituents can also be measured using similar techniques, and these are also intended to be covered by this disclosure. In other embodiments, blood constituents such as proteins, albumin, urea, creatinine or nitrites could also be measured. For instance, the same type of SWIR optical techniques might be used, but the pattern matching algorithms and software could use different library features or functions for the different constituents.

[0168] In yet another embodiment, the optical techniques described in this disclosure could also be used to measure levels of triglycerides. Triglycerides are bundles of fats that may be found in the blood stream, particularly after ingesting meals. The body manufactures triglycerides from carbohydrates and fatty foods that are eaten. In other words, triglycerides are the body's storage form of fat. Triglycerides are comprised of three fatty acids attached to a glycerol molecule, and measuring the level of triglycerides may be important for diabetics. The triglyceride levels or concentrations in blood may be rated as follows: desirable or normal may be less than 150 mg/dl; borderline high may be 150-199 mg/dl; high may be 200-499 mg/dl; and very high may be 500mg/dl or greater. FIGURE 8B illustrates one example of the near-infrared absorbance 825 for

triglycerides. There are distinct absorbance peaks in the spectrum that should be measurable. The characteristic absorption bands may be assigned as follows: (a) the first overtones of C-H stretching vibrations (1600-1900nm); (b) the region of second overtones of C-H stretching vibrations (1100-1250nm); and, (c) two regions (2000-2200nm and 1350-1500nm) that comprise bands due to combinations of C-H stretching vibrations and other vibrational modes.

[0169] A further example of blood compositions that can be detected or measured using near-infrared light includes cholesterol monitoring. For example, FIGURE 8C shows the near-infrared reflectance spectrum for cholesterol 850 with wavelength in microns (μm). Distinct absorption peaks are observable near 1210nm (1.21 μm), 1720nm (1.72 μm), and between 2300-2500nm (2.3-2.5μm). Also, there are other features near 1450nm (1.45μm) and 2050nm (2.05μm). In FIGURE 8D the near-infrared reflectances 875 are displayed versus wavelength (nm) for various blood constituents. The spectrum for cholesterol 876 is overlaid with glucose 877, albumin 878, uric acid 879, and urea 880. As may be noted from FIGURE 8D, at about 1720nm and 2300nm, cholesterol 876 reaches approximate reflectance peaks, while some of the other analytes are in a more gradual mode. Various signal processing methods may be used to identify and quantify the concentration of cholesterol 876 and/or glucose 877, or some of the other blood constituents.

[0170] As illustrated by FIGURES 5 and 7, one of the issues in measuring a particular blood constituent is the interfering and overlapping signal from other blood constituents. The selection of the constituent of interest may be improved using a number of techniques. For example, a higher light level or intensity may improve the signal-to-noise ratio for the measurement. Second, mathematical modeling and signal processing methodologies may help to reduce the interference, such as multivariate techniques, multiple linear regression, and factor-based algorithms, for example. For instance, a number of mathematical approaches include multiple linear regression, partial least squares, and principal component regression (PCR). Also, as illustrated in FIGURE 8A, various mathematical derivatives, including the first and second derivatives, may help to accentuate differences between spectra. In addition, by using a wider wavelength range and using more sampling wavelengths may improve the ability to discriminate one signal from another. These are just examples of some of the methods of improving the ability

to discriminate between different constituents, but other techniques may also be used and are intended to be covered by this disclosure.

[0171] INTERFERENCE FROM SKIN

[0172] Several proposed non-invasive glucose monitoring techniques rely on transmission, absorption, and/or diffuse reflection through the skin to measure blood constituents or blood analytes in veins, arteries, capillaries or in the tissue itself. However, on top of the interference from other blood constituents or analytes, the skin also introduces significant interference. For example, chemical, structural, and physiological variations occur that may produce relatively large and nonlinear changes in the optical properties of the tissue sample. In one embodiment, the near-infrared reflectance or absorbance spectrum may be a complex combination of the tissue scattering properties that result from the concentration and characteristics of a multiplicity of tissue components including water, fat, protein, collagen, elastin, and/or glucose. Moreover, the optical properties of the skin may also change with environmental factors such as humidity, temperature and pressure. Physiological variation may also cause changes in the tissue measurement over time and may vary based on lifestyle, health, aging, etc. The structure and composition of skin may also vary widely among individuals, between different sites within an individual, and over time on the same individual. Thus, the skin introduces a dynamic interference signal that may have a wide variation due to a number of parameters.

[0173] FIGURE 9 shows a schematic cross-section of human skin 900, 901. The top layer of the skin is epidermis 902, followed by a layer of dermis 903 and then subcutaneous fat 904 below the dermis. The epidermis 902, with a thickness of approximately 10-150 microns, may provide a barrier to infection and loss of moisture and other body constituents. The dermis 903 ranges in thickness from approximately 0.5mm to 4mm (averages approximately 1.2mm over most of the body) and may provide the mechanical strength and elasticity of skin.

[0174] In the dermis 903, water may account for approximately 70% of the volume. The next most abundant constituent in the dermis 903 may be collagen 905, a fibrous protein comprising 70-75% of the dry weight of the dermis 903. Elastin fibers 906, also a protein, may also be plentiful in the dermis 903, although they constitute a smaller portion of the bulk. In addition, the dermis 903 may contain a variety of structures (e.g., sweat glands, hair follicles with

adipose rich sebaceous glands 907 near their roots, and blood vessels) and other cellular constituents.

[0175] Below the dermis 903 lies the subcutaneous layer 904 comprising mostly adipose tissue. The subcutaneous layer 904 may be by volume approximately 10% water and may be comprised primarily of cells rich in triglycerides or fat. With this complicated structure of the skin 900,901, the concentration of glucose may vary in each layer according to a variety of factors including the water content, the relative sizes of the fluid compartments, the distribution of capillaries, the perfusion of blood, the glucose uptake of cells, the concentration of glucose in blood, and the driving forces (e.g., osmotic pressure) behind diffusion.

[0176] To better understand the interference that the skin introduces when attempting to measure glucose, the absorption coefficient for the various skin constituents should be examined. For example, FIGURE 10 illustrates 1000 the absorption coefficients for water (including scattering) 1001, adipose 1002, collagen 1003 and elastin 1004. Note that the absorption curves for water 1001 and adipose 1002 are calibrated, whereas the absorption curves for collagen 1003 and elastin 1004 are in arbitrary units. Also shown are vertical lines demarcating the wavelengths near 1210nm 1005 and 1720nm 1006. In general, the water absorption increases with increasing wavelength. With the increasing absorption beyond about 2000nm, it may be difficult to achieve deeper penetration into biological tissue in the infrared wavelengths beyond approximately 2500nm.

[0177] Although the absorption coefficient may be useful for determining the material in which light of a certain infrared wavelength will be absorbed, to determine the penetration depth of the light of a certain wavelength may also require the addition of scattering loss to the curves. For example, the water curve 1001 includes the scattering loss curve in addition to the water absorption. In particular, the scattering loss can be significantly higher at shorter wavelengths. In one embodiment, near the wavelength of 1720nm (vertical line 1006 shown in FIGURE 10), the adipose absorption 1002 can still be higher than the water plus scattering loss 1001. For tissue that contains adipose, collagen and elastin, such as the dermis of the skin, the total absorption can exceed the light energy lost to water absorption and light scattering at 1720nm. On the other hand,

at 1210nm the adipose absorption 1002 can be considerably lower than the water plus scattering loss 1001, particularly since the scattering loss can be dominant at these shorter wavelengths.

[0178] The interference for glucose lines observed through skin may be illustrated by overlaying the glucose lines over the absorption curves 1000 for the skin constituents. For example, FIGURE 2 illustrated that the glucose absorption 202 included features centered around 1587nm, 1750nm, 2120nm, 2270nm and 2320nm. On FIGURE 10 vertical lines have been drawn at the glucose line wavelengths of 1587nm 1007, 1750nm 1008, 2120nm 1009, 2270nm 1010 and 2320nm 1011. In one embodiment, it may be difficult to detect the glucose lines near 1750nm 1008, 2270nm 1010 and 2320nm 1011 due to significant spectral interference from other skin constituents. On the other hand, the glucose line near 1587m 1007 may be more easily detected because it peaks while most of the other skin constituents are sloped downward toward an absorption valley. Moreover, the glucose line near 2120nm 1009 may also be detectable for similar reasons, although adipose may have conflicting behavior due to local absorption minimum and maximum nearby in wavelength.

[0179] Thus, beyond the problem of other blood constituents or analytes having overlapping spectral features (e.g., FIGURE 5), it may be difficult to observe glucose spectral signatures through the skin and its constituents of water, adipose, collagen and elastin. One approach to overcoming this difficulty may be to try to measure the blood constituents in veins that are located at relatively shallow distances below the skin. Veins may be more beneficial for the measurement than arteries, since arteries tend to be located at deeper levels below the skin. Also, in one embodiment it may be advantageous to use a differential measurement to subtract out some of the interfering absorption lines from the skin. For example, an instrument head may be designed to place one probe above a region of skin over a blood vein, while a second probe may be placed at a region of the skin without a noticeable blood vein below it. Then, by differencing the signals from the two probes, at least part of the skin interference may be cancelled out.

[0180] Two representative embodiments for performing such a differential measurement are illustrated in FIGURE 11 and FIGURE 12. In one embodiment shown in FIGURE 11, the dorsal of the hand 1100 may be used for measuring blood constituents or analytes. The dorsal of the hand 1100 may have regions that have distinct veins 1101 as well as regions where the veins

are not as shallow or pronounced 1102. By stretching the hand and leaning it backwards, the veins 1101 may be accentuated in some cases. A near-infrared diffuse reflectance measurement may be performed by placing one probe 1103 above the vein-rich region 1101. To turn this into a differential measurement, a second probe 1104 may be placed above a region without distinct veins 1102. Then, the outputs from the two probes may be subtracted 1105 to at least partially cancel out the features from the skin. The subtraction may be done preferably in the electrical domain, although it can also be performed in the optical domain or digitally/mathematically using sampled data based on the electrical and/or optical signals. Although one example of using the dorsal of the hand 1100 is shown, many other parts of the hand can be used within the scope of this disclosure. For example, alternate methods may use transmission through the webbing between the thumb and the fingers 1106, or transmission or diffuse reflection through the tips of the fingers 1107.

[0181] In another embodiment, the dorsal of the foot 1200 may be used instead of the hand. One advantage of such a configuration may be that for self-testing by a user, the foot may be easier to position the instrument using both hands. One probe 1203 may be placed over regions where there are more distinct veins 1201, and a near-infrared diffuse reflectance measurement may be made. For a differential measurement, a second probe 1204 may be placed over a region with less prominent veins 1202, and then the two probe signals may be subtracted, either electronically or optically, or may be digitized/sampled and processed mathematically depending on the particular application and implementation. As with the hand, the differential measurements may be intended to compensate for or subtract out (at least in part) the interference from the skin. Since two regions are used in close proximity on the same body part, this may also aid in removing some variability in the skin from environmental effects such as temperature, humidity, or pressure. In addition, it may be advantageous to first treat the skin before the measurement, by perhaps wiping with a cloth or treated cotton ball, applying some sort of cream, or placing an ice cube or chilled bag over the region of interest.

[0182] Although two embodiments have been described, many other locations on the body may be used using a single or differential probe within the scope of this disclosure. In yet another embodiment, the wrist may be advantageously used, particularly where a pulse rate is typically monitored. Since the pulse may be easily felt on the wrist, there is underlying the region a distinct

blood flow. Other embodiments may use other parts of the body, such as the ear lobes, the tongue, the inner lip, the nails, the eye, or the teeth. Some of these embodiments will be further described below. The ear lobes or the tip of the tongue may be advantageous because they are thinner skin regions, thus permitting transmission rather than diffuse reflection. However, the interference from the skin is still a problem in these embodiments. Other regions such as the inner lip or the bottom of the tongue may be contemplated because distinct veins are observable, but still the interference from the skin may be problematic in these embodiments. The eye may seem as a viable alternative because it is more transparent than skin. However, there are still issues with scattering in the eye. For example, the anterior chamber of the eye (the space between the cornea and the iris) comprises a fluid known as aqueous humor. However, the glucose level in the eye chamber may have a significant temporal lag on changes in the glucose level compared to the blood glucose level.

[0183] Because of the complexity of the interference from skin in non-invasive glucose monitoring (e.g., FIGURE 10), other parts of the body without skin above blood vessels or capillaries may be alternative candidates for measuring blood constituents. One embodiment may involve transmission or reflection through human nails. As an example, FIGURE 13 illustrates a typical human nail tissue structure 1300 and the capillary vessels below it. The fingernail 1301 is approximately 1mm thick, and below this resides a layer of epidermis 1302 with a thickness of approximately 1mm. The dermis 1304 is also shown, and within particularly the top about 0.5mm of dermis are a significant number of capillary vessels. To measure the blood constituents, the light exposed on the top of the fingernail must penetrate about 2-2.5mm or more, and the reflected light (round trip passage) should be sufficiently strong to measure. In one embodiment, the distance required to penetrate could be reduced by drilling a hole in the fingernail 1301.

[0184] In this alternative embodiment using the fingernail, there may still be interference from the nail's spectral features. For example, FIGURE 14 illustrates the attenuation coefficient 1400 for seven nail samples that are allowed to stand in an environment with a humidity level of 14%. These coefficients are measured using an FTIR spectrometer over the near-infrared wavelength range of approximately 1 to 2.5 microns. These spectra are believed to correspond to the spectra of keratin contained in the nail plate. The base lines for the different samples are believed to differ because of the influence of scattering. Several of the absorption peaks observed

correspond to peaks of keratin absorption, while other features may appear from the underlying epidermis and dermis. It should also be noted that the attenuation coefficients 1400 also vary considerably depending on humidity level or water content as well as temperature and other environmental factors. Moreover, the attenuation coefficient may also change in the presence of nail polish of various sorts.

[0185] Similar to skin, the large variations in attenuation coefficient for fingernails also may interfere with the absorption peaks of glucose. As an example, in FIGURE 14 below the fingernail spectrum is also shown the glucose spectrum 1401 for two different glucose concentrations. The vertical lines 1402, 1403, 1404, 1405 and 1406 are drawn to illustrate the glucose absorption peaks and where they lie on the fingernail spectra 1400. As is apparent, the nail has interfering features that may be similar to skin, particularly since both have spectra that vary not only in wavelength but also with environmental factors. In one embodiment, it may be possible to see the glucose peaks 1402 and 1404 through the fingernail, but it may be much more difficult to observe the glucose peaks near 1403, 1405 and 1406.

[0186] TRANSMISSION OR REFLECTION THROUGH TEETH

[0187] Yet another embodiment may observe the transmittance or reflectance through teeth to measure blood constituents or analytes. FIGURE 15 illustrates an exemplary structure of a tooth 1500. The tooth 1500 has a top layer called the crown 1501 and below that a root 1502 that reaches well into the gum 1506 and bone 1508 of the mouth. The exterior of the crown 1501 is an enamel layer 1503, and below the enamel is a layer of dentine 1504 that sits atop a layer of cementum 1507. Below the dentine 1504 is a pulp region 1505, which comprises within it blood vessels 1509 and nerves 1510. If the light can penetrate the enamel 1503 and dentine 1504, then the blood flow and blood constituents can be measured through the blood vessels in the dental pulp 1505. While it may be true that the amount of blood flow in the dental pulp 1505 may be less since it comprises capillaries, the smaller blood flow could still be advantageous if there is less interfering spectral features from the tooth.

[0188] The transmission, absorption and reflection from teeth has been studied in the near infrared, and, although there are some features, the enamel and dentine appear to be fairly transparent in the near infrared (particularly wavelengths between 1500 and 2500nm). For

example, the absorption or extinction ratio for light transmission has been studied. FIGURE 16A illustrates the attenuation coefficient 1600 for dental enamel 1601 (filled circles) and the absorption coefficient of water 1602 (open circles) versus wavelength. Near-infrared light may penetrate much further without scattering through all the tooth enamel, due to the reduced scattering coefficient in normal enamel. Scattering in enamel may be fairly strong in the visible, but decreases as approximately 1/(wavelength)3 [i.e., inverse of the cube of the wavelength] with increasing wavelength to a value of only 2-3 cm-1 at 1310nm and 1550nm in the near infrared. Therefore, enamel may be virtually transparent in the near infrared with optical attenuation 1-2 orders of magnitude less than in the visible range.

[0189] As another example, FIGURE 16B illustrates the absorption spectrum 1650 of intact enamel 1651 (dashed line) and dentine 1652 (solid line) in the wavelength range of approximately 1.2 to 2.4 microns. In the near infrared there are two absorption bands around 1.5 and 2 microns. The band with a peak around 1.57 microns may be attributed to the overtone of valent vibration of water present in both enamel and dentine. In this band, the absorption is greater for dentine than for enamel, which may be related to the large water content in this tissue. In the region of 2 microns, dentine may have two absorption bands, and enamel one. The band with a maximum near 2.1 microns may belong to the overtone of vibration of PO hydroxyapatite groups, which is the main substance of both enamel and dentine. Moreover, the band with a peak near 1.96 microns in dentine may correspond to water absorption (dentine may contain substantially higher water than enamel).

[0190] In addition to the absorption coefficient, the reflectance from intact teeth and teeth with dental caries (e.g., cavities) has been studied. In one embodiment, FIGURE 17 shows the near infrared spectral reflectance 1700 over the wavelength range of approximately 800nm to 2500nm from an occlusal (e.g., top/bottom) tooth surface 1704. The curve with black diamonds 1701 corresponds to the reflectance from a sound, intact tooth section. The curve with asterisks * 1702 corresponds to a tooth section with an enamel lesion. The curve with circles 1703 corresponds to a tooth section with a dentine lesion. Thus, when there is a lesion, more scattering occurs and there may be an increase in the reflected light.

[0191] For wavelengths shorter than approximately 1400nm, the shapes of the spectra remain similar, but the amplitude of the reflection changes with lesions. Between approximately 1400nm and 2500nm, an intact tooth 1701 has low reflectance (e.g., high transmission), and the reflectance appears to be more or less independent of wavelength. On the other hand, in the presence of lesions 1702 and 1703, there is increased scattering, and the scattering loss may be wavelength dependent. For example, the scattering loss may decrease as $1/(\text{wavelength})^3$ -- so, the scattering loss decreases with longer wavelengths. When there is a lesion in the dentine 1703, more water can accumulate in the area, so there is also increased water absorption. For example, the dips near 1450nm and 1900nm correspond to water absorption, and the reflectance dips are particularly pronounced in the dentine lesion 1703. One other benefit of the absorption, transmission or reflectance in the near infrared may be that stains and non-calcified plaque are not visible in this wavelength range, enabling better discrimination of defects, cracks, and demineralized areas.

[0192] Compared with the interference from skin 1000 in FIGURE 10 or fingernails 1400 in FIGURE 14, the teeth appear to introduce much less interference for non-invasive monitoring of blood constituents. The few features in FIGURES 16B or 17 may be calibrated out of the measurement. Also, using an intact tooth 1701 may further minimize any interfering signals. Furthermore, since the tooth comprises relatively hard tissue, higher power from the light sources in the near infrared may be used without damaging the tissue, such as with skin.

[0193] HUMAN INTERFACE FOR MEASUREMENT SYSTEM

[0194] A number of different types of measurements may be used to sample the blood in the dental pulp. The basic feature of the measurements should be that the optical properties are measured as a function of wavelength at a plurality of wavelengths. As further described below, the light source may output a plurality of wavelengths, or a continuous spectrum over a range of wavelengths. In a preferred embodiment, the light source may cover some or all of the wavelength range between approximately 1400nm and 2500nm. The signal may be received at a receiver, which may also comprise a spectrometer or filters to discriminate between different wavelengths. The signal may also be received at a camera, which may also comprise filters or a spectrometer. In an alternate embodiment, the spectral discrimination using filters or a spectrometer may be

placed after the light source rather than at the receiver. The receiver usually comprises one or more detectors (optical-to-electrical conversion element) and electrical circuitry. The receiver may also be coupled to analog to digital converters, particularly if the signal is to be fed to a digital device.

[0195] Referring to FIGURE 15, one or more light sources 1511 may be used for illumination. In one embodiment, a transmission measurement may be performed by directing the light source output 1511 to the region near the interface between the gum 1506 and dentine 1504. In one embodiment, the light may be directed using a light guide or a fiber optic. The light may then propagate through the dental pulp 1505 to the other side, where the light may be incident on one or more detectors or another light guide to transport the signal to a spectrometer, receiver or camera 1512. In another embodiment, the light source may be directed to one or more locations near the interface between the gum 1506 and dentine 1504 (in one example, could be from the two sides of the tooth). The transmitted light may then be detected in the occlusal surface above the tooth using a spectrometer, receiver, or camera 1512. In yet another embodiment, a reflectance measurement may be conducted by directing the light source output 1511 to, for example, the occlusal surface of the tooth, and then detecting the reflectance at a spectrometer, receiver or camera 1513. Although a few embodiments for measuring the blood constituents through a tooth are described, other embodiments and techniques may also be used and are intended to be covered by this disclosure.

[0196] The human interface for the non-invasive measurement of blood constituents may be of various forms. In one embodiment, a "clamp" design 1800 may be used to cap over one or more teeth, as illustrated in FIGURE 18A. The clamp design may be different for different types of teeth, or it may be flexible enough to fit over different types of teeth. For example, different types of teeth include the molars (toward the back of the mouth), the premolars, the canine, and the incisors (toward the front of the mouth). One embodiment of the clamp-type design is illustrated in FIGURE 18A for a molar tooth 1808. The C-clamp 1801 may be made of a plastic or rubber material, and it may comprise a light source input 1802 and a detector output 1803 on the front or back of the tooth.

[0197] The light source input 1802 may comprise a light source directly, or it may have light guided to it from an external light source. Also, the light source input 1802 may comprise a lens system to collimate or focus the light across the tooth. The detector output 1803 may comprise a detector directly, or it may have a light guide to transport the signal to an external detector element. The light source input 1802 may be coupled electrically or optically through 1804 to a light input 1806. For example, if the light source is external in 1806, then the coupling element 1804 may be a light guide, such as a fiber optic. Alternately, if the light source is contained in 1802, then the coupling element 1804 may be electrical wires connecting to a power supply in 1806. Similarly, the detector output 1803 may be coupled to a detector output unit 1807 with a coupling element 1805, which may be one or more electrical wires or a light guide, such as a fiber optic. This is just one example of a clamp over one or more teeth, but other embodiments may also be used and are intended to be covered by this disclosure.

[0198] In yet another embodiment, one or more light source ports and sensor ports may be used in a mouth-guard type design. For example, one embodiment of a dental mouth guard 1850 is illustrated in FIGURE 18B. The structure of the mouth guard 1851 may be similar to mouth guards used in sports (e.g., when playing football or boxing) or in dental trays used for applying fluoride treatment, and the mouth guard may be made from plastic or rubber materials, for example. As an example, the mouth guard may have one or more light source input ports 1852, 1853 and one or more detector output ports 1854, 1855. Although six input and output ports are illustrated, any number of ports may be used.

[0199] Similar to the clamp design describe above, the light source inputs 1852, 1853 may comprise one or more light sources directly, or they may have light guided to them from an external light source. Also, the light source inputs 1852, 1853 may comprise lens systems to collimate or focus the light across the teeth. The detector outputs 1854, 1855 may comprise one or more detectors directly, or they may have one or more light guides to transport the signals to an external detector element. The light source inputs 1852, 1853 may be coupled electrically or optically through 1856 to a light input 1857. For example, if the light source is external in 1857, then the one or more coupling elements 1856 may be one or more light guides, such as a fiber optic. Alternately, if the light sources are contained in 1852, 1853, then the coupling element 1856 may be one or more electrical wires connecting to a power supply in 1857. Similarly, the detector

outputs 1854, 1855 may be coupled to a detector output unit 1859 with one or more coupling elements 1858, which may be one or more electrical wires or one or more light guides, such as a fiber optic. This is just one example of a mouth guard design covering a plurality of teeth, but other embodiments may also be used and are intended to be covered by this disclosure. For instance, the position of the light source inputs and detector output ports could be exchanged, or some mixture of locations of light source inputs and detector output ports could be used.

[0200] Other elements may be added to the human interface designs of FIGURE 18 and are also intended to be covered by this disclosure. For instance, in one embodiment it may be desirable to have replaceable inserts that may be disposable. Particularly in a doctor's office or hospital setting, the same instrument may be used with a plurality of patients. Rather than disinfecting the human interface after each use, it may be preferable to have disposable inserts that can be thrown away after each use. In one embodiment, a thin plastic coating material may enclose the clamp design of FIGURE 18A or mouth guard design of FIGURE 18B. The coating material may be inserted before each use, and then after the measurement is exercised the coating material may be peeled off and replaced. Such a design may save the physician or user considerable time, while at the same time provide the business venture with a recurring cost revenue source. Any coating material or other disposable device may be constructed of a material having suitable optical properties that may be considered during processing of the signals used to detect any anomalies in the teeth.

[0201] LIGHT SOURCES FOR NEAR INFRARED

[0202] There are a number of light sources that may be used in the near infrared. To be more specific, the discussion below will consider light sources operating in the so-called short wave infrared (SWIR), which may cover the wavelength range of approximately 1400nm to 2500nm. Other wavelength ranges may also be used for the applications described in this disclosure, so the discussion below is merely provided for exemplary types of light sources. The SWIR wavelength range may be valuable for a number of reasons. First, the SWIR corresponds to a transmission window through water and the atmosphere. For example, 302 in FIGURE 3A and 1602 in FIGURE 16A illustrate the water transmission windows. Also, through the atmosphere, wavelengths in the SWIR have similar transmission windows due to water vapor in

the atmosphere. Second, the so-called "eye-safe" wavelengths are wavelengths longer than approximately 1400nm. Third, the SWIR covers the wavelength range for nonlinear combinations of stretching and bending modes as well as the first overtone of C-H stretching modes. Thus, for example, glucose and ketones among other substances may have unique signatures in the SWIR. Moreover, many solids have distinct spectral signatures in the SWIR, so particular solids may be identified using stand-off detection or remote sensing. For instance, many explosives have unique signatures in the SWIR.

[0203] Different light sources may be selected for the SWIR based on the needs of the application. Some of the features for selecting a particular light source include power or intensity, wavelength range or bandwidth, spatial or temporal coherence, spatial beam quality for focusing or transmission over long distance, and pulse width or pulse repetition rate. Depending on the application, lamps, light emitting diodes (LEDs), laser diodes (LD's), tunable LD's, super-luminescent laser diodes (SLDs), fiber lasers or super-continuum sources (SC) may be advantageously used. Also, different fibers may be used for transporting the light, such as fused silica fibers, plastic fibers, mid-infrared fibers (e.g., tellurite, chalcogenides, fluorides, ZBLAN, etc), or a hybrid of these fibers.

[0204] Lamps may be used if low power or intensity of light is required in the SWIR, and if an incoherent beam is suitable. In one embodiment, in the SWIR an incandescent lamp that can be used is based on tungsten and halogen, which have an emission wavelength between approximately 500nm to 2500nm. For low intensity applications, it may also be possible to use thermal sources, where the SWIR radiation is based on the black body radiation from the hot object. Although the thermal and lamp based sources are broadband and have low intensity fluctuations, it may be difficult to achieve a high signal-to-noise ratio in a non-invasive blood constituent measurement due to the low power levels. Also, the lamp based sources tend to be energy inefficient.

[0205] In another embodiment, LED's can be used that have a higher power level in the SWIR wavelength range. LED's also produce an incoherent beam, but the power level can be higher than a lamp and with higher energy efficiency. Also, the LED output may more easily be modulated, and the LED provides the option of continuous wave or pulsed mode of operation.

LED's are solid state components that emit a wavelength band that is of moderate width, typically between about 20nm to 40nm. There are also so-called super-luminescent LEDs that may even emit over a much wider wavelength range. In another embodiment, a wide band light source may be constructed by combining different LEDs that emit in different wavelength bands, some of which could preferably overlap in spectrum. One advantage of LEDs as well as other solid state components is the compact size that they may be packaged into.

[0206] In yet another embodiment, various types of laser diodes may be used in the SWIR wavelength range. Just as LEDs may be higher in power but narrower in wavelength emission than lamps and thermal sources, the LDs may be yet higher in power but yet narrower in wavelength emission than LEDs. Different kinds of LDs may be used, including Fabry-Perot LDs, distributed feedback (DFB) LDs, distributed Bragg reflector (DBR) LDs. Since the LDs have relatively narrow wavelength range (typically under 10nm), in one embodiment a plurality of LDs may be used that are at different wavelengths in the SWIR. For example, in a preferred embodiment for non-invasive glucose monitoring, it may be advantageous to use LDs having emission spectra near some or all of the glucose spectral peaks (e.g., near 1587nm, 1750nm, 2120nm, 2270nm, and 2320nm). The various LDs may be spatially multiplexed, polarization multiplexed, wavelength multiplexed, or a combination of these multiplexing methods. Also, the LDs may be fiber pig-tailed or have one or more lenses on the output to collimate or focus the light. Another advantage of LDs is that they may be packaged compactly and may have a spatially coherent beam output. Moreover, tunable LDs that can tune over a range of wavelengths are also available. The tuning may be done by varying the temperature, or electrical current may be used in particular structures, such as distributed Bragg reflector LDs. In another embodiment, external cavity LDs may be used that have a tuning element, such as a fiber grating or a bulk grating, in the external cavity.

[0207] In another embodiment, super-luminescent laser diodes may provide higher power as well as broad bandwidth. An SLD is typically an edge emitting semiconductor light source based on super-luminescence (e.g., this could be amplified spontaneous emission). SLDs combine the higher power and brightness of LDs with the low coherence of conventional LEDs, and the emission band for SLD's may be 5 to 100nm wide, preferably in the 60 to 100nm range. Although

currently SLDs are commercially available in the wavelength range of approximately 400nm to 1700nm, SLDs could and may in the future be made to cover a broader region of the SWIR.

[0208] In yet another embodiment, high power LDs for either direct excitation or to pump fiber lasers and SC light sources may be constructed using one or more laser diode bar stacks. As an example, FIGURE 19 shows an example of the block diagram 1900 or building blocks for constructing the high power LDs. In this embodiment, one or more diode bar stacks 1901 may be used, where the diode bar stack may be an array of several single emitter LDs. Since the fast axis (e.g., vertical direction) may be nearly diffraction limited while the slow-axis (e.g., horizontal axis) may be far from diffraction limited, different collimators 1902 may be used for the two axes.

[0209] Then, the brightness may be increased by spatially combining the beams from multiple stacks 1903. The combiner may include spatial interleaving, it may include wavelength multiplexing, or it may involve a combination of the two. Different spatial interleaving schemes may be used, such as using an array of prisms or mirrors with spacers to bend one array of beams into the beam path of the other. In another embodiment, segmented mirrors with alternate high-reflection and anti-reflection coatings may be used. Moreover, the brightness may be increased by polarization beam combining 1904 the two orthogonal polarizations, such as by using a polarization beam splitter. In one embodiment, the output may then be focused or coupled into a large diameter core fiber. As an example, typical dimensions for the large diameter core fiber range from approximately 100 microns in diameter to 400 microns or more. Alternatively or in addition, a custom beam shaping module 1905 may be used, depending on the particular application. For example, the output of the high power LD may be used directly 1906, or it may be fiber coupled 1907 to combine, integrate, or transport the high power LD energy. These high power LDs may grow in importance because the LD powers can rapidly scale up. For example, instead of the power being limited by the power available from a single emitter, the power may increase in multiples depending on the number of diodes multiplexed and the size of the large diameter fiber. Although FIGURE 19 is shown as one embodiment, some or all of the elements may be used in a high power LD, or additional elements may also be used.

[0210] SWIR SUPER-CONTINUUM LASERS

[0211] Each of the light sources described above have particular strengths, but they also may have limitations. For example, there is typically a trade-off between wavelength range and power output. Also, sources such as lamps, thermal sources, and LEDs produce incoherent beams that may be difficult to focus to a small area and may have difficulty propagating for long distances. An alternative source that may overcome some of these limitations is an SC light source. Some of the advantages of the SC source may include high power and intensity, wide bandwidth, spatially coherent beam that can propagate nearly transform limited over long distances, and easy compatibility with fiber delivery.

[0212] Supercontinuum lasers may combine the broadband attributes of lamps with the spatial coherence and high brightness of lasers. By exploiting a modulational instability initiated supercontinuum (SC) mechanism, an all-fiber-integrated SC laser with no moving parts may be built using commercial-off-the-shelf (COTS) components. Moreover, the fiber laser architecture may be a platform where SC in the visible, near-infrared / SWIR, or mid-IR can be generated by appropriate selection of the amplifier technology and the SC generation fiber. But until now, SC lasers were used primarily in laboratory settings since typically large, table-top, mode-locked lasers were used to pump nonlinear media such as optical fibers to generate SC light. However, those large pump lasers may now be replaced with diode lasers and fiber amplifiers that gained maturity in the telecommunications industry.

[0213] In one embodiment, an all-fiber-integrated, high-powered SC light source 2000 may be elegant for its simplicity (FIGURE 20). The light may be first generated from a seed laser diode 2001. For example, the seed LD 2001 may be a distributed feedback laser diode with a wavelength near 1542 or 1550 nm, with approximately 0.5–2.0 ns pulsed output, and with a pulse repetition rate between a kilohertz to about 100MHz or more. The output from the seed laser diode may then be amplified in a multiple-stage fiber amplifier 2002 comprising one or more gain fiber segments. In one embodiment, the first stage pre-amplifier 2003 may be designed for optimal noise performance. For example, the pre-amplifier 2003 may be a standard erbium-doped fiber amplifier or an erbium/ytterbium doped cladding pumped fiber amplifier. Between amplifier stages 2003 and 2006, it may be advantageous to use band-pass filters 2004 to block amplified

spontaneous emission and isolators 2005 to prevent spurious reflections. Then, the power amplifier stage 2006 may use a cladding-pumped fiber amplifier that may be optimized to minimize nonlinear distortion. The power amplifier fiber 2006 may also be an erbium-doped fiber amplifier, if only low or moderate power levels are to be generated.

[0214] The SC generation 2007 may occur in the relatively short lengths of fiber that follow the pump laser. In one exemplary embodiment, the SC fiber length may range from a few millimeters to 100m or more. In one embodiment, the SC generation may occur in a first fiber 2008 where the modulational-instability initiated pulse break-up primarily occurs, followed by a second fiber 2009 where the SC generation and spectral broadening primarily occurs.

[0215] In one embodiment, one or two meters of standard single-mode fiber (SMF) after the power amplifier stage may be followed by several meters of SC generation fiber. For this example, in the SMF the peak power may be several kilowatts and the pump light may fall in the anomalous group-velocity dispersion regime—often called the soliton regime. For high peak powers in the dispersion regime, the nanosecond pulses may be unstable due to a phenomenon known as modulational instability, which is basically parametric amplification in which the fiber nonlinearity helps to phase match the pulses. As a consequence, the nanosecond pump pulses may be broken into many shorter pulses as the modulational instability tries to form soliton pulses from the quasi-continuous-wave background. Although the laser diode and amplification process starts with approximately nanosecond-long pulses, modulational instability in the short length of SMF fiber may form approximately 0.5 ps to several-picosecond-long pulses with high intensity. Thus, the few meters of SMF fiber may result in an output similar to that produced by mode-locked lasers, except in a much simpler and cost-effective manner.

[0216] The short pulses created through modulational instability may then be coupled into a nonlinear fiber for SC generation. The nonlinear mechanisms leading to broadband SC may include four-wave mixing or self-phase modulation along with the optical Raman effect. Since the Raman effect is self-phase-matched and shifts light to longer wavelengths by emission of optical photons, the SC may spread to longer wavelengths very efficiently. The short-wavelength edge may arise from four-wave mixing, and often times the short wavelength edge may be limited by increasing group-velocity dispersion in the fiber. In many instances, if the particular fiber used

has sufficient peak power and SC fiber length, the SC generation process may fill the long-wavelength edge up to the transmission window.

[0217] Mature fiber amplifiers for the power amplifier stage 2006 include ytterbium-doped fibers (near 1060 nm), erbium-doped fibers (near 1550nm), erbium/ytterbium-doped fibers (near 1550 nm), or thulium-doped fibers (near 2000 nm). In various embodiments, candidates for SC fiber 2009 include fused silica fibers (for generating SC between 0.8–2.7 μm), mid-IR fibers such as fluorides, chalcogenides, or tellurites (for generating SC out to 4.5 μm or longer), photonic crystal fibers (for generating SC between 0.4 and 1.7 μm), or combinations of these fibers. Therefore, by selecting the appropriate fiber-amplifier doping for 2006 and nonlinear fiber 2009, SC may be generated in the visible, near-IR / SWIR, or mid-IR wavelength region.

[0218] The configuration 2000 of FIGURE 20 is just one particular example, and other configurations can be used and are intended to be covered by this disclosure. For example, further gain stages may be used, and different types of lossy elements or fiber taps may be used between the amplifier stages. In another embodiment, the SC generation may occur partially in the amplifier fiber and in the pig-tails from the pump combiner or other elements. In yet another embodiment, polarization maintaining fibers may be used, and a polarizer may also be used to enhance the polarization contrast between amplifier stages. Also, not discussed in detail are many accessories that may accompany this set-up, such as driver electronics, pump laser diodes, safety shut-offs, and thermal management and packaging.

[0219] One example of an SC laser that operates in the SWIR used in one embodiment is illustrated in FIGURE 21. This SWIR SC source 2100 produces an output of up to approximately 5W over a spectral range of about 1.5 to 2.4 microns, and this particular laser is made out of polarization maintaining components. The seed laser 2101 is a distributed feedback (DFB) laser operating near 1542nm producing approximately 0.5nanosecond (ns) pulses at an about 8MHz repetition rate. The pre-amplifier 2102 is forward pumped and uses about 2m length of erbium/ytterbium cladding pumped fiber 2103 (often also called dual-core fiber) with an inner core diameter of 12 microns and outer core diameter of 130 microns. The pre-amplifier gain fiber 2103 is pumped using a 10W 940nm laser diode 2105 that is coupled in using a fiber combiner 2104.

[0220] In this particular 5W unit, the mid-stage between amplifier stages 2102 and 2106 comprises an isolator 2107, a band-pass filter 2108, a polarizer 2109 and a fiber tap 2110. The power amplifier 2106 uses a 4m length of the 12/130 micron erbium/ytterbium doped fiber 2111 that is counter-propagating pumped using one or more 30W 940nm laser diodes 2112 coupled in through a combiner 2113. An approximately 1-2 meter length of the combiner pig-tail helps to initiate the SC process, and then a length of PM-1550 fiber 2115 (polarization maintaining, single-mode, fused silica fiber optimized for 1550nm) is spliced 2114 to the combiner output.

[0221] If an output fiber of about 10m in length is used, then the resulting output spectrum 2200 is shown in FIGURE 22. The details of the output spectrum 2200 depend on the peak power into the fiber, the fiber length, and properties of the fiber such as length and core size, as well as the zero dispersion wavelength and the dispersion properties. For example, if a shorter length of fiber is used, then the spectrum actually reaches to longer wavelengths (e.g., a 2m length of SC fiber broadens the spectrum to ~2500nm). Also, if extra-dry fibers are used with less O-H content, then the wavelength edge may also reach to a longer wavelength. To generate more spectrum toward the shorter wavelengths, the pump wavelength (in this case ~1542nm) should be close to the zero dispersion wavelength in the fiber. For example, by using a dispersion shifted fiber or so-called non-zero dispersion shifted fiber, the short wavelength edge may shift to shorter wavelengths.

[0222] Although one particular example of a 5W SWIR-SC has been described, different components, different fibers, and different configurations may also be used consistent with this disclosure. For instance, another embodiment of the similar configuration 2100 in FIGURE 21 may be used to generate high powered SC between approximately 1060 and 1800nm. For this embodiment, the seed laser 2101 may be a 1064nm distributed feedback (DFB) laser diode, the pre-amplifier gain fiber 2103 may be a ytterbium-doped fiber amplifier with 10/125 microns dimensions, and the pump laser 2105 may be a 10W 915nm laser diode. In the mid-stage, a mode field adapter may be included in addition to the isolator 2107, band pass filter 2108, polarizer 2109 and tap 2110. The gain fiber 2111 in the power amplifier may be a 20m length of ytterbium-doped fiber with 25/400 microns dimension for example. The pump 2112 for the power amplifier may be up to six pump diodes providing 30W each near 915nm, for example. For this much pump power, the output power in the SC may be as high as 50W or more.

[0223] In another embodiment, it may be desirous to generate high power SWIR SC over 1.4-1.8 microns and separately 2-2.5 microns (the window between 1.8 and 2 microns may be less important due to the strong water and atmospheric absorption). For example, the top SC source of FIGURE 23 can lead to bandwidths ranging from about 1400nm to 1800nm or broader, while the lower SC source of FIGURE 23 can lead to bandwidths ranging from about 1900nm to 2500nm or broader. Since these wavelength ranges are shorter than about 2500nm, the SC fiber can be based on fused silica fiber. Exemplary SC fibers include standard single-mode fiber SMF, high-nonlinearity fiber, high-NA fiber, dispersion shifted fiber, dispersion compensating fiber, and photonic crystal fibers. Non-fused-silica fibers can also be used for SC generation, including chalcogenides, fluorides, ZBLAN, tellurites, and germanium oxide fibers.

[0224] In one embodiment, the top of FIGURE 23 illustrates a block diagram for an SC source 2300 capable of generating light between approximately 1400 and 1800nm or broader. As an example, a pump fiber laser similar to FIGURE 21 can be used as the input to a SC fiber 2309. The seed laser diode 2301 can comprise a DFB laser that generates, for example, several milliwatts of power around 1542 or 1553nm. The fiber pre-amplifier 2302 can comprise an erbium-doped fiber amplifier or an erbium/ytterbium doped double clad fiber. In this example a mid-stage amplifier 2303 can be used, which can comprise an erbium/ytterbium doped double-clad fiber. A bandpass filter 2305 and isolator 2306 may be used between the pre-amplifier 2302 and mid-stage amplifier 2303. The power amplifier stage 2304 can comprise a larger core size erbium/ytterbium doped double-clad fiber, and another bandpass filter 2307 and isolator 2308 can be used before the power amplifier 2304. The output of the power amplifier can be coupled to the SC fiber 2309 to generate the SC output 2310. This is just one exemplary configuration for an SC source, and other configurations or elements may be used consistent with this disclosure.

[0225] In yet another embodiment, the bottom of FIGURE 23 illustrates a block diagram for an SC source 2350 capable of generating light between approximately 1900 and 2500nm or broader. As an example, the seed laser diode 2351 can comprise a DFB or DBR laser that generates, for example, several milliwatts of power around 1542 or 1553nm. The fiber pre-amplifier 2352 can comprise an erbium-doped fiber amplifier or an erbium/ytterbium doped double-clad fiber. In this example a mid-stage amplifier 2353 can be used, which can comprise an erbium/ytterbium doped double-clad fiber. A bandpass filter 2355 and isolator 2356 may be

used between the pre-amplifier 2352 and mid-stage amplifier 2353. The power amplifier stage 2354 can comprise a thulium doped double-clad fiber, and another isolator 2357 can be used before the power amplifier 2354. Note that the output of the mid-stage amplifier 2353 can be approximately near 1550nm, while the thulium-doped fiber amplifier 2354 can amplify wavelengths longer than approximately 1900nm and out to about 2100nm. Therefore, for this configuration wavelength shifting may be required between 2353 and 2354. In one embodiment, the wavelength shifting can be accomplished using a length of standard single-mode fiber 2358, which can have a length between approximately 5 and 50 meters, for example. The output of the power amplifier 2354 can be coupled to the SC fiber 2359 to generate the SC output 2360. This is just one exemplary configuration for an SC source, and other configurations or elements can be used consistent with this disclosure. For example, the various amplifier stages can comprise different amplifier types, such as erbium doped fibers, ytterbium doped fibers, erbium/ytterbium co-doped fibers and thulium doped fibers. One advantage of the SC lasers illustrated in FIGURES 20-23 are that they may use all-fiber components, so that the SC laser can be all-fiber, monolithically integrated with no moving parts. The all-integrated configuration can consequently be robust and reliable.

[0226] FIGURES 20-23 are examples of SC light sources that may be advantageously used for SWIR light generation in various medical diagnostic and therapeutic applications. However, many other versions of the SC light sources may also be made that are intended to also be covered by this disclosure. For example, the SC generation fiber could be pumped by a mode-locked laser, a gain-switched semiconductor laser, an optically pumped semiconductor laser, a solid state laser, other fiber lasers, or a combination of these types of lasers. Also, rather than using a fiber for SC generation, either a liquid or a gas cell might be used as the nonlinear medium in which the spectrum is to be broadened.

[0227] Even within the all-fiber versions illustrated such as in FIGURE 21, different configurations could be used consistent with the disclosure. In an alternate embodiment, it may be desirous to have a lower cost version of the SWIR SC laser of FIGURE 21. One way to lower the cost could be to use a single stage of optical amplification, rather than two stages, which may be feasible if lower output power is required or the gain fiber is optimized. For example, the pre-amplifier stage 2102 might be removed, along with at least some of the mid-stage elements. In

yet another embodiment, the gain fiber could be double passed to emulate a two stage amplifier. In this example, the pre-amplifier stage 2102 might be removed, and perhaps also some of the mid-stage elements. A mirror or fiber grating reflector could be placed after the power amplifier stage 2106 that may preferentially reflect light near the wavelength of the seed laser 2101. If the mirror or fiber grating reflector can transmit the pump light near 940nm, then this could also be used instead of the pump combiner 2113 to bring in the pump light 2112. The SC fiber 2115 could be placed between the seed laser 2101 and the power amplifier stage 2106 (SC is only generated after the second pass through the amplifier, since the power level may be sufficiently high at that time). In addition, an output coupler may be placed between the seed laser diode 2101 and the SC fiber, which now may be in front of the power amplifier 2106. In a particular embodiment, the output coupler could be a power coupler or divider, a dichroic coupler (e.g., passing seed laser wavelength but outputting the SC wavelengths), or a wavelength division multiplexer coupler. This is just one further example, but a myriad of other combinations of components and architectures could also be used for SC light sources to generate SWIR light that are intended to be covered by this disclosure.

[0228] WIRELESS LINK TO THE CLOUD

[0229] The non-invasive blood constituent or analytes measurement device may also benefit from communicating the data output to the "cloud" (e.g., data servers and processors in the web remotely connected) via wired and/or wireless communication strategies. The non-invasive devices may be part of a series of biosensors applied to the patient, and collectively these devices form what might be called a body area network or a personal area network. The biosensors and non-invasive devices may communicate to a smart phone, tablet, personal data assistant, computer, and/or other microprocessor-based device, which may in turn wirelessly or over wire and/or fiber optically transmit some or all of the signal or processed data to the internet or cloud. The cloud or internet may in turn send the data to doctors or health care providers as well as the patients themselves. Thus, it may be possible to have a panoramic, high-definition, relatively comprehensive view of a patient that doctors can use to assess and manage disease, and that patients can use to help maintain their health and direct their own care.

[0230] In a particular embodiment 2400, the physiological measurement device or non-invasive blood constituent measurement device 2401 may comprise a transmitter 2403 to communicate over a first communication link 2404 in the body area network or personal area network to a receiver in a smart phone, tablet cell phone, PDA, or computer 2405. For the measurement device 2401, it may also be advantageous to have a processor 2402 to process some of the physiological data, since with processing the amount of data to transmit may be less (hence, more energy efficient). The first communication link 2404 may operate through the use of one of many wireless technologies such as Bluetooth, Zigbee, WiFi, IrDA (infrared data association), wireless USB, or Z-wave, to name a few. Alternatively, the communication link 2404 may occur in the wireless medical band between 2360 and 2390MHz, which the FCC allocated for medical body area network devices, or in other designated medical device or WMTS bands. These are examples of devices that can be used in the body area network and surroundings, but other devices could also be used and are included in the scope of this disclosure.

[0231] The personal device 2405 may store, process, display, and transmit some of the data from the measurement device 2401. The device 2405 may comprise a receiver, transmitter, display, voice control and speakers, and one or more control buttons or knobs and a touch screen. Examples of the device 2405 include smart phones such as the Apple iPhones® or phones operating on the Android or Microsoft systems. In one embodiment, the device 2405 may have an application, software program, or firmware to receive and process the data from the measurement device 2401. The device 2405 may then transmit some or all of the data or the processed data over a second communication link 2406 to the internet or "cloud" 2407. The second communication link 2406 may advantageously comprise at least one segment of a wireless transmission link, which may operate using WiFi or the cellular network. The second communication link 2406 may additionally comprise lengths of fiber optic and/or communication over copper wires or cables.

[0232] The internet or cloud 2407 may add value to the measurement device 2401 by providing services that augment the physiological data collected. In a particular embodiment, some of the functions performed by the cloud include: (a) receive at least a fraction of the data from the device 2405; (b) buffer or store the data received; (c) process the data using software stored on the cloud; (d) store the resulting processed data; and (e) transmit some or all of the data

either upon request or based on an alarm. As an example, the data or processed data may be transmitted 2408 back to the originator (e.g., patient or user), it may be transmitted 2409 to a health care provider or doctor, or it may be transmitted 2410 to other designated recipients.

[0233] The cloud 2407 may provide a number of value-add services. For example, the cloud application may store and process the physiological data for future reference or during a visit with the healthcare provider. If a patient has some sort of medical mishap or emergency, the physician can obtain the history of the physiological parameters over a specified period of time. In another embodiment, if the physiological parameters fall out of acceptable range, alarms may be delivered to the user 2408, the healthcare provider 2409, or other designated recipients 2410. These are just some of the features that may be offered, but many others may be possible and are intended to be covered by this disclosure. As an example, the device 2405 may also have a GPS sensor, so the cloud 2407 may be able to provide time, data and position along with the physiological parameters. Thus, if there is a medical emergency, the cloud 2407 could provide the location of the patient to the healthcare provider 2409 or other designated recipients 2410. Moreover, the digitized data in the cloud 2407 may help to move toward what is often called "personalized medicine." Based on the physiological parameter data history, medication or medical therapies may be prescribed that are customized to the particular patient.

[0234] Beyond the above benefits, the cloud application 2407 and application on the device 2405 may also have financial value for companies developing measurement devices 2401 such as a non-invasive blood constituent monitor. In the case of glucose monitors, the companies make the majority of their revenue on the measurement strips. However, with a non-invasive monitor, there is no need for strips, so there is less of an opportunity for recurring costs (e.g., the razor/razor blade model does not work for non-invasive devices). On the other hand, people may be willing to pay a periodic fee for the value-add services provided on the cloud 2407. Diabetic patients, for example, would probably be willing to pay a periodic fee for monitoring their glucose levels, storing the history of the glucose levels, and having alarm warnings when the glucose level falls out of range. Similarly, patients taking ketone bodies supplement for treatment of disorders characterized by impaired glucose metabolism (e.g., Alzheimer's, Parkinson's, Huntington's or ALS) may need to monitor their ketone bodies level. These patients would also probably be willing to pay a periodic fee for the value-add services provided on the cloud 2407. Thus, by

leveraging the advances in wireless connectivity and the widespread use of handheld devices such as smart phones that can wirelessly connect to the cloud, businesses can build a recurring cost business model even using non-invasive measurement devices.

[0235] Described herein are just some examples of the beneficial use of near-infrared or SWIR lasers for non-invasive monitoring of glucose, ketones, HbA1c and other blood constituents. However, many other medical procedures can use the near-infrared or SWIR light consistent with this disclosure and are intended to be covered by the disclosure.

[0236] SECTION 2: SHORT-WAVE INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF DENTAL CARIES

[0237] Near-infrared (NIR) and SWIR light may be preferred for caries detection compared to visible light imaging because the NIR/SWIR wavelengths generally have lower absorption by stains and deeper penetration into teeth. Hence, NIR/SWIR light may provide a caries detection method that can be non-invasive, non-contact and relatively stain insensitive. Broadband light may provide further advantages because carious regions may demonstrate spectral signatures from water absorption and the wavelength dependence of porosity in the scattering of light.

[0238] In general, the near-infrared region of the electromagnetic spectrum covers between approximately 0.7 microns (700nm) to about 2.5 microns (2500nm). However, it may also be advantageous to use just the short-wave infrared between approximately 1.4 microns (1400nm) and about 2.5 microns (2500nm). One reason for preferring the SWIR over the entire NIR may be to operate in the so-called "eye safe" window, which corresponds to wavelengths longer than about 1400nm. Therefore, for the remainder of the disclosure the SWIR will be used for illustrative purposes. However, it should be clear that the discussion that follows could also apply to using the NIR wavelength range, or other wavelength bands.

[0239] In particular, wavelengths in the eye safe window may not transmit down to the retina of the eye, and therefore, these wavelengths may be less likely to create permanent eye damage from inadvertent exposure. The near-infrared wavelengths have the potential to be dangerous, because the eye cannot see the wavelengths (as it can in the visible), yet they can

penetrate and cause damage to the eye. Even if a practitioner is not looking directly at the laser beam, the practitioner's eyes may receive stray light from a reflection or scattering from some surface. Hence, it can always be a good practice to use eye protection when working around lasers. Since wavelengths longer than about 1400nm are substantially not transmitted to the retina or substantially absorbed in the retina, this wavelength range is known as the eye safe window. For wavelengths longer than 1400nm, in general only the cornea of the eye may receive or absorb the light radiation.

[0240] FIGURE 25 illustrates the structure of an exemplary cross-section of a tooth 2500. The tooth 2500 has a top layer called the crown 2501 and below that a root 2502 that reaches well into the gum 2506 and bone 2508 of the mouth. The exterior of the crown 2501 is an enamel layer 2503, and below the enamel is a layer of dentine 2504 that sits atop a layer of cementum 2507. Below the dentine 2504 is a pulp region 2505, which comprises within it blood vessels 2509 and nerves 2510. If the light can penetrate the enamel 2503 and dentine 2504, then the blood flow and blood constituents may be measured through the blood vessels in the dental pulp 2505. While the amount of blood flow in the capillaries of the dental pulp 2505 may be less than an artery or vein, the smaller blood flow could still be advantageous for detecting or measuring blood constituents as compared to detection through the skin if there is less interfering spectral features from the tooth.

[0241] As used throughout this document, the term "couple" and or "coupled" refers to any direct or indirect communication between two or more elements, whether or not those elements are physically connected to one another. As used throughout this disclosure, the term "spectroscopy" means that a tissue or sample is inspected by comparing different features, such as wavelength (or frequency), spatial location, transmission, absorption, reflectivity, scattering, refractive index, or opacity. In one embodiment, "spectroscopy" may mean that the wavelength of the light source is varied, and the transmission, absorption, or reflectivity of the tissue or sample is measured as a function of wavelength. In another embodiment, "spectroscopy" may mean that the wavelength dependence of the transmission, absorption or reflectivity is compared between different spatial locations on a tissue or sample. As an illustration, the "spectroscopy" may be performed by varying the wavelength of the light source, or by using a broadband light source and analyzing the signal using a spectrometer, wavemeter, or optical spectrum analyzer.

[0242] As used throughout this disclosure, the term "fiber laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein at least a part of the laser comprises an optical fiber. For instance, the fiber in the "fiber laser" may comprise one of or a combination of a single mode fiber, a multi-mode fiber, a mid-infrared fiber, a photonic crystal fiber, a doped fiber, a gain fiber, or, more generally, an approximately cylindrically shaped waveguide or light-pipe. In one embodiment, the gain fiber may be doped with rare earth material, such as ytterbium, erbium, and/or thulium, for example. In another embodiment, the mid-infrared fiber may comprise one or a combination of fluoride fiber, ZBLAN fiber, chalcogenide fiber, tellurite fiber, or germanium doped fiber. In yet another embodiment, the single mode fiber may include standard single-mode fiber, dispersion shifted fiber, non-zero dispersion shifted fiber, high-nonlinearity fiber, and small core size fibers.

[0243] As used throughout this disclosure, the term "pump laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein the output light or optical beam is coupled to a gain medium to excite the gain medium, which in turn may amplify another input optical signal or beam. In one particular example, the gain medium may be a doped fiber, such as a fiber doped with ytterbium, erbium, and/or thulium. In one embodiment, the "pump laser" may be a fiber laser, a solid state laser, a laser involving a nonlinear crystal, an optical parametric oscillator, a semiconductor laser, or a plurality of semiconductor lasers that may be multiplexed together. In another embodiment, the "pump laser" may be coupled to the gain medium by using a fiber coupler, a dichroic mirror, a multiplexer, a wavelength division multiplexer, a grating, or a fused fiber coupler.

[0244] As used throughout this document, the term "super-continuum" and or "supercontinuum" and or "SC" refers to a broadband light beam or output that comprises a plurality of wavelengths. In a particular example, the plurality of wavelengths may be adjacent to one-another, so that the spectrum of the light beam or output appears as a continuous band when measured with a spectrometer. In one embodiment, the broadband light beam may have a bandwidth or at least 10nm. In another embodiment, the "super-continuum" may be generated through nonlinear optical interactions in a medium, such as an optical fiber or nonlinear crystal. For example, the "super-continuum" may be generated through one or a combination of nonlinear

activities such as four-wave mixing, the Raman effect, modulational instability, and self-phase modulation.

[0245] As used throughout this disclosure, the terms "optical light" and or "optical beam" and or "light beam" refer to photons or light transmitted to a particular location in space. The "optical light" and or "optical beam" and or "light beam" may be modulated or unmodulated, which also means that they may or may not contain information. In one embodiment, the "optical light" and or "optical beam" and or "light beam" may originate from a fiber, a fiber laser, a laser, a light emitting diode, a lamp, a pump laser, or a light source.

[0246] TRANSMISSION OR REFLECTION THROUGH TEETH

[0247] The transmission, absorption and reflection from teeth has been studied in the near infrared, and, although there are some features, the enamel and dentine appear to be fairly transparent in the near infrared (particularly SWIR wavelengths between about 1400 and 2500nm). For example, the absorption or extinction ratio for light transmission has been studied. FIGURE 26A illustrates the attenuation coefficient 2600 for dental enamel 2601 (filled circles) and the absorption coefficient of water 2602 (open circles) versus wavelength. Near-infrared light may penetrate much further without scattering through all the tooth enamel, due to the reduced scattering coefficient in normal enamel. Scattering in enamel may be fairly strong in the visible, but decreases as approximately 1/(wavelength)3 [i.e., inverse of the cube of the wavelength] with increasing wavelength to a value of only 2-3 cm-1 at 1310nm and 1550nm in the near infrared. Therefore, enamel may be virtually transparent in the near infrared with optical attenuation 1-2 orders of magnitude less than in the visible range.

[0248] As another example, FIGURE 26B illustrates the absorption spectrum 2650 of intact enamel 2651 (dashed line) and dentine 2652 (solid line) in the wavelength range of approximately 1.2 to 2.4 microns. In the near infrared there are two absorption bands in the areas of about 1.5 and 2 microns. The band with a peak around 1.57 microns may be attributed to the overtone of valent vibration of water present in both enamel and dentine. In this band, the absorption is greater for dentine than for enamel, which may be related to the large water content in this tissue. In the region of 2 microns, dentine may have two absorption bands, and enamel one. The band with a maximum near 2.1 microns may belong to the overtone of vibration of PO

hydroxyapatite groups, which is the main substance of both enamel and dentine. Moreover, the band with a peak near 1.96 microns in dentine may correspond to water absorption (dentine may contain substantially higher water than enamel).

[0249] In addition to the absorption coefficient, the reflectance from intact teeth and teeth with dental caries (e.g., cavities) has been studied. In one embodiment, FIGURE 27 shows the near infrared spectral reflectance 2700 over the wavelength range of approximately 800nm to 2500nm from an occlusal (e.g., top) tooth surface 2704. The curve with black diamonds 2701 corresponds to the reflectance from a sound, intact tooth section. The curve with asterisks (*) 2702 corresponds to a tooth section with an enamel lesion. The curve with circles 2703 corresponds to a tooth section with a dentine lesion. Thus, when there is a lesion, more scattering occurs and there may be an increase in the reflected light.

[0250] For wavelengths shorter than approximately 1400nm, the shapes of the spectra remain similar, but the amplitude of the reflection changes with lesions. Between approximately 1400nm and 2500nm, an intact tooth 2701 has low reflectance (e.g., high transmission), and the reflectance appears to be more or less independent of wavelength. On the other hand, in the presence of lesions 2702 and 2703, there is increased scattering, and the scattering loss may be wavelength dependent. For example, the scattering loss may decrease as the inverse of some power of wavelength, such as 1/(wavelength)3 -- so, the scattering loss decreases with longer wavelengths. When there is a lesion in the dentine 2703, more water can accumulate in the area, so there is also increased water absorption. For example, the dips near 1450nm and 1900nm may correspond to water absorption, and the reflectance dips are particularly pronounced in the dentine lesion 2703.

[0251] FIGURE 27 may point to several novel techniques for early detection and quantification of carious regions. One method may be to use a relatively narrow wavelength range (for example, from a laser diode or super-luminescent laser diode) in the wavelength window below 1400nm. In one embodiment, wavelengths in the vicinity of 1310nm may be used, which is a standard telecommunications wavelength where appropriate light sources are available. Also, it may be advantageous to use a super-luminescent laser diode rather than a laser diode, because the broader bandwidth may avoid the production of laser speckle that can produce interference

patterns due to light's scattering after striking irregular surfaces. As FIGURE 27 shows, the amplitude of the reflected light (which may also be proportional to the inverse of the transmission) may increase with dental caries. Hence, comparing the reflected light from a known intact region with a suspect region may help identify carious regions. However, one difficulty with using a relatively narrow wavelength range and relying on amplitude changes may be the calibration of the measurement. For example, the amplitude of the reflected light may depend on many factors, such as irregularities in the dental surface, placement of the light source and detector, distance of the measurement instrument from the tooth, etc.

[0252] In one embodiment, use of a plurality of wavelengths can help to better calibrate the dental caries measurement. For example, a plurality of laser diodes or super-luminescent laser diodes may be used at different center wavelengths. Alternately, a lamp or alternate broadband light source may be used followed by appropriate filters, which may be placed after the light source or before the detectors. In one example, wavelengths near 1090nm, 1440nm and 1610nm may be employed. The reflection from the tooth 2705 appears to reach a local maximum near 1090nm in the representative embodiment illustrated. Also, the reflectance near 1440nm 2706 is higher for dental caries, with a distinct dip particularly for dentine caries 2703. Near 1610nm 2707, the reflection is also higher for carious regions. By using a plurality of wavelengths, the values at different wavelengths may help quantify a caries score. In one embodiment, the degree of enamel lesions may be proportional to the ratio of the reflectance near 1610nm divided by the reflectance near 1090nm. Also, the degree of dentine lesion may be proportional to the difference between the reflectance near 1610nm and 1440nm, with the difference then divided by the reflectance near 1090nm. Although one set of wavelengths has been described, other wavelengths may also be used and are intended to be covered by this disclosure.

[0253] In yet another embodiment, it may be further advantageous to use all of some fraction of the SWIR between approximately 1400 and 2500nm. For example, a SWIR super-continuum light source could be used, or a lamp source could be used. On the receiver side, a spectrometer and/or dispersive element could be used to discriminate the various wavelengths. As FIGURE 27 shows, an intact tooth 2701 has a relatively low and featureless reflectance over the SWIR. On the other hand, with a carious region there is more scattering, so the reflectance 2702, 2703 increases in amplitude. Since the scattering is inversely proportional to wavelength or some

power of wavelength, the carious region reflectance 2702, 2703 also decreases with increasing wavelength. Moreover, the carious region may contain more water, so there are dips in the reflectance near the water absorption lines 2706 and 2708. The degree of caries or caries score may be quantified by the shape of the spectrum over the SWIR, taking ratios of different parts of the spectrum, or some combination of this and other spectral processing methods.

[0254] Although several methods of early caries detection using spectral reflectance have been described, other techniques could also be used and are intended to be covered by this disclosure. For example, transmittance may be used rather than reflectance, or a combination of the two could be used. Moreover, the transmittance, reflectance and/or absorbance could also be combined with other techniques, such as quantitative light-induced fluorescence or fiber-optic trans-illumination. Also, the SWIR could be advantageous, but other parts of the infrared, near-infrared or visible wavelengths may also be used consistent with this disclosure.

[0255] One other benefit of the absorption, transmission or reflectance in the near infrared and SWIR may be that stains and non-calcified plaque are not visible in this wavelength range, enabling better discrimination of defects, cracks, and demineralized areas. For example, dental calculus, accumulated plaque, and organic stains and debris may interfere significantly with visual diagnosis and fluorescence-based caries detection schemes in occlusal surfaces. In the case of using quantitative light-induced fluorescence, such confounding factors typically may need to be removed by prophylaxis (abrasive cleaning) before reliable measurements can be taken. Surface staining at visible wavelengths may further complicate the problem, and it may be difficult to determine whether pits and fissures are simply stained or demineralized. On the other hand, staining and pigmentation generally interfere less with NIR or SWIR imaging. For example, NIR and SWIR light may not be absorbed by melanin and porphyrins produced by bacteria and those found in food dyes that accumulate in dental plaque and are responsible for the pigmentation.

[0256] HUMAN INTERFACE FOR MEASUREMENT SYSTEM

[0257] A number of different types of measurements may be used to image for dental caries, particularly early detection of dental caries. A basic feature of the measurements may be that the optical properties are measured as a function of wavelength at a plurality of wavelengths. As further described below, the light source may output a plurality of wavelengths, or a continuous

spectrum over a range of wavelengths. In one embodiment, the light source may cover some or all of the wavelength range between approximately 1400nm and 2500nm. The signal may be received at a receiver, which may also comprise a spectrometer or filters to discriminate between different wavelengths. The signal may also be received at a camera, which may also comprise filters or a spectrometer. In one embodiment, the spectral discrimination using filters or a spectrometer may be placed after the light source rather than at the receiver. The receiver usually comprises one or more detectors (optical-to-electrical conversion element) and electrical circuitry. The receiver may also be coupled to analog to digital converters, particularly if the signal is to be fed to a digital device.

[0258] Referring to FIGURE 25, one or more light sources 2511 may be used for illumination. In one embodiment, a transmission measurement may be performed by directing the light source output 2511 to the region near the interface between the gum 2506 and dentine 2504. In one embodiment, the light may be directed using a light guide or a fiber optic. The light may then propagate through the dental pulp 2505 to the other side, where the light may be incident on one or more detectors or another light guide to transport the signal to 2512 a spectrometer, receiver, and/or camera, for example. In one embodiment, the light source may be directed to one or more locations near the interface between the gum 2506 and dentine 2504 (in one example, could be from the two sides of the tooth). The transmitted light may then be detected in the occlusal surface above the tooth using a 2512 spectrometer, receiver, or camera, for example. In another embodiment, a reflectance measurement may be conducted by directing the light source output 2511 to, for example, the occlusal surface of the tooth, and then detecting the reflectance at a 2513 spectrometer, receiver or camera. Although a few embodiments for imaging the tooth are described, other embodiments and techniques may also be used and are intended to be covered by this disclosure. These optical techniques may measure optical properties such as reflectance, transmittance, absorption, or luminescence.

[0259] In one embodiment, FIGURE 28 shows that the light source and/or detection system may be integrated with a dental hand-piece 2800. The hand-piece 2800 may also include other dental equipment, such as a drill, pick, air spray or water cooling stream. The dental hand-piece 2800 may include a housing 2801 and a motor housing 2802 (in some embodiments such as with a drill, a motor may be placed in this section). The end of hand-piece 2803 that interfaces

with the tooth may be detachable, and it may also have the light input and output end. The dental hand-piece 2800 may also have an umbilical cord 2804 for connecting to power supplies, diagnostics, or other equipment, for example.

[0260] A light guide 2805 may be integrated with the hand-piece 2800, either inside the housing 2801, 2802 or adjacent to the housing. In one embodiment, a light source 2810 may be contained within the housing 2801, 2802. In an alternative embodiment, the hand-piece 2800 may have a coupler 2810 to couple to an external light source 2811 and/or detection system or receiver 2812. The light source 2811 may be coupled to the hand-piece 2800 using a light guide or fiber optic cable 2806. In addition, the detection system or receiver 2812 may be coupled to the hand-piece 2800 using one or more light guides, fiber optic cable or a bundle of fibers 2807.

[0261] The light incident on the tooth may exit the hand-piece 2800 through the end 2803. The end 2803 may also have a lens system or curved mirror system to collimate or focus the light. In one embodiment, if the light source is integrated with a tool such as a drill, then the light may reach the tooth at the same point as the tip of the drill. The reflected or transmitted light from the tooth may then be observed externally and/or guided back through the light guide 405 in the hand-piece 2800. If observed externally, there may be a lens system 408 for collecting the light and a detection system 2809 that may have one or more detectors and electronics. If the light is to be guided back through the hand-piece 2800, then the reflected light may transmit through the light guide 2805 back to the detection system or receiver 2812. In one embodiment, the incident light may be guided by a fiber optic through the light guide 2805, and the reflected light may be captured by a series of fibers forming a bundle adjacent to or surrounding the incident light fiber.

[0262] In another embodiment, a "clamp" design 2900 may be used as a cap over one or more teeth, as illustrated in FIGURE 29. The clamp design may be different for different types of teeth, or it may be flexible enough to fit over different types of teeth. For example, different types of teeth include the molars (toward the back of the mouth), the premolars, the canine, and the incisors (toward the front of the mouth). One embodiment of the clamp-type design is illustrated in FIGURE 29 for a molar tooth 2908. The C-clamp 2901 may be made of a plastic or rubber material, and it may comprise a light source input 2902 and a detector output 2903 on the front or back of the tooth, for example.

[0263] The light source input 2902 may comprise a light source directly, or it may have light guided to it from an external light source. Also, the light source input 2902 may comprise a lens system to collimate or focus the light across the tooth. The detector output 2903 may comprise a detector directly, or it may have a light guide to transport the signal to an external detector element. The light source input 2902 may be coupled electrically or optically through 2904 to a light input 2906. For example, if the light source is external in 2906, then the coupling element 2904 may be a light guide, such as a fiber optic. Alternately, if the light source is contained in 2902, then the coupling element 2904 may be electrical wires connecting to a power supply in 2906. Similarly, the detector output 2903 may be coupled to a detector output unit 2907 with a coupling element 2905, which may be one or more electrical wires or a light guide, such as a fiber optic. This is just one example of a clamp over one or more teeth, but other embodiments may also be used and are intended to be covered by this disclosure. For example, if reflectance from the teeth is to be used in the measurement, then the light input 2902 and detected light input 2903 may be on the same side of the tooth.

[0264] In yet another embodiment, one or more light source ports and sensor ports may be used in a mouth-guard type design. For example, one embodiment of a dental mouth guard 3000 is illustrated in FIGURE 30. The structure of the mouth guard 3001 may be similar to mouth guards used in sports (e.g., when playing football or boxing) or in dental trays used for applying fluoride treatment, and the mouth guard may be made from plastic, rubber, or any other suitable materials. As an example, the mouth guard may have one or more light source input ports 3002, 3003 and one or more detector output ports 3004, 3005. Although six input and output ports are illustrated, any number of ports may be used.

[0265] Similar to the clamp design described above, the light source inputs 3002, 3003 may comprise one or more light sources directly, or they may have light guided to them from an external light source. Also, the light source inputs 3002, 3003 may comprise lens systems to collimate or focus the light across the teeth. The detector outputs 3004, 3005 may comprise one or more detectors directly, or they may have one or more light guides to transport the signals to an external detector element. The light source inputs 3002, 3003 may be coupled electrically or optically through 3006 to a light input 3007. For example, if the light source is external in 3007, then the one or more coupling elements 3006 may be one or more light guides, such as a fiber

optic. Alternately, if the light sources are contained in 3002, 3003, then the coupling element 3006 may be one or more electrical wires connecting to a power supply in 3007. Similarly, the detector outputs 3004, 3005 may be coupled to a detector output unit 3009 with one or more coupling elements 3008, which may be one or more electrical wires or one or more light guides, such as a fiber optic. This is just one example of a mouth guard design covering a plurality of teeth, but other embodiments may also be used and are intended to be covered by this disclosure. For instance, the position of the light source inputs and detector output ports could be exchanged, or some mixture of locations of light source inputs and detector output ports could be used. Also, if reflectance from the teeth is to be measured, then the light sources and detectors may be on the same side of the tooth. Moreover, it may be advantageous to pulse the light source with a particular pulse width and pulse repetition rate, and then the detection system can measure the pulsed light returned from or transmitted through the tooth. Using a lock-in type technique (e.g., detecting at the same frequency as the pulsed light source and also possibly phase locked to the same signal), the detection system may be able to reject background or spurious signals and increase the signal-to-noise ratio of the measurement.

[0266] Other elements may be added to the human interface designs of FIGURES 28-30 and are also intended to be covered by this disclosure. For instance, in one embodiment it may be desirable to have replaceable inserts that may be disposable. Particularly in a dentist's or doctor's office or hospital setting, the same instrument may be used with a plurality of patients. Rather than disinfecting the human interface after each use, it may be preferable to have disposable inserts that can be thrown away after each use. In one embodiment, a thin plastic coating material may enclose the clamp design of FIGURE 29 or mouth guard design of FIGURE 30. The coating material may be inserted before each use, and then after the measurement is exercised the coating material may be peeled off and replaced. The coating or covering material may be selected based on suitable optical properties that do not affect the measurement, or known optical properties that can be calibrated or compensated for during measurement. Such a design may save the dentist or physician or user considerable time, while at the same time provide the business venture with a recurring cost revenue source.

[0267] WIRELESS LINK TO THE CLOUD

[0268] The non-invasive dental caries measurement device may also benefit from communicating the data output to the "cloud" (e.g., data servers and processors in the web remotely connected) via wireless means. The non-invasive devices may be part of a series of biosensors applied to the patient, and collectively these devices form what might be called a body area network or a personal area network. The biosensors and non-invasive devices may communicate to a smart phone, tablet, personal data assistant, computer and/or other microprocessor-based device, which may in turn wirelessly or over wire and/or fiber optic transmit some or all of the signal or processed data to the internet or cloud. The cloud or internet may in turn send the data to dentists, doctors or health care providers as well as the patients themselves. Thus, it may be possible to have a panoramic, high-definition, relatively comprehensive view of a patient that doctors and dentists can use to assess and manage disease, and that patients can use to help maintain their health and direct their own care.

[0269] In a particular embodiment 3100, the non-invasive measurement device 3101 may comprise a transmitter 3103 to communicate over a first communication link 3104 in the body area network or personal area network to a receiver in a smart phone, tablet, cell phone, PDA, and/or computer 3105, for example. For the measurement device 3101, it may also be advantageous to have a processor 3102 to process some of the measured data, since with processing the amount of data to transmit may be less (hence, more energy efficient). The first communication link 3104 may operate through the use of one of many wireless technologies such as Bluetooth, Zigbee, WiFi, IrDA (infrared data association), wireless USB, or Z-wave, to name a few. Alternatively, the communication link 3104 may occur in the wireless medical band between 2360MHz and 2390MHz, which the FCC allocated for medical body area network devices, or in other designated medical device or WMTS bands. These are examples of devices that can be used in the body area network and surroundings, but other devices could also be used and are included in the scope of this disclosure.

[0270] The personal device 3105 may store, process, display, and transmit some of the data from the measurement device 3101. The device 3105 may comprise a receiver, transmitter, display, voice control and speakers, and one or more control buttons or knobs and a touch screen. Examples of the device 3105 include smart phones such as the Apple iPhones® or phones operating on the Android or Microsoft systems. In one embodiment, the device 3105 may have

an application, software program, or firmware to receive and process the data from the measurement device 3101. The device 3105 may then transmit some or all of the data or the processed data over a second communication link 3106 to the internet or "cloud" 3107. The second communication link 3106 may advantageously comprise at least one segment of a wireless transmission link, which may operate using WiFi or the cellular network. The second communication link 3106 may additionally comprise lengths of fiber optic and/or communication over copper wires or cables.

[0271] The internet or cloud 3107 may add value to the measurement device 3101 by providing services that augment the measured data collected. In a particular embodiment, some of the functions performed by the cloud include: (a) receive at least a fraction of the data from the device 3105; (b) buffer or store the data received; (c) process the data using software stored on the cloud; (d) store the resulting processed data; and (e) transmit some or all of the data either upon request or based on an alarm. As an example, the data or processed data may be transmitted 3108 back to the originator (e.g., patient or user), it may be transmitted 3109 to a health care provider or doctor or dentist, or it may be transmitted 3110 to other designated recipients.

[0272] Service providers coupled to the cloud 3107 may provide a number of value-add services. For example, the cloud application may store and process the dental data for future reference or during a visit with the dentist or healthcare provider. If a patient has some sort of medical mishap or emergency, the physician can obtain the history of the dental or physiological parameters over a specified period of time. In another embodiment, alarms, warnings or reminders may be delivered to the user 3108, the healthcare provider 3109, or other designated recipients 3110. These are just some of the features that may be offered, but many others may be possible and are intended to be covered by this disclosure. As an example, the device 3105 may also have a GPS sensor, so the cloud 3107 may be able to provide time, date, and position along with the dental or physiological parameters. Thus, if there is a medical or dental emergency, the cloud 3107 could provide the location of the patient to the dental or healthcare provider 3109 or other designated recipients 3110. Moreover, the digitized data in the cloud 3107 may help to move toward what is often called "personalized medicine." Based on the dental or physiological parameter data history, medication or medical/dental therapies may be prescribed that are customized to the particular patient. Another advantage for commercial entities may be that by

leveraging the advances in wireless connectivity and the widespread use of handheld devices such as smart phones that can wirelessly connect to the cloud, businesses can build a recurring cost business model even using non-invasive measurement devices.

[0273] Described herein are just some examples of the beneficial use of near-infrared or SWIR lasers for non-invasive measurements of dental caries and early detection of carious regions. However, many other dental or medical procedures can use the near-infrared or SWIR light consistent with this disclosure and are intended to be covered by the disclosure.

[0274] SECTION 3: SHORT-WAVE INFRARED SUPER-CONTINUUM LASERS FOR NATURAL GAS LEAK DETECTION, EXPLORATION, AND OTHER ACTIVE REMOTE SENSING APPLICATIONS

[0275] One advantage of optical systems is that they can perform non-contact, stand-off or remote sensing distance spectroscopy of various materials. For remote sensing particularly, it may also be necessary to operate in atmospheric transmission windows. For example, two windows in the SWIR that transmit through the atmosphere are approximately 1.4-1.8 microns and 2-2.5 microns. In general, the near-infrared region of the electromagnetic spectrum covers between approximately 0.7 microns (700nm) to about 2.5 microns (2500nm). However, it may also be advantageous to use just the short-wave infrared between approximately 1.4 microns (1400nm) and about 2.5 microns (2500nm). One reason for preferring the SWIR over the entire NIR may be to operate in the so-called "eye safe" window, which corresponds to wavelengths longer than about 1400nm. Therefore, for the remainder of the disclosure the SWIR will be used for illustrative purposes. However, it should be clear that the discussion that follows could also apply to using the NIR wavelength range, or other wavelength bands.

[0276] In particular, wavelengths in the eye safe window may not transmit down to the retina of the eye, and therefore, these wavelengths may be less likely to create permanent eye damage from inadvertent exposure. The near-infrared wavelengths have the potential to be dangerous, because the eye cannot see the wavelengths (as it can in the visible), yet they can penetrate and cause damage to the eye. Even if a practitioner is not looking directly at the laser beam, the practitioner's eyes may receive stray light from a reflection or scattering from some surface. Hence, it can always be a good practice to use eye protection when working around lasers.

Since wavelengths longer than about 1400nm are substantially not transmitted to the retina or substantially absorbed in the retina, this wavelength range is known as the eye safe window. For wavelengths longer than 1400nm, in general only the cornea of the eye may receive or absorb the light radiation.

[0277] The SWIR wavelength range may be particularly valuable for identifying materials based on their chemical composition because the wavelength range comprises overtones and combination bands for numerous chemical bonds. As an example, FIGURE 32 illustrates some of the wavelength bands for different chemical compositions. In 100 is plotted wavelength ranges in the SWIR (between 1400 and 2500nm) for different chemical compounds that have vibrational or rotational resonances, along with whether the bands are overtone or combination bands. Numerous hydro-carbons are represented, along with oxygen-hydrogen and carbon-oxygen bonds. Thus, gases, liquids and solids that comprise these chemical compounds may exhibit spectral features in the SWIR wavelength range. In a particular embodiment, the spectra of organic compounds may be dominated by the C-H stretch. The C-H stretch fundamental occurs near 3.4 microns, the first overtone is near 1.7 microns, and a combination band occurs near 2.3 microns.

[0278] One embodiment of remote sensing that is used to identify and classify various materials is so-called "hyper-spectral imaging." Hyper-spectral sensors may collect information as a set of images, where each image represents a range of wavelengths over a spectral band. Hyper-spectral imaging may deal with imaging narrow spectral bands over an approximately continuous spectral range. As an example, in hyper-spectral imaging the sun may be used as the illumination source, and the daytime illumination may comprise direct solar illumination as well as scattered solar (skylight), which is caused by the presence of the atmosphere. However, the sun illumination changes with time of day, clouds or inclement weather may block the sun light, and the sun light is not accessible in the night time. Therefore, it would be advantageous to have a broadband light source covering the SWIR that may be used in place of the sun to identify or classify materials in remote sensing or stand-off detection applications.

[0279] As used throughout this document, the term "couple" and or "coupled" refers to any direct or indirect communication between two or more elements, whether or not those elements are physically connected to one another. As used throughout this disclosure, the term

"spectroscopy" means that a tissue or sample is inspected by comparing different features, such as wavelength (or frequency), spatial location, transmission, absorption, reflectivity, scattering, refractive index, or opacity. In one embodiment, "spectroscopy" may mean that the wavelength of the light source is varied, and the transmission, absorption or reflectivity of the tissue or sample is measured as a function of wavelength. In another embodiment, "spectroscopy" may mean that the wavelength dependence of the transmission, absorption or reflectivity is compared between different spatial locations on a tissue or sample. As an illustration, the "spectroscopy" may be performed by varying the wavelength of the light source, or by using a broadband light source and analyzing the signal using a spectrometer, wavemeter, or optical spectrum analyzer.

[0280] As used throughout this document, the term "fiber laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein at least a part of the laser comprises an optical fiber. For instance, the fiber in the "fiber laser" may comprise one of or a combination of a single mode fiber, a multi-mode fiber, a mid-infrared fiber, a photonic crystal fiber, a doped fiber, a gain fiber, or, more generally, an approximately cylindrically shaped waveguide or light-pipe. In one embodiment, the gain fiber may be doped with rare earth material, such as ytterbium, erbium, and/or thulium. In another embodiment, the mid-infrared fiber may comprise one or a combination of fluoride fiber, ZBLAN fiber, chalcogenide fiber, tellurite fiber, or germanium doped fiber. In yet another embodiment, the single mode fiber may include standard single-mode fiber, dispersion shifted fiber, non-zero dispersion shifted fiber, high-nonlinearity fiber, and small core size fibers.

[0281] As used throughout this disclosure, the term "pump laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein the output light or optical beam is coupled to a gain medium to excite the gain medium, which in turn may amplify another input optical signal or beam. In one particular example, the gain medium may be a doped fiber, such as a fiber doped with ytterbium, erbium and/or thulium. In one embodiment, the "pump laser" may be a fiber laser, a solid state laser, a laser involving a nonlinear crystal, an optical parametric oscillator, a semiconductor laser, or a plurality of semiconductor lasers that may be multiplexed together. In another embodiment, the "pump laser" may be coupled to the gain medium by using a fiber coupler, a dichroic mirror, a multiplexer, a wavelength division multiplexer, a grating, or a fused fiber coupler.

[0282] As used throughout this document, the term "super-continuum" and or "supercontinuum" and or "SC" refers to a broadband light beam or output that comprises a plurality of wavelengths. In a particular example, the plurality of wavelengths may be adjacent to one-another, so that the spectrum of the light beam or output appears as a continuous band when measured with a spectrometer. In one embodiment, the broadband light beam may have a bandwidth of at least 10nm. In another embodiment, the "super-continuum" may be generated through nonlinear optical interactions in a medium, such as an optical fiber or nonlinear crystal. For example, the "super-continuum" may be generated through one or a combination of nonlinear activities such as four-wave mixing, parametric amplification, the Raman effect, modulational instability, and self-phase modulation.

[0283] As used throughout this disclosure, the terms "optical light" and or "optical beam" and or "light beam" refer to photons or light transmitted to a particular location in space. The "optical light" and or "optical beam" and or "light beam" may be modulated or unmodulated, which also means that they may or may not contain information. In one embodiment, the "optical light" and or "optical beam" and or "light beam" may originate from a fiber, a fiber laser, a laser, a light emitting diode, a lamp, a pump laser, or a light source.

[0284] As used throughout this disclosure, the term "remote sensing" may include the measuring of properties of an object from a distance, without physically sampling the object, for example by detection of the interactions of the object with an electromagnetic field. In one embodiment, the electromagnetic field may be in the optical wavelength range, including the infrared or SWIR. One particular form of remote sensing may be stand-off detection, which may range from non-contact up to hundreds of meters away, for example.

[0285] REMOTE SENSING OF NATURAL GAS LEAKS

[0286] Natural gas may be a hydro-carbon gas mixture comprising primarily methane, with other hydro-carbons, carbon dioxide, nitrogen and hydrogen sulfide. Natural gas is important because it is an important energy source to provide heating and electricity. Moreover, it may also be used as fuel for vehicles and as a chemical feedstock in the manufacture of plastics and other commercially important organic chemicals. Although methane is the primary component of natural gas, to uniquely identify natural gas through spectroscopy requires monitoring of both

methane and ethane. If only methane is used, then areas like cow pastures could be mistaken for natural gas fields or leaks. More specifically, the typical composition of natural gas is as follows:

Component	Range (mole %)
Methane	87.0-96.0
Ethane	1.5-5.1
Propane	0.1-1.5
Iso-butane	0.01-0.3
Normal-butane	0.01-0.3
Iso-pentane	Trace-0.14
Normal-pentane	Trace-0.04
Hexanes plus	Trace-0.06
Nitrogen	0.7-5.6
Carbon dioxide	0.1-1.0
Oxygen	0.01-0.1
Hydrogen	Trace-0.02

[0287] As one example of remote sensing of natural gas, a helicopter or aircraft may be flown at some elevation. The light source for remote sensing may direct the light beam toward the ground, and the diffuse reflected light may then be measured using a detection system on the aircraft. Thus, the helicopter or aircraft may be sampling a column area below it for natural gas, or whatever the material of interest is. In yet another embodiment, the column may sense aerosols of various sorts, as an example. Various kinds of SWIR light sources will be discussed later in this disclosure. The detection system may comprise, in one embodiment, a spectrometer followed by one or more detectors. In another embodiment, the detection system may be a dispersive element (examples include prisms, gratings, or other wavelength separators) followed by one or more detectors or detector arrays. In yet another embodiment, the detection system may comprise a gas-filter correlation radiometer. These are merely specific examples of the detection system, but combinations of these or other detection systems may also be used and are contemplated within the scope of this disclosure. Also, the use of aircraft is one particular example of a remote sensing system, but other system configurations may also be used and are included in the scope of this disclosure. For example, the light source and detection system may be placed in a fixed location, and for reflection the light source and detectors may be close to one another, while for transmission the light source and detectors may be at different locations. In yet another embodiment, the system

could be placed on a vehicle such as an automobile or a truck, or the light source could be placed on one vehicle, while the detection system is on another vehicle. If the light source and detection system are compact and lightweight, they might even be carried by a person in the field, either in their hands or in a backpack.

[0288] Both methane and ethane are hydro-carbons with unique spectral signatures. For example, ethane is C2H6, while methane is CH4. Also, methane and ethane have infrared absorption bands near 1.6 microns, 2.4 microns, 3.3 microns and 7 microns. It should be noted that the approximately 7 micron lines cannot be observed generally due to atmospheric absorption. Although the fundamental lines near 3.3 microns are stronger absorption features, the light sources and detectors in the mid-infrared may be more difficult to implement. Hence, the focus here is on observing the SWIR lines that fall in atmospheric transparency windows.

[0289] FIGURE 33 illustrates the absorption spectra for methane (FIGURE 33A) and ethane (FIGURE 33B) (from http://vpl.astro.washington.edu/spectra). The curves 3300 plot on a linear scale the absorption cross-section versus wavelength (in microns) for various methane lines. The curve 3301 covers the wavelength range between approximately 1.5-16 microns, while the curves below provide blown-up views of different wavelength ranges (3302 for approximately 1.62-1.7 microns, 3303 for approximately 1.7-1.84 microns, 3304 for approximately 2.15-2.45 microns, and 3305 for approximately 2.45-2.65 microns). The curves 3302 and 3303 fall within about the first SWIR atmospheric transmission window between approximately 1.4-1.8 microns, while the curves 3304 and 3305 fall within the second SWIR atmospheric transmission window between approximately 2-2.5 microns. As can be seen, there are numerous spectral features for identifying methane in the SWIR. In addition, there are even stronger features near 3.4-3.6 microns and around 7-8 microns, although these require different light sources and detection systems.

[0290] FIGURE 33B illustrates the absorption spectra for ethane. The curves 3350 plot on a linear scale the absorption cross-section versus wavelength (in microns) for various ethane lines. The curve 3351 covers the wavelength range between approximately 1.5-16 microns, while the curve 3352 expands the scale between about 1.6-3.2 microns. The features 3353 fall within about the first SWIR atmospheric transmission window between approximately 1.4-1.8 microns, while

the features 3354 and 3355 fall within the second SWIR atmospheric transmission window between approximately 2-2.5 microns. There are distinct spectral features for identifying ethane as well in the SWIR. In addition, there are even stronger features near 3.4-3.6 microns and around 7 microns.

[0291] For detecting natural gas leaks, a SWIR light source and a detection system could be used in transmission or reflection. The area surrounding the source or natural gas pipeline may be surveyed, and the detection system may monitor the methane and ethane concentration, or even the presence of these two gases. The region may be scanned to cover an area larger than the laser beam. Also, if a certain quantity of natural gas is detected, an alarm may be set-off to alert the operator or people nearby. This is just one example of the natural gas leak detection, but other configurations and techniques may be used and are intended to be covered by this disclosure.

[0292] Natural gas leak detection is one example where active remote sensing or hyper-spectral imaging can be used to detect hydro-carbons or organic compounds. However, there are many other examples where the technique may be used to perform reflectance spectroscopy of organic compounds, and these are also intended to be covered by this disclosure. In one particular embodiment, alkanes may be detected, where alkanes are hydro-carbon molecules comprising single carbon-carbon bonds. Alkanes have the general formula CnH2n+2 and are open chain, aliphatic or non-cyclic molecules. Below are examples of some of the alkanes, which include methane and ethane, as well as more complicated compounds.

	Formula
Methane	CH_4
Ethane	C_2H_6
Propane	C_3H_8
Butane	C_4H_{10}
Pentane	C_5H_{12}
Hexane	C_6H_{14}
Heptane	C_7H_{16}
Octane	C_8H_{18}
Nonane	C_9H_{20}
Decane	$C_{10}H_{22}$
Paraffin	$C_{20+}H_{42+}$
Polyethylene (LDPE, HDPE)	$(C_2H_4)_n$ or $(CH_2CH_2)_n$
Polyvinylchloride (PVC)	$(C_2H_3Cl)_n$ or $(CHClCH_2)_n$
Polypropylene	$(C_3H_6)_n$ or $\{CH(CH_3)CH_2\}_n$
Polyethylene terephthalate (PETE)	$C_{10}H_8O_4$ or $\{(CO_2)_2C_6H_4(CH_2)_2\}_n$
Nylon (polyamide)	$C_{12}H_{24}O_4N_2$ or $\{C_{10}H_{22}(CO_2)_2(NH)_2\}_n$

[0293] FIGURE 34 illustrates the reflectance spectra 3400 for some members of the alkane family plus paraffin. The vertical lines indicate positions of constant wavelength and are aligned with apparent absorptions in the methane spectrum at 1.19, 1.67, 2.32, 3.1, 4.23 and 4.99 microns. The spectra ore offset to enable easier viewing, and the offsets are of the following amounts: 3401 methane 4.1; 3402 ethane 3.6; 3403 propane 3.3; 3404 butane 2.8; 3405 pentane 2.3; 3406 hexane 2.0; 3407 heptane 1.5; 3408 octane 1.2; 3409 nonane 0.85; 3410 decane 0.4; and 3411 paraffin 0.05. The reflectance of alkanes in the near-infrared may be dominated by absorptions due to combinations and overtones of bands at longer wavelengths. Although this wavelength range is mostly unexplored by organic spectroscopists, the near-infrared may be valuable for terrestrial and planetary remote sensing studies. Alkanes may have the fundamental absorptions due to a variety of C-H stretches between approximately 3.3-3.5 microns. The first overtone may be a relatively deep triplet near 1.7 microns. This triplet appears in most of the series, but the exact wavelength position may move. Another absorption band may be present near 1.2 microns, and this is likely the second overtone of the C-H stretch. The third C-H stretch overtone is near 0.9 microns. There is yet another near-infrared feature near 1.396 microns, which may correspond to the combinations

of the first overtone of the C-H stretch with each of the two C-H band positions at approximately 1.35 microns and 1.37 microns. Moreover, there may be complex absorptions between 2.2-2.5 microns. For example, there may be a number of narrow individual absorption bands atop an overall absorption suite about 0.3 microns wide. A few absorption lines retain their location for most of the series 300, notably the 2.311 micron and 2.355 micron absorptions. This wavelength window may have multiple combinations and overtones, including contributions from the C-H stretch, CH3 asymmetric bend combination, and C-H stretch/CH3 symmetric bend combination.

[0294] REMOTE SENSING FOR NATURAL GAS EXPLORATION

[0295] In addition to remote sensing to detect natural gas leaks, the same or similar system could also be used to explore for natural gas fields, whether under land or under water. Whereas a natural gas leak from a pipeline or building may be above the ground or only a few meters below the ground, natural gas exploration may occur for gas and oil that are much further below the ground, or under the water in a bay, lake, sea or ocean. For example, the exploration for natural gas and oil may be performed by determining the reflectance spectra of surface anomalies. The surface manifestations of oil and gas reservoirs may be used to map the petroleum potential of an area, particularly related to the seepage of oil and gas to the surface along faults or imperfect reservoir seals. The visible products of such seepage (e.g., oil and tar deposits) are generally referred to as macro-seeps, whereas the invisible gaseous products may be referred to as micro-seeps.

[0296] As illustrated by 3500 in FIGURE 35, micro-seepages may result from the vertical movement of hydrocarbons 3501 from their respective reservoirs to the surface. These hydrocarbon micro-seepages involve buoyant, relatively rapid, vertical ascent of ultra-small bubbles of light hydrocarbons (primarily methane through the butanes) through a network of interconnected, groundwater-filled joints and bedding planes (3501). One of the assumptions required for micro-seepage to occur is that a rock column, including the seal rock, comprises extensive interconnected fractures or micro-fracture systems.

[0297] Direct detection methods may involve measurements of hydrocarbons, either in the form of oil accumulations or concentrations of escaping vapors, such as methane through butane. In addition, there are also indirect methods that may involve the measurement of secondary

alternations that arise from the seepage of the hydrocarbons. For instance, hydrocarbon-induced alterations may include microbial anomalies, mineralogical changes, bleaching of red beds, clay mineral alterations, and electrochemical changes. These alterations occur because leaking hydrocarbons set up near-surface oxidation and/or reduction zones that favor the development of a diverse array of chemical and mineralogical changes, c.f. 3502 in FIGURE 35. Such alterations 3502 may be distinct from adjacent rocks and, thus, may in some instance be detectable by various remote sensing techniques.

[0298] The diagnostic spectral features of methane and crude oil may comprise four distinct hydrocarbon absorption bands. For example, two bands near 1.18 microns and 1.38 microns may be narrow and sharply defined, although they may also be fairly weak. The other two spectral features may be near 1.68-1.72 microns and 2.3-2.45 microns; these bands may be broader, but they are also stronger than the previous two bands. The bands near 1.7 microns and 2.3 microns are spectral overtones or combinations of C-H vibrational modes. Moreover, hydrocarbon induced alterations associated with indirect detection may express themselves in a variety of spectral changes, such as mineralogical changes (calcium carbonate mineralization, near 2.35 microns), bleaching of red beds (near 1 micron), and clay minerals alterations (near 2.2 microns), among other changes.

[0299] Various field tests have been conducted that verify the spectral signatures associated with natural gas fields, either land-based or water-based (e.g., in bays). In one example shown in FIGURE 36A, the reflectance spectra 3600 was collected for different locations between approximately 2 microns and 2.4 microns. In 3601 the reflectance is plotted versus wavelength for locations with gas fields, while in 3602 the reflectance is plotted for locations without gas fields. The macroscopic features of the reflectance spectra of surface soils show two broad absorption bands near 2.2 microns and 2.33 microns with complex shapes. The slightly positive slope in the region of 2.3-2.4 microns with natural gas suggests that hydrocarbons are overriding the spectral signature of clays in this region.

[0300] In yet another embodiment, field tests were conducted over a wider spectra range from approximately 0.5 microns to 2.5 microns (FIGURE 36B). As the curve 3650 illustrates, two absorption features are found for the hydrocarbon spectral reflectance curve: one near 1.725

microns 3651 and a double absorption at approximately 2.311-2.36 microns 3652. Thus, in these two field trial examples, oil-gas reservoir areas were identifiable using feature bands of 1650-1750nm and 2000-2400nm. In addition, the remote sensing method may be used for off-shore oil and gas exploration and marine pollution investigation, to name just a few examples.

[0301] OTHER USES OF ACTIVE REMOTE SENSING OR HYPERSPECTRAL IMAGING

[0302] Active and/or hyper-spectral remote sensing may be used in a wide array of applications. Although originally developed for mining and geology (the ability of spectral imaging to identify various minerals may be ideal for the mining and oil industries, where it can be used to look for ore and oil), hyper-spectral remote sensing has spread to fields as diverse as ecology and surveillance. The table below illustrates some of the applications that can benefit from hyper-spectral remote sensing.

Atmosphere	Water vapor, cloud properties, aerosols
Ecology	Chlorophyll, leaf water, cellulose, pigments, lignin
Geology	Mineral and soil types
Coastal Waters	Chlorophyll, phytoplankton, dissolved organic materials, suspended sediments
Snow / Ice	Snow cover fraction, grainsize, melting
Biomass Burning	Subpixel temperatures, smoke
Commercial	Mineral (oil) exploration, agriculture and forest production

[0303] In one embodiment, near-infrared imaging spectroscopy data may be used to create qualitative images of thick oil or oil spills on water. This may provide a rapid remote sensing method to map the locations of thick parts of an oil spill. While color imagery may show locations

of thick oil, it is difficult to assess relative thickness or volume with just color imagery. As an example, FIGURE 37 illustrates the reflectance spectra 3700 of a sample of oil emulsion from the Gulf of Mexico 2010 oil spill. Curve 3701 is a 4mm thickness of oil, while curve 3702 is a 0.5mm thickness. Whereas the data in the visible hardly changes with oil thickness, in the near-infrared the change in reflectance spectra is much more dependent on the oil thickness. The data shows, for example, the C-H features near 1.2 microns 3703, 1.73 microns 3704, and 2.3 microns 3705. Thus, in the infrared wavelengths, both the reflectance levels and absorption features due to organic compounds may vary in strength with oil thickness.

[0304] Remote sensing may also be used for geology and mineralogy mapping or inspection. FIGURE 38 shows the reflectance spectra 3800 for some representative minerals that are major components of rocks and soils. In inorganic materials such as minerals, chemical composition and crystalline structure may control the shape of the spectral curve and the locations of absorption bands. Wavelength-specific absorption may arise from particular chemical elements or ions and the geometry of chemical bonds between elements, which is related to the crystal structure. In hematite 3801, the strong absorption in the visible may be caused by ferric iron. In calcite 3805, the carbonate ion may be responsible for the series of absorption bands between 1.8 and 2.4 microns. Kaolinite 3804 and montmorillonite 3802 are clay minerals common in soils. The strong absorption near 1.4 microns in both spectra, along with a weak 1.9 micron band in kaolinite arise from the hydroxide ions, while the stronger 1.9 micron band in montmorillonite may be caused by bound water molecules in the hydrous clay. In contrast to these spectra, orthoclase feldspar 3803, a dominant mineral in granite, shows very little absorption features in the visible or infrared.

[0305] Remote sensing or hyper-spectral imaging may also be used for agriculture as well as vegetation monitoring. For example, hyper-spectral data may be used to detect the chemical composition of plants, which can be used to detect the nutrient and water status of crops. FIGURE 39 illustrates the reflectance spectra 3900 of different types of green vegetation compared with dry, yellowed grass. In the visible spectra, the shape may be determined by absorption effects from chlorophyll and other leaf pigments. The reflectance rises rapidly across the boundary between red and infrared wavelengths, which may be due to interactions with the internal cellular structure of leaves. Leaf structure may vary significantly between plant species, as well as from

plant stress. Beyond 1.3 microns the reflectance decreases with increasing wavelength, except for two water absorption bands near 1.4 microns and 1.9 microns. Illustrated in FIGURE 39 are the reflectance for green grass 3901, walnut tree canopy 3902, fir tree 3903 and senescent 3904, which is dry, yellowed grass.

[0306] Active remote sensing may also be used to measure or monitor gases in the earth's atmosphere, including greenhouse gases, environmental pollutants and aerosols. For instance, greenhouse gases are those that can absorb and emit infrared radiation: In order, the most abundant greenhouse gasses in the Earth's atmosphere are: water vapor (H2O), carbon dioxide (CO2), methane (CH4), nitrous oxide (N2O) and ozone (O3). FIGURE 40 shows the atmospheric absorption and scattering of greenhouse gases 4000 at different wavelengths. Included in this figure are the total absorption and scattering 4001, along with the breakdown by major components: water vapor 4002, carbon dioxide 4003, oxygen and ozone 4004, methane 4005, and nitrous oxide 4006. Also shown is the Rayleigh scattering 4007 through the atmosphere, which dominates at shorter wavelengths, particularly wavelengths shorter than about 1 micron. In one embodiment, environmental concerns of climate change have led to the need to monitor the level of carbon dioxide in the atmosphere, and this may be achieved, for example, by performing spectroscopy in the vicinity of 1.6 microns and 2 microns.

[0307] In yet another embodiment, different building materials may be identified and distinguished from surrounding vegetation and forestry. FIGURE 41 overlays different reflectance data 4100 for samples cataloged in the ASTER spectra library (http://speclib.jpl.nasa.gov). This library has been made available by NASA as part of the Advanced Spaceborne Thermal Emission and Reflection Radiometer, ASTER, imaging instrumentation program. Included in this and other libraries are reflection spectra of natural and man-made materials, including minerals, rocks, soils, water and snow. In FIGURE 41 several spectra are included over the SWIR atmospheric transmission bands, and the water absorption between approximately 1.8 and 2 microns has been blocked out (features in there are either due to water or would be masked by the atmospheric moisture). Included in the graph are the spectra for silver metallic paint 4101, light brown loamy sand 4102, construction concrete-1 4103, construction concrete-cement 4104, gypsum 4105, asphaltic concrete 4106, construction concrete-bridges 4107, grass 4108 and conifer trees 4109. As an example, active remote sensing can be used to distinguish different concrete structures,

including roadways, buildings, and reinforced structures such as bridges. Also, building materials such as gypsum, painted structures, plywood, and concrete of various sorts, may be distinguished from plant life, soil and trees. Thus, beyond three dimensional imaging, this can add a fourth dimension – namely, identification of objects based on their chemical signature.

[0308] In a further embodiment, remote sensing or hyper-spectral imaging might be used for process control in a factory or manufacturing setting, particularly when the measurements are to be made at some stand-off or remote distance. As an example, plastics show distinct signatures in the SWIR, and process control may be used for monitoring the manufacture of plastics. Alternately, SWIR light could be used to see through plastics, since the signature for plastics can be subtracted off and there are large wavelength windows where the plastics are transparent. FIGURE 42 illustrates the absorbance 4200 for two common plastics: polyethylene 4201 and polystyrene 4202. Because of the hydro-carbon bonds, there are absorption features near 1.7 microns and 2.2-2.5 microns (c.f., discussion on alkanes). In general, the absorption bands in the near infrared are due to overtones and combination bands for various functional group vibrations, including signals from C-H, O-H, C=O, N-H, -COOH, and aromatic C-H groups. It may be difficult to assign an absorption band to a specific functional group due to overlapping of several combinations and overtones. However, with advancements in computational power and chemometrics or multivariate analysis methods, complex systems may be better analyzed. In one embodiment, using software analysis tools the absorption spectrum may be converted to its second derivative equivalent. The spectral differences may permit a fast, accurate, non-destructive and reliable identification of materials. Although particular derivatives are discussed, other mathematical manipulations may be used in the analysis, and these other techniques are also intended to be covered by this disclosure.

[0309] In another specific embodiment, experiments have been performed for stand-off detection of solid targets with diffuse reflection spectroscopy using a fiber-based super-continuum source (further described herein). In particular, the diffuse reflection spectrum of solid samples such as explosives (TNT, RDX, PETN), fertilizers (ammonium nitrate, urea), and paints (automotive and military grade) have been measured at stand-off distances of 5m. Although the measurements were done at 5m, calculations show that the distance could be anywhere from a few meters to over 150m. These are specific samples that have been tested, but more generally other

materials (particularly comprising hydro-carbons) could also be tested and identified using similar methods. The experimental set-up 4300 for the reflection-spectroscopy-based stand-off detection system is shown in FIGURE 43, while details of the SC source 4301 are described later in this disclosure (c.f. FIGURES 20,21, and 23). First, the diverging SC output is collimated to a 1 cm diameter beam using a 25 mm focal length, 90 degrees off-axis, gold coated, parabolic mirror 4302. To reduce the effects of chromatic aberration, refractive optics are avoided in the setup. All focusing and collimation is done using metallic mirrors that have almost constant reflectivity and focal length over the entire SC output spectrum. The sample 4304 is kept at a distance of 5m from the collimating mirror 4302, which corresponds to a total round trip path length of 10m before reaching the collection optics 4305. A 12cm diameter silver coated concave mirror 4305 with a 75cm focal length is kept 20cm to the side of the collimation mirror 4302. The mirror 4305 is used to collect a fraction of the diffusely reflected light from the sample, and focus it into the input slit of a monochromator 4306. Thus, the beam is incident normally on the sample 4304, but detected at a reflection angle of tan-1(0.2/5) or about 2.3 degrees. Appropriate long wavelength pass filters mounted in a motorized rotating filter wheel are placed in the beam path before the input slit 4306 to avoid contribution from higher wavelength orders from the grating (300 grooves/mm, 2μm blaze). The output slit width is set to 2mm corresponding to a spectral resolution of 10.8nm, and the light is detected by a 2mm x 2mm liquid nitrogen cooled (77K) indium antimonide (InSb) detector 4307. The detected output is amplified using a trans-impedance pre-amplifier 4307 with a gain of about 105V/A and connected to a lock-in amplifier 4308 setup for high sensitivity detection. The chopper frequency is 400Hz, and the lock-in time constant is set to 100ms corresponding to a noise bandwidth of about 1Hz. These are exemplary elements and parameter values, but other or different optical elements may be used consistent with this disclosure.

[0310] Three sets of solid samples are chosen to demonstrate the stand-off diffuse reflection spectra measurement in the laboratory. The first set comprises 'Non-hazardous Explosives for Security Training and Testing' (NESTT) manufactured by the XM Division of VanAken International. These samples contain small amounts of explosives deposited on an inert fused silica powder substrate. The experiments are conduced with the following samples – trinitrotoluene (TNT), research department explosive (RDX), Pentaerythritol tetranitrate (PETN),

and potassium nitrate. The TNT, RDX and potassium nitrate NESTT samples have 8% (by weight) explosives, while the PETN sample has 4%.

[0311] The second sample set consists of ammonium nitrate, urea, gypsum, and pinewood. Ammonium nitrate and urea are common fertilizers, but are also often used as explosives. These samples are ground to a fine powder in a mortar and pestle, and filled to a depth of about 5mm in a shallow glass container. We also measure the reflection spectrum of a 10cm diameter x 0.5cm thick Gypsum (CaSO4.2H2O) disk and a 5cm x 5cm x 0.5m piece of pine wood, since these samples are relevant for the remote sensing community (minerals and vegetation).

[0312] The final set of samples is selected to distinguish between commercial automotive and military vehicle paints based on their reflection signatures. Red, black, and green acrylic based spray paints are obtained from an auto supply store and sprayed 3 coats on different areas of a sanded Aluminum block to make the automotive paint samples. The sample of the military paint consisted of an Aluminum block coated with a chemical agent resistant coating (CARC) green paint.

[0313] The chemical structure and molecular formula of the 4 NESTT samples are shown in FIGURE 44 (4401, 4402, 4403, 4404), while the absorbance spectra obtained using the SC source are shown below in the same figure (4405, 4406, 4407, 4408). For each sample, the positions of the strongest/unique peaks have been labeled for clarity. TNT 4401, 4405 belongs to a class of compounds known as nitro-aromatics, in which the carbon directly attached to the nitro (NO2) group is part of an aromatic ring. The strongest peaks in the spectrum observed at 3230nm and 3270nm are due to the fundamental C-H stretching vibrations in the aromatic ring. There are also features between 2200-2600nm, which may arise from the combination between the C-H stretch and C-H bend vibrations. RDX 4402, 4406 belongs to the nitramines class containing the N-NO2 bond and also has multiple features in the 3200-3500nm band due to the C-H stretch vibrations. This spectrum also contains the C-H combination bands from 2200-2600nm. PETN 4403, 4407 is classified as a nitrate ester containing the C-O-NO2 bond, and its reflection spectrum is characterized by a triplet of peaks at 3310nm, 3350nm and 3440nm due to the C-H stretch vibration from the aliphatic groups. The C-H combination band is also present from 2200-2600nm. Potassium nitrate 4404, 4408 being an inorganic compound does not contain any absorption

features due to the C-H bond present in the other three samples. Instead, the unique spectral feature for this sample is a pair of peaks at 3590nm and 3650nm, which arise due to the first overtone of the asymmetric N-O stretching vibration of the nitrate ion (NO3-).

[0314] FIGURE 45A illustrates the reflection spectra 4500 for gypsum 4501, pinewood 4502, ammonium nitrate 4503 and urea 4504. The predominant spectral features in the gypsum 4501 (CaSO4.2H2O) reflectance occur due to the fundamental as well as combination bands of the water molecule near 1450nm, 1750nm, 1940nm and 2860nm. In addition, small dips in the spectrum at 2220, 2260 and 2480nm which arise due to the first overtone of the S-O bending vibration. Moreover, the valley at 3970nm occurs due to the first overtone of the –O-S-O stretching vibration of the sulfate (SO42-) ion. The pine wood spectrum 4502 comprises of bands due to its main constituents – cellulose, lignin and water. The valleys at 1450nm, 1920nm and 2860nm are attributed to water. The dip at 2100nm is due to the first overtone of the C-O asymmetric stretch, the one at 2270 nm due to the combination band of O-H and C-H, and the one at 2490nm due to combination band of C-H and C-O. Finally, the broad feature around 3450nm is due to the C-H stretching vibration. The ammonium nitrate (NH4NO3) spectrum 4503 has three prominent features in the near-IR region. The dip at 1270nm is due to the combination of N-H stretching and N-H bending vibrations, while the dip at 1570nm is due to the first overtone of N-H stretch. The doublet at 2050nm and 2140nm is possibly due to the second overtone of the N-H bending vibrations, while the fundamental N-H stretch appears as a broad feature around 3000 nm. Urea (NH2)2CO 4504 has two amide (-NH2) groups joined by a carbonyl (C=O) functional group. The absorption line at 1490nm occurs due to the third overtone of the C=O stretching vibration while the line at 1990nm is due to the second overtone of the same.

[0315] FIGURE 45B shows the reflection spectra 4550 for three commercial automotive paints 4551, 4552, 4553 and military grade CARC (chemical agent resistant coating) paint 4554. The paints consist of a complex mixture of many different chemicals, and, hence, it is very difficult to identify individual absorption lines. Since all four paints contain a variety of organic compounds, features are observed between 3200-3500nm from the C-H stretch and from 2200-2600nm due to the C-H stretch and C-H bond combination band. However, the primary difference between the automotive 45451, 4552, 4553 and CARC paint 4554 is the presence of a strong dip

between 1200-1850nm in the latter, which might be attributed to the absorption from Cobalt chromite - a green pigment found in CARC-green.

[0316] Thus, FIGURES 44 and 45 show that various materials, including explosives, fertilizers, vegetation, and paints have features in the near-infrared and SWIR that can be used to identify the various samples. Although stronger features are found in the mid-infrared, the near-infrared may be easier to measure due to higher quality detection systems, more mature fiber optics and light sources, and transmission through atmospheric transmission windows. Because of these distinct spectral signatures, these materials could also be detected using active remote sensing or hyper-spectral imaging, as described in this disclosure. These are just particular samples that have been tested at stand-off distances, but other materials and samples may also be identified using the SWIR remote sensing or hyper-spectral imaging methods, and these samples are also intended to be covered within this disclosure. As just another example, illicit drugs may be detectable using remote sensing or hyper-spectral imaging. FIGURE 46 shows the mid-wave infrared and long-wave infrared absorption spectra 1500 for various illicit drugs. The absorbance for cocaine 4601, methamphetamine 4602, MDMA (ecstasy) 4603, and heroin 4604 are plotted versus wavelength from approximately 2.5-20 microns. Although the fundamental resonances for these drugs may lie in the longer wavelength regions, there are corresponding overtones and combination bands in the SWIR and near-infrared wavelength range. Therefore, the active remote sensing or hyper-spectral imaging techniques described herein may also be applicable to detecting illicit drugs from aircraft, vehicles, or hand held devices.

[0317] DETECTION SYSTEMS

[0318] As discussed earlier, the active remote sensing system or hyper-spectral imaging system may be on an airborne platform, mounted on a vehicle, a stationary transmission or reflection set-up, or even held by a human for a compact system. For such a system, there are fundamentally two hardware parts: the transmitter or light source and the detection system. Between the two, perhaps in a transmission or reflection setting, may be the sample being tested or measured. Moreover, the output from the detection system may go to a computational system, comprising computers or other processing equipment. The output from the computational system may be displayed graphically as well as with numerical tables and perhaps an identification of the

material composition. These are just some of the parts of the systems, but other elements may be added or be eliminated, and these modified configurations are also intended to be covered by this disclosure.

[0319] By use of an active illuminator, a number of advantages may be achieved. First, the variations due to sunlight and time-of-day may be factored out. The effects of the weather, such as clouds and rain, might also be reduced. Also, higher signal-to-noise ratios may be achieved. For example, one way to improve the signal-to-noise ratio would be to use modulation and lock-in techniques. In one embodiment, the light source may be modulated, and then the detection system would be synchronized with the light source. In a particular embodiment, the techniques from lock-in detection may be used, where narrow band filtering around the modulation frequency may be used to reject noise outside the modulation frequency. In an alternate embodiment, change detection schemes may be used, where the detection system captures the signal with the light source on and with the light source off. Again, for this system the light source may be modulated. Then, the signal with and without the light source is differenced. This may enable the sun light changes to be subtracted out. In addition, change detection may help to identify objects that change in the field of view. In the following some exemplary detection systems are described.

[0320] In one embodiment, a SWIR camera or infrared camera system may be used to capture the images. The camera may include one or more lenses on the input, which may be adjustable. The focal plane assemblies may be made from mercury cadmium telluride material (HgCdTe), and the detectors may also include thermo-electric coolers. Alternately, the image sensors may be made from indium gallium arsenide (InGaAs), and CMOS transistors may be connected to each pixel of the InGaAs photodiode array. The camera may interface wirelessly or with a cable (e.g., USB, Ethernet cable, or fiber optics cable) to a computer or tablet or smart phone, where the images may be captured and processed. These are a few examples of infrared cameras, but other SWIR or infrared cameras may be used and are intended to be covered by this disclosure.

[0321] In another embodiment, an imaging spectrometer may be used to detect the light received from the sample. For example, FIGURE 47A shows a schematic diagram 4700 of the

basic elements of an imaging spectrometer. The input light 4701 from the sample may first be directed by a scanning mirror and/or other optics 4702. An optical dispersing element 4703, such as a grating or prism, in the spectrometer may split the light into many narrow, adjacent wavelength bands, which may then be passed through imaging optics 4704 onto one or more detectors or detector arrays 4705. Some sensors may use multiple detector arrays to measure hundreds of narrow wavelength bands.

[0322] An example of a typical imaging spectrometer 4750 used in hyper-spectral imaging systems is illustrated in FIGURE 47B. In this particular embodiment, the input light may be directed first by a tunable mirror 4751. A front lens 4752 may be placed before the entrance slit 4753 and the collector lens 4754. In this embodiment, the dispersing element is a holographic grating with a prism 4755, which separates the different wavelength bands. Then, a camera lens 4756 may be used to image the wavelengths onto a detector or camera 4757.

[0323] FIGURES 47A and 47B provide particular examples, but some of the elements may not be used, or other elements may be added, and these embodiments are also intended to be covered by this disclosure. For instance, a scanning spectrometer may be used before the detector, where a grating or dispersive element is scanned to vary the wavelength being measured by the detector. In yet another embodiment, filters may be used before one or more detectors to select the wavelengths or wavelength bands to be measured. This may be particularly useful if only a few bands or wavelengths are to be measured. The filters may be dielectric filters, Fabry-Perot filters, absorption or reflection filters, fiber gratings, or any other wavelength selective filter. In an alternate embodiment, a wavelength division multiplexer, WDM, may be used followed by one or more detectors or detector arrays. One example of a planar wavelength division multiplexer may be a waveguide grating router or an arrayed waveguide grating. The WDM may be fiber coupled, and detectors may be placed directly at the output or the detectors may be coupled through fibers to the WDM. Some of these components may also be combined with the configurations in FIGURES 47A and 47B.

[0324] While the above detection systems could be categorized as single path detection systems, it may be advantageous in some cases to use multi-path detection systems. In one embodiment, when the aim is to measure particular gases or material (rather than identify out of a

library of materials), it may be advantageous to use gas-filter correlation radiometry (GFCR), such as 4800 in FIGURE 48. A GFCR is a detection system that uses a sample of the gas of interest as a spectral filter for the gas. As shown in FIGURE 48, the incoming radiation 4801 may first be passed through a narrow band pass filter 4802. The beam may then be split by a beam splitter 4803 along two paths; one path comprising a gas cell filled with the gas of interest 4804 (known as the correlation cell) and the other path comprising no gas 4805. The light from each path may then be measured using two detectors 4806, 4807, and the signals may then be analyzed 4808. The difference in the transmission along the two paths may correspond primarily to the absorption of the gas along the correlation cell path. This GFCR configuration may be advantageous, for example, in the detection of natural gas. Since the goal is to measure methane and ethane, the correlation cells may contain these gases, either in combination or separately. Although a particular configuration for the GFCR has been described, variations of this configuration as well as addition of other components may also be used and are intended to be covered by this disclosure. For example, collection optics and lenses may be used with this configuration, and various modulation techniques may also be used to increase the signal to noise ratio.

[0325] In yet another example of multi-beam detection systems, a dual-beam set-up 4900 such as in FIGURE 49 may be used to subtract out (or at least minimize the adverse effects of) light source fluctuations. In one embodiment, the output from an SC source 4901 may be collimated using a calcium fluoride (CaF2) lens 4902 and then focused into the entrance slit of the monochromator 4903. At the exit slit, light at the selected wavelength is collimated again and may be passed through a polarizer 4904 before being incident on a calcium fluoride beam splitter 4905. After passing through the beam splitter 4905, the light is split into a sample 4906 and reference 4907 arm to enable ratiometric detection that may cancel out effects of intensity fluctuations in the SC source 4901. The light in the sample arm 4906 passes through the sample of interest and is then focused onto a HgCdTe detector 4908 connected to a pre-amp. A chopper 4902 and lock-in amplifier 4910 setup enable low noise detection of the sample arm signal. The light in the reference arm 4907 passes through an empty container (cuvette, gas cell etc.) of the same kind as used in the sample arm. A substantially identical detector 4909, pre-amp and lock-in amplifier 4910 is used for detection of the reference arm signal. The signal may then be analyzed using a computer system 4911. This is one particular example of a method to remove fluctuations from the light

source, but other components may be added and other configurations may be used, and these are also intended to be covered by this disclosure.

[0326] Although particular examples of detection systems have been described, combinations of these systems or other systems may also be used, and these are also within the scope of this disclosure. As one example, environmental fluctuations (such as turbulence or winds) may lead to fluctuations in the beam for active remote sensing or hyper-spectral imaging. A configuration such as illustrated in the representative embodiment of FIGURE 49 may be able to remove the effect of environmental fluctuations. Yet another technique may be to "wobble" the light beam after the light source using a vibrating mirror. The motion may lead to the beam moving enough to wash out spatial fluctuations within the beam waist at the sample or detection system. If the vibrating mirror is scanned faster than the integration time of the detectors, then the spatial fluctuations in the beam may be integrated out. Alternately, some sort of synchronous detection system may be used, where the detection is synchronized to the vibrating frequency.

[0327] Described herein are just some examples of the beneficial use of near-infrared or SWIR lasers for active remote sensing or hyper-spectral imaging. However, many other spectroscopy and identification procedures can use the near-infrared or SWIR light consistent with this disclosure and are intended to be covered by the disclosure. As one example, the fiber-based super-continuum lasers may have a pulsed output with pulse durations of approximately 0.5-2nsec and pulse repetition rates of several Megahertz. Therefore, the active remote sensing or hyper-spectral imaging applications may also be combined with LIDAR-type applications. Namely, the distance or time axis can be added to the information based on time-of-flight measurements. For this type of information to be used, the detection system would also have to be time-gated to be able to measure the time difference between the pulses sent and the pulses received. By calculating the round-trip time for the signal, the distance of the object may be judged. In another embodiment, GPS (global positioning system) information may be added, so the active remote sensing or hyper-spectral imagery would also have a location tag on the data. Moreover, the active remote sensing or hyper-spectral imaging information could also be combined with two-dimensional or three-dimensional images to provide a physical picture as well as a chemical composition identification of the materials. These are just some modifications of the active remote sensing or hyper-spectral imaging system described in this disclosure, but other techniques may also be added or

combinations of these techniques may be added, and these are also intended to be covered by this disclosure.

[0328] SECTION 4: SHORT-WAVE INFRARED SUPER-CONTINUUM LASERS FOR DETECTING COUNTERFEIT OR ILLICIT DRUGS AND PHARMACEUTICAL PROCESS CONTROL

[0329] One advantage of optical systems is that they can perform non-contact, stand-off or remote sensing distance spectroscopy of various materials. As an example, optical systems can be used for identification of counterfeit drugs, detection of illicit drugs, or process control in the pharmaceutical industry, especially when the sensing is to be done at remote or stand-off distances in a non-contact, rapid manner. In general, the near-infrared region of the electromagnetic spectrum covers between approximately 0.7 microns (700nm) to about 2.5 microns (2500nm). However, it may also be advantageous to use just the short-wave infrared (SWIR) between approximately 1.4 microns (1400nm) and about 2.5 microns (2500nm). One reason for preferring the SWIR over the entire NIR may be to operate in the so-called "eye safe" window, which corresponds to wavelengths longer than about 1400nm. Therefore, for the remainder of the disclosure the SWIR will be used for illustrative purposes. However, it should be clear that the discussion that follows could also apply to using the near infrared – NIR -- wavelength range, or other wavelength bands.

[0330] In particular, wavelengths in the eye safe window may not transmit down to the retina of the eye, and therefore, these wavelengths may be less likely to create permanent eye damage from inadvertent exposure. The near-infrared wavelengths have the potential to be dangerous, because the eye cannot see the wavelengths (as it can in the visible), yet they can penetrate and cause damage to the eye. Even if a practitioner is not looking directly at the laser beam, the practitioner's eyes may receive stray light from a reflection or scattering some surface. Hence, it can always be a good practice to use eye protection when working around lasers. Since wavelengths longer than about 1400nm are substantially not transmitted to the retina or substantially absorbed in the retina, this wavelength range is known as the eye safe window. For wavelengths longer than 1400nm, in general only the cornea of the eye may receive or absorb the light radiation.

[0331] The SWIR wavelength range may be particularly valuable for identifying materials based on their chemical composition because the wavelength range comprises overtones and combination bands for numerous chemical bonds. For example, in the SWIR numerous hydro-carbon chemical compounds have overtone and combinational bands, along with oxygen-hydrogen and carbon-oxygen compounds. Thus, gases, liquids and solids that comprise these chemical compounds may exhibit spectral features in the SWIR wavelength range. In a particular embodiment, the spectra of organic compounds may be dominated by the C-H stretch. The C-H stretch fundamental occurs near 3.4 microns, the first overtone is near 1.7 microns, and a combination band occurs near 2.3 microns.

[0332] One embodiment of remote sensing that is used to identify and classify various materials is so-called "hyper-spectral imaging." Hyper-spectral sensors may collect information as a set of images, where each image represents a range of wavelengths over a spectral band. Hyper-spectral imaging may deal with imaging narrow spectral bands over an approximately continuous spectral range. As an example, in hyper-spectral imaging a lamp may be used as the light source. However, the incoherent light from a lamp may spatially diffract rapidly, thereby making it difficult to perform spectroscopy at stand-off distances or remote distances. Therefore, it would be advantageous to have a broadband light source covering the SWIR that may be used in place of a lamp to identify or classify materials in remote sensing or stand-off detection applications.

[0333] As used throughout this document, the term "couple" and or "coupled" refers to any direct or indirect communication between two or more elements, whether or not those elements are physically connected to one another. As used throughout this disclosure, the term "spectroscopy" means that a tissue or sample is inspected by comparing different features, such as wavelength (or frequency), spatial location, transmission, absorption, reflectivity, scattering, fluorescence, refractive index, or opacity. In one embodiment, "spectroscopy" may mean that the wavelength of the light source is varied, and the transmission, absorption, fluorescence, or reflectivity of the tissue or sample is measured as a function of wavelength. In another embodiment, "spectroscopy" may mean that the wavelength dependence of the transmission, absorption, fluorescence or reflectivity is compared between different spatial locations on a tissue or sample. As an illustration, the "spectroscopy" may be performed by varying the wavelength of

the light source, or by using a broadband light source and analyzing the signal using a spectrometer, wavemeter, or optical spectrum analyzer.

[0334] As used throughout this document, the term "fiber laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein at least a part of the laser comprises an optical fiber. For instance, the fiber in the "fiber laser" may comprise one of or a combination of a single mode fiber, a multi-mode fiber, a mid-infrared fiber, a photonic crystal fiber, a doped fiber, a gain fiber, or, more generally, an approximately cylindrically shaped waveguide or light-pipe. In one embodiment, the gain fiber may be doped with rare earth material, such as ytterbium, erbium, and/or thulium. In another embodiment, the mid-infrared fiber may comprise one or a combination of fluoride fiber, ZBLAN fiber, chalcogenide fiber, tellurite fiber, or germanium doped fiber. In yet another embodiment, the single mode fiber may include standard single-mode fiber, dispersion shifted fiber, non-zero dispersion shifted fiber, high-nonlinearity fiber, and small core size fibers.

[0335] As used throughout this disclosure, the term "pump laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein the output light or optical beam is coupled to a gain medium to excite the gain medium, which in turn may amplify another input optical signal or beam. In one particular example, the gain medium may be a doped fiber, such as a fiber doped with ytterbium, erbium and/or thulium. In one embodiment, the "pump laser" may be a fiber laser, a solid state laser, a laser involving a nonlinear crystal, an optical parametric oscillator, a semiconductor laser, or a plurality of semiconductor lasers that may be multiplexed together. In another embodiment, the "pump laser" may be coupled to the gain medium by using a fiber coupler, a dichroic mirror, a multiplexer, a wavelength division multiplexer, a grating, or a fused fiber coupler.

[0336] As used throughout this document, the term "super-continuum" and or "supercontinuum" and or "SC" refers to a broadband light beam or output that comprises a plurality of wavelengths. In a particular example, the plurality of wavelengths may be adjacent to one-another, so that the spectrum of the light beam or output appears as a continuous band when measured with a spectrometer. In one embodiment, the broadband light beam may have a bandwidth of at least 10nm. In another embodiment, the "super-continuum" may be generated

through nonlinear optical interactions in a medium, such as an optical fiber or nonlinear crystal. For example, the "super-continuum" may be generated through one or a combination of nonlinear activities such as four-wave mixing, parametric amplification, the Raman effect, modulational instability, and self-phase modulation.

[0337] As used throughout this disclosure, the terms "optical light" and or "optical beam" and or "light beam" refer to photons or light transmitted to a particular location in space. The "optical light" and or "optical beam" and or "light beam" may be modulated or unmodulated, which also means that they may or may not contain information. In one embodiment, the "optical light" and or "optical beam" and or "light beam" may originate from a fiber, a fiber laser, a laser, a light emitting diode, a lamp, a pump laser, or a light source.

[0338] As used throughout this disclosure, the term "remote sensing" may include the measuring of properties of an object from a distance, without physically sampling the object, for example by detection of the interactions of the object with an electromagnetic field. In one embodiment, the electromagnetic field may be in the optical wavelength range, including the infrared or SWIR. One particular form of remote sensing may be stand-off detection, which may range exemplary from non-contact up to hundreds of meters away.

[0339] IDENTIFICATION OF COUNTERFEIT DRUGS

[0340] Pharmaceutical counterfeiting is a growing and significant issue for the healthcare community as well as the pharmaceutical industry worldwide. As a result of counterfeiting, users may be threatened by substandard drug quality or harmful ingredients, and legitimate companies may lose significant revenues. The definition for "counterfeit drug" by the World Health Organization was as follows: "A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging." Later this definition was slightly modified, "Counterfeiting in relation to medicinal products means the deliberate and fraudulent mislabeling with respect to the identity, composition and/or source of a finished medicinal product, or ingredient for the preparation of a medicinal product."

[0341] A rapid screening technique such as near-infrared or SWIR spectroscopy could aid in the search for and identification of counterfeit drugs. In particular, using a non-lamp based light source could lead to contact-free control and analysis of drugs. In a particular embodiment, remote sensing, stand-off detection, or hyper-spectral imaging may be used for process control or counterfeit drug identification in a factory or manufacturing setting, or in a retail, wholesale, or warehouse setting. In one embodiment, the light source for remote sensing may direct the light beam toward the region of interest (e.g., conveyor belt, stocking shelves, boxes or cartons, etc), and the diffuse reflected light may then be measured using a detection system. Various kinds of SWIR light sources will be discussed later in this disclosure. The detection system may comprise, in one embodiment, a spectrometer followed by one or more detectors. In another embodiment, the detection system may be a dispersive element (examples include prisms, gratings, or other wavelength separators) followed by one or more detectors or detector arrays. In yet another embodiment, the detection system may comprise a Fourier transform infrared spectrometer. These are merely specific examples of the detection system, but combinations of these or other detection systems may also be used and are contemplated within the scope of this disclosure.

[0342] For monitoring drugs, the SWIR light source and the detection system could be used in transmission, reflection, fluorescence, or diffuse reflection. Also, different system configurations may also be used and are included in the scope of this disclosure. For example, the light source and detection system may be placed in a fixed location, and for reflection the light source and detectors may be close to one another, while for transmission the light source and detectors may be at different locations. The region of interest may be surveyed, and the light beam may also be scanned to cover an area larger than the light source beam. In yet another embodiment, the system could be placed on a vehicle such as an automobile or a truck, or the light source could be placed on one vehicle, while the detection system is on another vehicle. If the light source and detection system are compact and lightweight, they might even be carried by a person in the field, either in their hands or in a backpack.

[0343] Another advantage of using the near-infrared or SWIR is that most drug packaging materials are at least partially transparent in this wavelength range, so that drug compositions may be detected and identified through the packaging non-destructively. As an example, SWIR light could be used to see through plastics, since the signature for plastics can be subtracted off and

there are large wavelength windows where the plastics are transparent. FIGURE 50 illustrates the absorbance 5000 for two common plastics: polyethylene 5001 and polystyrene 5002. Because of the hydro-carbon bonds, there are absorption features near 1.7 microns and 2.2-2.5 microns. In general, the absorption bands in the near infrared are due to overtones and combination bands for various functional group vibrations, including signals from C-H, O-H, C=O, N-H, -COOH, and aromatic C-H groups. It may be difficult to assign an absorption band to a specific functional group due to overlapping of several combinations and overtones. However, with advancements in computational power and chemometrics or multivariate analysis methods, complex systems may be better analyzed. In one embodiment, using software analysis tools the absorption spectrum may be converted to its second derivative equivalent. The spectral differences may permit a fast, accurate, non-destructive and reliable identification of materials. Although particular derivatives are discussed, other mathematical manipulations may be used in the analysis, and these other techniques are also intended to be covered by this disclosure.

[0344] Spectroscopy in the near-infrared or SWIR may be sensitive to both the chemical and physical nature of the sample composition and may be performed rapidly with minimal sample preparation. For example, near-infrared or SWIR spectroscopy may be used to study the homogeneity of powder samples, particle size determinations, product composition, the determination of the concentrations and distribution of components in solid tablets and content uniformity, among other applications. In yet other embodiments, applications include tablet identification, determination of moisture, residual solvents, active ingredient potency, the study of blending operations, and the detection of capsule tampering.

[0345] FIGURE 51 illustrates one example of the difference in near-infrared spectrum 5100 between an authentic tablet and a counterfeit tablet. Two grades of film coated tablets comprising drugs were investigated: curve 5101 is the genuine drug, while 5102 is a counterfeit drug. These two grades of capsules have noticeably different contents, and the differences are apparent in the near-infrared or SWIR spectra. In some cases the differences may not be as distinct. For these cases, more signal processing may be necessary to distinguish between samples.

[0346] In another embodiment, it may be advantageous to take a first, second or higher order derivative to elucidate the difference between real and counterfeit drugs. For example,

FIGURE 52 shows the second derivative 5200 of the spectral comparison of Prozac 5201 and a similarly formulated generic 5202, which had a fluoxetine hydrochloride (10mg). Although the reflectance curves from the two samples are close and, therefore, difficult to distinguish, the second derivative of the data helps to bring out the differences more clearly. Although a second derivative is used in this example, any number of signal processing algorithms and methods may be used, and these are also intended to be covered by this disclosure. For example, partial least square algorithms, multivariate data analysis, principal component analysis, or chemometric software may be implemented without departing from the scope of this disclosure.

[0347] In yet another embodiment, near-infrared or SWIR spectroscopy may be used to measure and calibrate various pharmaceutical formulations based on the active pharmaceutical ingredients and excipients. An excipient may be a pharmacologically inactive substance used as a carrier for the active ingredients of a medication. In some cases, the active substance may not be easily administered and/or absorbed by the human body; in such cases the active ingredient may be dissolved into or mixed with an excipient. Also, excipients are also sometimes used to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid in the handling of the active substance concerned.

[0348] FIGURE 53 shows an example of the near-infrared spectra 5300 for different pure components of a studied drug. The spectrum for the active pharmaceutical ingredient (API) 5301 is plotted, along with the spectra for five different excipients 5302, 5303, 5304, 5305 and 5306. Each spectrum has been baseline shifted to avoid overlapping. The near-infrared spectra have been obtained by averaging the spectra of each pixel of an area of a hyper-spectral image. As FIGURE 53 shows, each of the chemical compositions have a distinct spectrum, and the composition of a drug may be decomposed into its constitutive ingredients. These are just some examples of how near-infrared or SWIR spectroscopy may be applied to counterfeit drug detection, but other methods and analysis techniques may also be used without departing from the scope of this disclosure. As one other example, once the active pharmaceutical ingredient and the excipients spectral distribution of a drug formulation are understood, feedback may be provided of this information to the drug development stages.

[0349] RAPID SCREENING FOR ILLICIT DRUGS

[0350] Thus, FIGURES 51-53 show that near-infrared or SWIR spectroscopy may be used to identify counterfeit drugs. More generally, various materials including illicit drugs, explosives, fertilizers, vegetation, and paints have features in the near-infrared and SWIR that can be used to identify the various samples, and these applications are also intended to be within the scope of this disclosure. Although stronger features may be found in the mid-infrared, the near-infrared may be easier to measure due to higher quality detection systems, more mature fiber optics and light sources, and transmission through atmospheric transmission windows. Because of these distinct spectral signatures, these materials could also be detected using active remote sensing, hyper-spectral imaging, or near-infrared or SWIR spectroscopy. As just another example, illicit drugs may be detectable using remote sensing, hyper-spectral imaging, or near-infrared spectroscopy. FIGURE 54 shows the mid-wave infrared and long-wave infrared absorption spectra 5400 for various illicit drugs. The absorbance for cocaine 5401, methamphetamine 5402, MDMA (ecstasy) 5403, and heroin 5404 are plotted versus wavelength from approximately 2.5-20 microns. Although the fundamental resonances for these drugs may lie in the longer wavelength regions, there are corresponding overtones and combination bands in the SWIR and near-infrared wavelength range. Therefore, the active remote sensing, hyper-spectral imaging, or near-infrared or SWIR spectroscopy techniques described herein may also be applicable to detecting illicit drugs from aircraft, vehicles, or hand held devices.

[0351] The diffuse reflectance technique may be useful with near-infrared or SWIR spectroscopy for rapid identification of illegal drugs due to simple handling and simple use of a search data library created using near-infrared diffuse reflectance. For instance, FIGURE 55 illustrates the absorbance 5500 versus wavelength in the near-infrared region for four classes of illegal drugs. In particular, the spectra are shown for methamphetamine (MA) 5501, amphetamine (AP) 5502, MDMA (street name: ecstasy) 5503, and MDA (street name: the love drug) 5504. Each of the illegal drugs have unique spectral features in the near-infrared and SWIR. Also, comparing the mid-infrared spectrum for MDMA (5403 in FIGURE 54) with the near-infrared spectrum for MDMA (5503 in FIGURE 55), it seems clear that the near-infrared region shows overtones and combination bands that should be discernible. Referring to FIGURE 55, sample

identification may be accomplished by using the region (indicated by the arrows) where the spectral absorptions may provide specific peaks depending on the drug component.

[0352] In another embodiment, FIGURE 56 shows the diffuse reflectance near-infrared spectrum 5600 of heroin samples. Heroin, the 3,6-diacetyl derivative of morphine (hence diacetyl-morphine) is an opiate drug synthesized from morphine, which is usually a naturally occurring substance extracted from the seedpod of certain varieties of poppy plants. In particular, 5601 is the near-infrared spectrum for an illicit street drug sample, while 5602 is the spectra for a pure heroin standard. The difference between the spectra may arise at least in part from cutting agents. The inset 5603 shows the molecular structure for heroin. As in the other examples, the absorption in the near-infrared range is caused by overtone and combination vibrations of O-H, C-H, N-H and C=O groups, which exhibit their fundamental molecular stretching and bending absorption in the mid-infrared range (c.f., the mid-infrared spectrum for heroin is shown 5404 in FIGURE 54). These overtone and combination bands do not behave in a simple way, making the near-infrared spectra complex and harder to directly interpret. Also, although the near-infrared signatures may be weaker in magnitude, they are probably easier to detect in the near-infrared, and the sample preparation may also be much simpler in the near-infrared. Moreover, for remote sensing, the near-infrared may be preferable because of atmospheric transmission windows between approximately 1.4-1.8 microns and 2-2.5 microns.

[0353] Pure heroin may be a white powder with a bitter taste that is rarely sold on the streets, while illicit heroin may be a powder varying in color from white to dark brown due to impurities left from the manufacturing process or the presence of additives. The purity of street heroin may also vary widely, as the drug can be mixed with other white powders. The impurity of the drug may often make it difficult to gauge the strength of the dosage, which runs the risk of overdose. One nice feature of near-infrared or SWIR spectroscopy is that the technique may be used in a non-destructive, non-contact manner to determine rapidly the concentration of compounds present in complex samples at percentage levels with very little sample preparation. In a particular embodiment, FIGURE 57 illustrates the diffuse reflectance near-infrared spectra 5700 of different seized illicit drugs containing heroin (between 10.7 and 21.8%) compared with the spectrum of pure heroin 5701. Curve 5702 is for 21.8% by weight, curve 5703 is 13.2% by

weight, curve 5704 is 17% by weight, and curve 5705 is 10.7% by weight of heroin. The spectra have been shifted along the vertical axis to better illustrate the differences.

[0354] Although quite complex in the near-infrared, it may be possible to identify from the pure heroin near-infrared spectrum (5701 in FIGURE 57 or 5602 in FIGURE 56) the main wavelengths related to the most common functional groups in heroin. For example, FIGURE 58 lists possible band assignments 5800 for the various spectral features in pure heroin. As can be seen from FIGURE 58, the absorption in the near-infrared may be mainly due to overtone and combination bands associated with O-H, C-H, N-H and C=O groups.

[0355] As can be appreciated from FIGURE 57, there may be significant differences between the spectrum of pure heroin and sample spectra. These differences may be due to the presence of different compounds used as cutting agents, which can affect the shape and intensity of the near-infrared signals. FIGURE 59 illustrates the diffuse reflectance near-infrared spectra 5900 of different compounds that may be frequently employed as cutting agents. In the bottom of FIGURE 59 are shown the spectra 5908 for pure heroin and the spectra 5907 for a seized illicit street drug sample comprising 21.8% of heroin. The spectra for various cutting agents include: 5901 for flour, 5902 for talcum powder, 5903 for chalk, 5904 for acetylsalicylic acid, 5905 for caffeine, and 5906 for paracetamol. Thus, near-infrared or SWIR spectroscopy may be used to work back to the composition of an unknown drug. Although particular examples of counterfeit and illicit drugs have been described, the near-infrared or SWIR spectroscopy (including diffuse reflectance, reflectance, fluorescence or transmission) may also be applied to the identification of other drugs and substances without departing from the scope of this disclosure. This spectroscopy may be used non-destructively and non-contact over stand-off distances or in remote sensing distances, whether from an airborne, vehicle, hand-held, or stationary platform.

[0356] PROCESS ANALYTICAL TECHNOLOGY (PAT)

[0357] One definition of process analytical technology, PAT, is "a system for designing, analyzing and controlling manufacturing through timely evaluations (i.e., during processing) of significant quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." Near-infrared or SWIR spectroscopy may have applications in the PAT of the pharmaceutical industry by providing, for example, quantitative

analysis of multiple components in a sample and in pack quantification of drugs in formulation, as well as quality of a drug and quality control of complex excipients used in formulation. The PAT process may benefit from near-infrared or SWIR spectroscopy for some steps, such as: raw material identification, active pharmaceutical ingredient applications, drying, granulation, blend uniformity and content uniformity. Some of the strengths of near-infrared or SWIR spectroscopy include: radiation has good penetration properties, and, thus, minimal sample preparation may be required; measurement results may be obtained rapidly, and simultaneous measurements may be obtained for several parameters; non-destructive methods with little or no chemical waste; and organic chemicals that comprise most pharmaceutical products have unique spectra in the near-infrared and SWIR ranges, for example.

[0358] FIGURE 60 shows one example of a flow-chart 6000 in the PAT for the pharmaceutical industry. While the center shows the steps of the manufacturing process 6001, the top and bottom sides show where near-infrared spectroscopy could be applicable for lab use 6002 (top) or in process monitoring control 6003 (bottom). Indeed, near-infrared or SWIR spectroscopy has the potential to benefit almost every step in the manufacturing process. Just to provide a few examples of using near-infrared or SWIR spectroscopy in the PAT process, the raw material testing and blending process will be examined briefly.

[0359] At the commencement of manufacture of a drug product, it may be required to identify the correct material and grade of the pharmaceutical excipients to be used in the formulation. FIGURE 61 illustrates the typical near-infrared spectra 6100 for a variety of excipients. Included in the graph 6100 are spectra for: magnesium stearate 6101, sorbitol 6102, mannitol 6103, talc 6104, lactose 6105, starch 6106, maltodextrin 6107, and microcrystalline cellulose 6108. A suitable spectral database may be used to rapidly identify and qualify excipients. One nice aspect of the spectroscopy is that the near-infrared and SWIR are sensitive to both the physical and chemical characteristics of the samples.

[0360] One of the next steps in the manufacture of a dosage form is the blending together of the active component with the excipients to produce a homogeneous blend. In one embodiment, the near-infrared or SWIR spectroscopy apparatus may comprise a fiber-optic probe, which may, for example, interface with the blending vessel. For such a fiber-optic probe, near infrared or

SWIR spectra may be collected in real-time from a blending process. FIGURE 62 exemplifies the absorbance 6200 from the blending process. Although the initial spectra 6201 shows differences from the eventual spectra, as the process continues the blend converges to the final spectra 6202 and continues to overlap that spectra. Similar converging or overlapping spectra may also be used to check the product uniformity at the end of the process. The near-infrared spectra may be acquired in real-time; and, using appropriate data pre-processing and chemometric analysis, blend homogeneity plots may be derived, such as 6200.

[0361] One goal of the manufacturing process and PAT may be the concept of a "smart" manufacturing process, which may be a system or manufacturing operation responding to analytical data generated in real-time. Such a system may also have an in-built "artificial intelligence" as decisions may be made whether to continue a manufacturing operation. For example, with respect to the raw materials, integration of the quality measurement into smart manufacturing processes could be used to improve manufacturing operations by ensuring that the correct materials of the appropriate quality are used in the manufacture. Similarly, a smart blender would be under software control and would respond to the real-time spectral data collected.

[0362] FIGURE 63 illustrates what might be an eventual flow-chart 6300 of a smart manufacturing process. The manufacturing process 6301 may have as input the process feed 6302 and result in a process output 6303. A process controller 6304 may at least partially control the manufacturing process 6301, and the controller 6304 may receive inputs from the closed loop control (process parameters) 6305 as well as the on-line monitoring of process parameters 6306. The feedback loops in the process could refine the manufacturing process 6301 and improve the quality of the process output 6303. These are particular embodiments of the use of near-infrared or SWIR spectroscopy in the PAT of the pharmaceutical industry, but other variations, combinations, and methods may also be used and are intended to be covered by this disclosure.

[0363] The discussion thus far has centered on use of near-infrared or SWIR spectroscopy in applications such as identification of counterfeit drugs, detection of illicit drugs, and pharmaceutical process control. Although drugs and pharmaceuticals are one example, many other fields and applications may also benefit from the use of near infrared or SWIR spectroscopy, and these may also be implemented without departing from the scope of this disclosure. As just another

example, near-infrared or SWIR spectroscopy may also be used as an analytic tool for food quality and safety control. Applications in food safety and quality assessment include contaminant detection, defect identification, constituent analysis, and quality evaluation. The techniques described in this disclosure are particularly valuable when non-destructive testing is desired at stand-off or remote distances.

[0364] In one example, near-infrared or SWIR spectroscopy may be used in cereal breeding. The breeding purposes may require knowledge on both composition and functional properties of grain, while the functionality of wheat grain is an issue for wheat breeders. Most of the wheat functionality parameters depend on the protein-proteinase complex of wheat grain, as well as the condition of the carbohydrate complex. FIGURE 64A illustrates the near-infrared reflectance spectrum 6400 of wheat flour. Since these samples are complex in composition, several organic bonds involving hydrogen vibrate to produce overlapped spectral bands. Thus, the resulting spectrum 6400 appears like a wavy line without clearly defined features. Analytical methods based on this type of spectroscopy may have the potential to improve the quality of final cereal products by testing the products through the entire production process in the processing industry.

[0365] In yet another embodiment, near-infrared or SWIR spectroscopy may be used for the assessment of fruit and vegetable quality. Most commercial quality classification systems for fruit and vegetables are based on external features of the product, such as shape, color, size, weight and blemishes. However, the external appearance of most fruit is generally not an accurate guide to the internal eating quality of the fruit. As an example, for avocado fruit the external color is not a maturity characteristic, and its smell is too weak and appears later in its maturity stage. Analysis of the near-infrared or SWIR absorption spectra may provide qualitative and quantitative determination of many constituents and properties of horticulture produce, including oil, water, protein, pH, acidity, firmness, and soluble solids content or total soluble solids of fresh fruits. FIGURE 64B shows the near-infrared absorbance spectra 6450 obtained in diffusion reflectance mode for a series of whole 'Hass' avocado fruit. Four oil absorption bands are near 2200-2400nm (CH2 stretch bend and combinations), with weaker absorption around 750nm, 1200nm, and 900-930nm ranges. On the other hand, near 1300-1750nm range may be useful for determining the protein and oil content. The 900-920nm absorbance band may be useful for sugar determination.

Although described in the context of grains, fruits, and vegetables, the near-infrared or SWIR spectroscopy may also be valuable for other food quality control and assessment, such as measuring the properties of meats. These and other applications also fall within the scope of this disclosure.

[0366] DETECTION SYSTEMS

[0367] The near-infrared or SWIR spectroscopy system, remote sensing system or hyper-spectral imaging system may be on an airborne platform, mounted on a vehicle, a stationary transmission or reflection set-up, or even held by a human for a compact system. For such a system, there are fundamentally two hardware parts: the transmitter or light source and the detection system. Between the two, perhaps in a transmission or reflection setting, may be the sample being tested or measured. Moreover, the output from the detection system may go to a computational system, comprising computers or other processing equipment. The output from the computational system may be displayed graphically as well as with numerical tables and perhaps an identification of the material composition. These are just some of the parts of the systems, but other elements may be added or be eliminated, and these modified configurations are also intended to be covered by this disclosure.

[0368] By use of an active illuminator, a number of advantages may be achieved. First, stand-off or remote distances may be achieved if a non-lamp system is used – i.e., if the beam does not rapidly diffract. Also, higher signal-to-noise ratios may be achieved. For example, one way to improve the signal-to-noise ratio would be to use modulation and lock-in techniques. In one embodiment, the light source may be modulated, and then the detection system would be synchronized with the light source. In a particular embodiment, the techniques from lock-in detection may be used, where narrow band filtering around the modulation frequency may be used to reject noise outside the modulation frequency. In another embodiment, change detection schemes may be used, where the detection system captures the signal with the light source on and with the light source off. Again, for this system the light source may be modulated. Then, the signal with and without the light source is differenced. Change detection may help to identify objects that change in the field of view. In the following some exemplary detection systems are described.

[0369] In one embodiment, a SWIR camera or infrared camera system may be used to capture the images. The camera may include one or more lenses on the input, which may be adjustable. The focal plane assemblies may be made from mercury cadmium telluride material (HgCdTe), and the detectors may also include thermo-electric coolers. Alternately, the image sensors may be made from indium gallium arsenide (InGaAs), and CMOS transistors may be connected to each pixel of the InGaAs photodiode array. The camera may interface wirelessly or with a cable (e.g., USB, Ethernet cable, or fiber optics cable) to a computer or tablet or smart phone, where the images may be captured and processed. These are a few examples of infrared cameras, but other SWIR or infrared cameras may be used and are intended to be covered by this disclosure.

[0370] In another embodiment, an imaging spectrometer may be used to detect the light received from the sample. For example, FIGURE 65A shows a schematic diagram 6500 of the basic elements of an imaging spectrometer. The input light 6501 from the sample may first be directed by a scanning mirror and/or other optics 6502. An optical dispersing element 6503, such as a grating or prism, in the spectrometer may split the light into many narrow, adjacent wavelength bands, which may then be passed through imaging optics 6504 onto one or more detectors or detector arrays 6505. Some sensors may use multiple detector arrays to measure hundreds of narrow wavelength bands.

[0371] An example of a typical imaging spectrometer 6550 used in hyper-spectral imaging systems is illustrated in FIGURE 65B. In this particular embodiment, the input light may be directed first by a tunable mirror 6551. A front lens 6552 may be placed before the entrance slit 6553 and the collector lens 6554. In this embodiment, the dispersing element is a holographic grating with a prism 6555, which separates the different wavelength bands. Then, a camera lens 6556 may be used to image the wavelengths onto a detector or camera 6557.

[0372] FIGURES 65 provide particular examples, but some of the elements may not be used, or other elements may be added, and these are also intended to be covered by this disclosure. For instance, a scanning spectrometer may be used before the detector, where a grating or dispersive element is scanned to vary the wavelength being measured by the detector. In yet another embodiment, filters may be used before one or more detectors to select the wavelengths

or wavelength bands to be measured. This may be particularly useful if only a few bands or wavelengths are to be measured. The filters may be dielectric filters, Fabry-Perot filters, absorption or reflection filters, fiber gratings, or any other wavelength selective filter. In one embodiment, a wavelength division multiplexer, WDM, may be used followed by one or more detectors or detector arrays. One example of a planar wavelength division multiplexer may be a waveguide grating router or an arrayed waveguide grating. The WDM may be fiber coupled, and detectors may be placed directly at the output or the detectors may be coupled through fibers to the WDM. Some of these components may also be combined with the configurations in FIGURE 65.

[0373] While the above detection systems could be categorized as single path detection systems, it may be advantageous in some cases to use multi-path detection systems. In one embodiment, a detection system from a Fourier transform infrared spectrometer, FTIR, may be used. The received light may be incident on a particular configuration of mirrors, called a Michelson interferometer, that allows some wavelengths to pass through but blocks others due to wave interference. The beam may be modified for each new data point by moving one of the mirrors, which changes the set of wavelengths that pass through. This collected data is called an interferogram. The interferogram is then processed, typically on a computing system, using an algorithm called the Fourier transform. One advantageous feature of FTIR is that it may simultaneously collect spectral data in a wide spectral range.

[0374] FIGURE 66 illustrates one example of the FTIR spectrometer 6600. Light from the near-infrared or SWIR light source 6601 may be collimated and directed to a beam splitter 6602. In one embodiment, the beam splitter 6602 may be a 50:50 beam splitter. One portion of the beam 6603 may be reflected toward a stationary mirror 6604, while the other portion of the beam 6605 may be transmitted towards a moving mirror 6606. Light may be reflected from the two mirrors 6604, 6606 back to the beam splitter 6602, and then a portion of the recombined beam 6607 may be directed toward the sample 6608. The recombined beam 6607 may be focused onto the sample 6608, in one embodiment. On leaving the sample 6608, the light may be refocused or at least collected at a detector 6609. A background interferogram may be obtained by using the set-up 6600 without a sample in the chamber 6608. When a sample is inserted into 6608, the background interferogram may be modulated by the presence of absorption bands in the sample.

The FTIR spectrometer may have several advantages compared to a scanning (dispersive) spectrometer. Since all the wavelengths may be collected simultaneously, the FTIR may result in a higher signal-to-noise ratio for a given scan time or a shorter scan time for a given resolution. Moreover, unlike a spectrometer where a slit may limit the amount of the beam detected, the FTIR may accommodate the entire diameter of the beam coming from the light source 6601. The configuration 6600 is one example of an FTIR, but other configurations may also be used, and these are also intended to be covered by this disclosure.

[0375] In yet another example of multi-beam detection systems, a dual-beam set-up 6700 such as in FIGURE 67 may be used to subtract out (or at least minimize the adverse effects of) light source fluctuations. In one embodiment, the output from an SC source 6701 may be collimated using a CaF2 lens 6702 and then focused into the entrance slit of the monochromator 6703. At the exit slit, light at the selected wavelength is collimated again and may be passed through a polarizer 6704 before being incident on a calcium fluoride beam splitter 6705. After passing through the beam splitter 6705, the light is split into a sample 6706 and reference 6707 arm to enable ratiometric detection that may cancel out effects of intensity fluctuations in the SC source 6701. The light in the sample arm 6706 passes through the sample of interest and is then focused onto a HgCdTe detector 6708 connected to a pre-amp. A chopper 6702 and lock-in amplifier 6710 setup enable low noise detection of the sample arm signal. The light in the reference arm 6707 passes through an empty container (cuvette, gas cell etc.) of the same kind as used in the sample arm. A substantially identical detector 6709, pre-amp and lock-in amplifier 6710 is used for detection of the reference arm signal. The signal may then be analyzed using a computer system 6711. This is one particular example of a method to remove fluctuations from the light source, but other components may be added and other configurations may be used, and these are also intended to be covered by this disclosure.

[0376] Although particular examples of detection systems have been described, combinations of these systems or other systems may also be used, and these are also within the scope of this disclosure. As one example, environmental fluctuations (such as turbulence or winds) may lead to fluctuations in the beam for active remote sensing or hyper-spectral imaging. A configuration such as FIGURE 67 may be able to remove the effect of environmental fluctuations. Yet another technique may be to "wobble" the light beam after the light source using a vibrating

mirror. The motion may lead to the beam moving enough to wash out spatial fluctuations within the beam waist at the sample or detection system. If the vibrating mirror is scanned faster than the integration time of the detectors, then the spatial fluctuations in the beam may be integrated out. Alternately, some sort of synchronous detection system may be used, where the detection is synchronized to the vibrating frequency.

[0377] Described herein are just some examples of the beneficial use of near-infrared or SWIR lasers for spectroscopy, active remote sensing or hyper-spectral imaging. However, many other spectroscopy and identification procedures can use the near-infrared or SWIR light consistent with this disclosure and are intended to be covered by the disclosure. As one example, the fiber-based super-continuum lasers may have a pulsed output with pulse durations of approximately 0.5-2nsec and pulse repetition rates of several Megahertz. Therefore, the near-infrared or SWIR spectroscopy, active remote sensing or hyper-spectral imaging applications may also be combined with LIDAR-type applications. Namely, the distance or time axis can be added to the information based on time-of-flight measurements. For this type of information to be used, the detection system would also have to be time-gated to be able to measure the time difference between the pulses sent and the pulses received. By calculating the round-trip time for the signal, the distance of the object may be judged. In another embodiment, GPS (global positioning system) information may be added, so the near-infrared or SWIR spectroscopy, active remote sensing or hyper-spectral imagery would also have a location tag on the data. Moreover, the near-infrared or SWIR spectroscopy, active remote sensing or hyper-spectral imaging information could also be combined with two-dimensional or three-dimensional images to provide a physical picture as well as a chemical composition identification of the materials. These are just some modifications of the near-infrared or SWIR spectroscopy, active remote sensing or hyper-spectral imaging system described in this disclosure, but other techniques may also be added or combinations of these techniques may be added, and these are also intended to be covered by this disclosure.

[0378] SECTION 5: NEAR-INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF BREAST AND OTHER CANCERS

[0379] To perform non-invasive optical mammography, one desired attribute is that the light may penetrate as far as possible into the breast tissue. In diffuse reflection spectroscopy, a

broadband light spectrum may be emitted into the tissue, and the spectrum of the reflected or transmitted light may depend on the absorption and scattering interactions within the target tissue. Since breast tissue has significant water and hemoglobin content, it is valuable to examine the wavelength range over which deep penetration of light is possible. FIGURE 68 illustrates the optical absorption 6800 of pure water (dotted line) 6801, hemoglobin without oxygen (thinner solid line) 6802, and hemoglobin saturated with oxygen (thicker solid line) 6803. It can be noted that above about 1100nm, the absorption of hemoglobin is almost the same as water absorption. The penetration depth may be proportional to the inverse of the optical absorption. Therefore, the highest penetration depth will be at the absorption valley, approximately in the wavelength range between about 900nm and about 1300nm. Although not as low in absorption compared to the first window, another absorption valley lies between about 1600nm and 1800nm. Thus, non-invasive imaging preferably should use wavelengths that fall in one of these two absorption valleys.

[0380] FIGURE 69 shows examples of various absorption bands of chemical species 6900 in the wavelength range between about 1200nm and 2200nm. Although the fundamental absorptions usually lie in the mid-infrared (e.g., wavelengths longer than about 3 microns), there are many absorption lines in the NIR corresponding to the second overtone region 6901 between about 1000nm and 1700nm, the first overtone region 6902 between about 1500nm and 2050nm, and the combination band region 6903 between about 1900nm and 2300nm. As an example, hydrocarbon bonds common in many biological substances have their fundamental absorption in the mid-IR near 3300-3600nm, but they also have many combination band lines between 2000-2500nm, and other lines at shorter wavelengths corresponding to the first and second overtones. Fortunately, there are spectral features of Figure 69 that overlap with the absorption valleys in Figure 68. These are likely to be the wavelengths of interest for spectroscopic analysis of cancerous regions.

[0381] In women, the breasts (FIGURE 70) 7000 overlay the pectoralis major muscles 7002 and cover much of the chest area and the chest walls 7001. The breast is an apocrine gland that produces milk to feed an infant child; the nipple 7004 of the breast is surrounded by an areola 7005, which has many sebaceous glands. The basic units of the breast are the terminal duct lobules 7003, which produce the fatty breast milk. They give the breast its function as a mammary gland. The lobules 7003 feed through the milk ducts 7006, and in turn these ducts drain to the nipple

7004. The superficial tissue layer (superficial fascia) may be separated from the skin 7008 by about 0.5-2.5cm of adipose of fatty tissue 7007.

[0382] Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts 7006, the lobules 7003 that supply the ducts with milk, and/or the connective tissue between the lobules. Cancers originating from ducts 7006 are known as ductal carcinomas, while those originating from lobules 7003 or their connective tissue are known as lobular carcinomas. While the overwhelming majority of human cases occur in women, male breast cancer may also occur.

[0383] Several particular embodiments of imaging systems 7100, 7150 for optically scanning a breast are illustrated in FIGURE 71. In these particular embodiments, the patient 7101, 7151 may lie in a prone position with her breasts inside a box 7102, 7152 with probably a transparent window on the detector side. A compression plate 7103, 7153 may hold the breast in place against the viewing window by mildly compressing the breast to a thickness between about 5.5 and 7.5cm. The box 7102, 7152 may then be filled with a matching fluid with optical properties similar to human breast. In one instance, the matching fluid may comprise water, india ink for absorption, and a fat emulsion for scattering. The embodiments in FIGURE 71 may also have one or more detectors 7104, 7155, one or more light sources 7104, 7154, various electronics, and even an imaging system based on charge coupled devices 7105. As illustrated in FIGURE 71, the light sources 7104, 7154 and detectors 7104, 7155 may be coupled to the box 7102, 7152 through one or more fibers 7106, 7156. Also, the imaging may be in reflection mode (top of FIGURE 71), transmission mode (bottom of FIGURE 71), or some combination.

[0384] Beyond the geometry and apparatus of FIGURE 71, the optical imaging system may use one or more of three different illumination methods: continuous wave, time-domain photon migration, and frequency-domain photon migration. In one embodiment, continuous-wave systems emit light at approximately constant intensity or modulated at low frequencies, such as 0.1-100kHz. In another embodiment, the time-domain photon migration technique uses relatively short, such as 50-400psec, light pulses to assess the temporal distribution of photons. Since scattering may increase the times of flight spent by photons migrating in tissues, the photons that arrive earliest at the detector probably encountered the fewest scattering events. In yet another

embodiment, the frequency-domain photon migration devices modulate the amplitude of the light that may be continuously transmitted at relatively high frequencies, such as 10MHz to 1GHz. For example, by measuring the phase shift and amplitude decay of photons as compared to a reference signal, information may be acquired on the optical properties of tissue, and scattering and absorption may be distinguished. Beyond these three methods, other techniques or combinations of these methods may be used, and these other methods are also intended to fall within the scope of this disclosure.

[0385] Although particular embodiments of imaging architectures are illustrated in FIGURE 71, other system architectures may also be used and are also intended to be covered by this disclosure. For example, in one embodiment several couples of optical fibers for light delivery and collection may be arranged along one or more rings placed at different distances from the nipple 7004. In an alternate embodiment a "cap" with fiber leads for light sources and detectors may be used that fits over the breast. In yet another embodiment, imaging optics and light sources and detectors may surround the nipple 7004 and areola 7005 regions of the breast. As yet another alternative, a minimally invasive procedure may involve inserting needles with fiber enclosure (to light sources and detectors or receivers) into the breast, so as to probe regions such as the lobules 7003 and connective tissue. Both non-invasive and minimally invasive optical imaging methods are intended to be covered by this disclosure.

[0386] OPTICAL WAVELENGTH RANGES FOR CANCER DETECTION

[0387] Many of the diffuse optical tomography studies previously conducted have relied on using NIR in the wavelength range of about 600-1000nm, where light absorption at these wavelengths may be minimal, allowing for sufficient tissue penetration (up to 15cm). In these wavelength ranges, it has been claimed that concentrations of oxy- and deoxy-hemoglobin, water, and lipids can be determined. For example, FIGURE 72 shows the normalized absorption spectra 7200 of main tissue absorbers in the NIR between about 600nm and 1100nm: deoxy-hemoglobin, Hb, 7201, oxy-hemoglobin, HbO2, 7202, water 7203, lipids 7204 and collagen 7205. It is speculated that in a malignant tumor, hemoglobin concentration may be directly related to angiogenesis, one of the main factors required for tumor growth and metastases. Moreover, the proportions of oxy- and deoxy-hemoglobin in a tumor may change due to its metabolism. Thus,

by measuring concentrations of the breast components, discrimination of benign and malignant tumors may be possible with diffuse optical imaging. Experiment evidence suggests that cancerous tissue is associated with higher hemoglobin and water concentrations, and a lower lipid concentration with respect to normal breast tissue.

[0388] Based on FIGURE 68 and the dynamics of carcinoma, it may be advantageous to perform spectroscopy in longer wavelengths, such as windows between 1000-1400nm or 1600-1800nm. For example, looking at the absorption curves 6800 in FIGURE 68, the absorption between approximately 1000-1300nm may be comparable to the 600-1000nm window described in FIGURE 72. However, the loss through the soft tissue medium (penetration depth may be inversely related to the loss) will be due to absorption and scattering. In fact, the scattering properties of tissue may also contain valuable information for lesion diagnosis. Since the scattering is inversely proportional to some power of wavelength (for example, in some tissue scattering is inversely proportional to the wavelength cubed), the scattering contribution to the loss may decrease at longer wavelengths. Moreover, these longer wavelength windows may contain diagnostic information on content of collagen and adipose, both of which may be significant indicators for breast cancer.

[0389] Breast cancer spectroscopy may benefit from the use of wavelengths longer than about 1000nm for a number of reasons. As one example, the main absorbers in soft tissues of the visible spectrum of light may be oxy- and deoxygenated hemoglobin and beta-carotene. On the other hand, primary absorbers in the near-infrared spectrum of light may be water, adipose tissue and collagen. Particularly adipose and collagen content may be valuable for early detection of cancers. In one embodiment, increased levels of collagen in breast malignancies are thought to be due to increased vascularity of the tumors. Collagen type I may be an important component of artery walls. FIGURE 73 illustrates the normalized absorption coefficient 7300 in the wavelength range between about 500nm and 1600nm for Hb 7301, HbO2 7302, beta-carotene 7303, water 7304, lipid 7305 and collagen 7306.

[0390] COLLAGEN AND ADIPOSE SIGNATURES IN NEAR-IR

[0391] Examining the collagen content may be a valuable indicator for breast cancer detection. Collagen is one of the important extracellular matrix proteins, and fibrillar collagens

help to determine stromal architecture. In turn, changes in the stromal architecture and composition are one of the aspects of both benign and malignant pathologies, and, therefore, may play an initial role in breast carcinogenesis. For example, collagen seems to be related to cancer development, because high mammographic density may be recognized as a risk factor for breast cancer. Moreover, collagen type in high-risk dense breasts may appear to be different from collagen in low-density breasts.

[0392] Experimental data also shows that malignant mammary gland tissues of animals and humans show a decrease in lipids when compared to normal tissues. The reduced amounts of lipids in the cancerous sites may be caused by a high metabolic demand of lipids in the malignant tumors. For example, due to the rapid proliferation of cancerous cells, there may be reduced lipid content in cancerous tissues. Thus, in addition to collagen, another valuable marker for breast cancer may be the lipid spectral features. It may also be possible to combine the markers from oxy- and deoxygenated hemoglobin and water with lipid and collagen lines to improve the diagnostics and/or therapeutics of optical imaging and/or treatment for breast and other types of cancer. Although specific examples of tissue constituents are discussed, other tissue constituents and related markers may also be associated with breast cancer and other cancers, and these other constituents are also intended to be covered by this disclosure.

[0393] As an example of the types of spectral signatures that may exist, in vivo investigations of progressive changes in rat mammary gland tumors were conducted using near-infrared spectroscopy with a Fourier-transform infrared spectrometer. In one embodiment, FIGURE 74 shows the typical spectra of the cancerous site of the treated rat and the corresponding site of the normal rat. FIGURE 74A shows the logarithm of the inverse of reflection spectra 7400, while FIGURE 74B shows their second derivative spectra 7450. The curves 7401, 7451 correspond to the spectra of the cancerous sites, while 7402, 7452 correspond to the spectra of the normal sites. Since the second derivative techniques may be useful in the analyses of NIR spectra to minimize baseline offsets and to resolve overlapping absorption without compromising signal-to-noise, FIGURE 74B may be used for interpretation of the spectral changes.

[0394] In FIGURE 74B identification may be made of several of the spectral features. In particular, there are DNA bands near 1471nm and 1911nm, while there are water bands near

967nm, 1154nm, 1402nm, and 1888nm. Moreover, there are lipid bands near 1209nm, 1721nm and 1764nm, and there are protein bands near 2055nm, 2172nm and 2347nm. The NIR spectra of FIGURE 74 show that the DNA and water contents in the cancerous tissue may be higher than those in normal tissues. On the other hand, the lipid content in the cancerous tissue may be less than the lipid content in normal tissues. With protein contents, however, little difference may be found between the normal and cancerous tissue.

[0395] These experiments on rats with breast cancer were also used to observe the temporal progression of the cancer. In this embodiment, as the cancer grew, the lipid band intensity decreased, and this band also shifted to higher wavelengths, and collagen peaks appeared in the tissues. In FIGURE 75, the second derivative spectral changes 7500 were investigated in the 1600nm to 1800nm wavelength range over several weeks. An early cancer was detected in the 5th week, and then it grew rapidly from the 6th 7501 to the 7th 7502 week. The cancer's temporal progression through the 8th 7503, 9th 7504, 10th 7505 and 11th 7506 week are shown in the various curves in FIGURE 75. With the cancer growth, the intensity of the lipid band in the vicinity of 1721nm decreased, and this band shifted to higher wavelengths by 7nm at the 11th week 7506 compared to the wavelength band at the 5th week. The higher wavelength shift may indicate that an order parameter of the lipids increases with progressive cancer growth.

[0396] Moreover, in the data of FIGURE 75 is seen that a new peak appeared as the cancer grew around 1690nm, which may be assigned to be a collagen absorption by comparison with the absorptions of standard collagen (c.f., FIGURE 78). The higher wavelength shift may be attributable to the formation of elastic fibers in the lipid layer with collagen induced in the cancer tissues, thus leading to an increased order parameter of the lipids. Thus, it can be seen that significant information about breast cancer tissue compared with normal tissue may be obtained by spectroscopy at the longer wavelengths in the near-infrared.

[0397] The second derivative spectra may also be insightful for observing and monitoring changes in tissue as well as characterizing tissue in the near-infrared wavelength range. As an example, FIGURE 76 illustrates the second derivative spectra 7600 for cholesterol (similar to one embodiment of lipids) 7601, collagen 7602, and elastin 7603. The left curve 7625 shows the second derivative data over the wavelength range of about 1150nm to 1300nm, while the right

curve 7650 shows the second derivative data over the wavelength range of about 1600nm to 1850nm. These wavelengths show numerous features for cholesterol/lipid 7601, collagen 7602, and elastin 7603, which again emphasizes the added value of using wavelengths longer than about 1000nm for cancer diagnostics.

[0398] To further illustrate the value of using longer wavelengths in the NIR or SWIR for observing changes in breast cancer and other cancer markers, the spectra of in water, lipids/adipose and collagen of different varieties may be studied. As one embodiment, the absorption coefficients 7700 are shown in FIGURE 77 as a function of wavelength between about 1000nm and 2600nm. FIGURE 77 overlaps the absorption coefficient for water 7701, adipose 7702 (forms of adipose include fatty tissue and acids, lipids, and cholesterol), and collagen type I 7703. One may note that particular absorption peaks for adipose 7702 and collagen type I 7703 align at wavelengths near 1210nm 7704 and 1720nm 7705, which also correspond to local minima in water absorption.

[0399] Moreover, the NIR spectra for collagen also depend on the type of collagen. As an example, FIGURE 78 illustrates the absorbance 7800 for four types of collagen: collagen I 7801, collagen II 7802, collagen III 7803, and collagen IV 7804. Collagen I, for instance, may be a major constituent of stroma. Also, collagen I and collagen III may be the principal collagens of the aorta. Since the spectra of the four collagens are distinctive, multicomponent analysis of collagens may possibly be used to distinguish the type of collagen involved.

[0400] The experimental results discussed thus far indicate that breast cancer detection may benefit from spectroscopy in the NIR and SWIR, particularly wavelengths between approximately 1000-1400nm and 1600-1800nm. These are wavelength windows that may have deep penetration into soft tissue, while still falling within lower absorption valleys of water. Moreover, the longer wavelengths lead to less scattering in tissue and water, again permitting deeper penetration of the light. In the NIR and SWIR wavelength range, the spectra of standard samples of cholesterol, protein, collagen, elastin and DNA were measured to obtain information on their characteristic bands in the spectra of mammary gland tissues. Absorption peaks in the standard samples occur at the following exemplary wavelengths:

Collagen: 1182nm, 1360nm, 1426nm, 1496nm, 1569nm, 1690nm, 1732nm;

Lipids: 1157nm, 1209nm, 1404nm, 1721nm, 1764nm;

Cholesterol: 918nm, 1195nm, 1376nm, 1585nm, 1711nm, 1757nm;

Protein: 910nm, 1143nm, 1186nm, 1279nm, 1420nm, 1503nm, 1579nm, 1690nm, 1739nm, 1799nm; and

DNA: 1414nm, 1471nm, 1626nm, 1728nm.

[0401] Comparing these absorption features with the data in FIGURES 73-78 shows that there are absorption features or signatures in the second derivatives that can be used to monitor changes in, for example, collagen and lipids. By using broadband light and performing spectroscopy in at least some part of the wavelength windows between about 1000-1400nm and/or 1600-1800nm, the collagen and lipid changes, or other constituent changes, may be monitored. In one embodiment, for breast cancer the decrease in lipid content, increase in collagen content, and possible shift in collagen peaks may be observed by performing broadband light spectroscopy and comparing normal regions to cancerous regions as well as the absorption strength as a function of wavelength. The spectroscopy may be in transmission, reflection, diffuse reflection, diffuse optical tomography, or some combination. Also, this spectroscopy may be augmented by fluorescence data, if particular tags or markers are added. Beyond looking at the absorbance, the data processing may involve also observing the first, second, or higher order derivatives.

[0402] Broadband spectroscopy is one example of the optical data that can be collected to study breast cancer and other types of cancer. However, other types of spectral analysis may also be performed to compare the collagen and lipid features between different wavelengths and different tissue regions (e.g., comparing normal regions to cancerous regions), and these methods also fall within the scope of this disclosure. For example, in one embodiment just a few discrete wavelengths may be monitored to see changes in lipid and collagen contents. In a particular embodiment, wavelengths near 1200nm may be monitored in the second derivative data of FIGURE 76 to measure the cholesterol/lipid peak below 1200nm in 7601 versus the collagen peak above 1200nm in 7602. In yet another embodiment, the absorption features in FIGURE 73 may be relied upon to monitor the lipid content 7305 by measuring near 1200nm and the collagen

content 7306 by measuring near 1300nm. Although these embodiments use only two wavelengths, any number of wavelengths may be used and are intended to be covered by this disclosure.

[0403] Thus, a breast cancer monitoring system, or a system to monitor different types of cancers, may comprise broadband light sources and detectors to permit spectroscopy in transmission, reflection, diffuse optical tomography, or some combination. In one particular embodiment, high signal-to-noise ratio may be achieved using a fiber-based super-continuum light source (described further herein). Other light sources may also be used, including a plurality of laser diodes, super-luminescent laser diodes, or fiber lasers.

[0404] Wavelength ranges that may be advantageous for cancer detection include the NIR and SWIR windows (or some part of these windows) between about 1000-1400nm and 1600-1800nm. These longer wavelengths fall within local minima of water absorption, and the scattering loss decreases with increasing wavelength. Thus, these wavelength windows may permit relatively high penetration depths. Moreover, these wavelength ranges contain information on the overtone and combination bands for various chemical bonds of interest, such as hydrocarbons.

[0405] These longer wavelength ranges may also permit monitoring levels and changes in levels of important cancer tissue constituents, such as lipids and collagen. Breast cancer tissue may be characterized by decreases in lipid content and increases in collagen content, possibly with a shift in the collagen peak wavelengths. The changes in collagen and lipids may also be augmented by monitoring the levels of oxy- and deoxy-hemoglobin and water, which are more traditionally monitored between 600-1000nm. Other optical techniques may also be used, such as fluorescent microscopy.

[0406] To permit higher signal-to-noise levels and higher penetration depths, higher intensity or brightness of light sources may be used. With the higher intensities and brightness, there may be a higher risk of pain or skin damage. At least some of these risks may be mitigated by using surface cooling and focused infrared light, as further described herein.

[0407] LASER EXPERIMENTS: PENETRATION DEPTH, FOCUSING, SKIN COOLING

[0408] Some preliminary experiments show the feasibility of using focused infrared light for non-invasive procedures, or other procedures where relatively shallow vessels below the skin are to be thermally coagulated or occluded with minimum damage to the skin upper layers. In one embodiment, the penetration depth and optically induced thermal damage has been studied in chicken breast samples. Chicken breast may be a reasonable optical model for smooth muscle tissue, comprising water, collagen and proteins. Commercially available chicken breast samples were kept in a warm bath (~32 degree Celsius) for about an hour, and then about half an hour at room temperature in preparation for the measurements.

[0409] An exemplary set-up 7900 for testing chicken breast samples using collimated light is illustrated in FIGURE 79. The laser light 7901 near 980nm, 1210nm, or 1700nm may be provided from one or more laser diodes or fiber lasers, as described further below. In this instance, laser diodes were used, which comprise a plurality of laser diode emitters that are combined using one or more multiplexers (particularly spatial multiplexers), and then the combined beam is coupled into a multi-mode fiber (typically 100 microns to 400 microns in diameter). The output from the laser diode fiber was then collimated using one or more lenses 7902. The resulting beam 7903 was approximately round with a beam diameter of about 3mm. The beam diameter was verified by blade measurements (i.e., translating a blade across the beam). Also, the time-averaged power was measured in the nearly collimated section after the lens using a large power meter. The chicken breast samples 7906 were mounted in a sample holder 7905, and the sampler holder 7905 was mounted in turn on a translation stage 7904 with a linear motor that could move perpendicular to the incoming laser beam. Although particular details of the experiment are described, other elements may be added or eliminated, and these alternate embodiments are also intended to be covered by this disclosure.

[0410] For these particular experiments, the measured depth of damage (in millimeters) versus the incident laser power (in Watts) is shown 8000 in FIGURE 80. In this embodiment, laser diodes were used at wavelengths near 980nm, 1210nm and 1700nm. The curve 8001 corresponds to about 980nm, the curve 8002 corresponds to about 1210nm, and the curve 8003 corresponds to about 1700nm. It may be noted that there is a threshold power, above which the damage depth increases relatively rapidly. For example, the threshold power for wavelengths around 980nm may be about 8W, the threshold power for wavelengths around 1210nm may be

3W, and the threshold power for wavelengths around 1700nm may be about 1W. The threshold powers may be different at the different wavelengths because of the difference in water absorption (e.g., 7701 in FIGURE 77). Part of the difference in threshold powers may also arise from the absorption of proteins such as collagen (e.g., 7703 in FIGURE 77). After a certain power level, the damage depth appears to saturate: i.e., the slope flattens out as a function of increasing pump power.

[0411] In one embodiment, if the penetration depth is defined as the depth where damage begins to approximately saturate, then for wavelengths of about 980nm 8001 the penetration depth 8006 may be defined as approximately 4mm, for wavelengths of about 1210nm 8002 the penetration depth 8005 may be defined as approximately 3mm, and for wavelengths of about 1700nm 8003 the penetration depth 8004 may be defined as approximately 2mm. These are only approximate values, and other values and criteria may be used to define the penetration depth. It may also be noted that the level of damage at the highest power points differs at the different wavelengths. For example, at the highest power point of 8003 near 1700nm, much more damage is observed, showing evidence of even boiling and cavitation. This may be due to the higher absorption level near 1700nm (e.g., 7701 in FIGURE 77). On the other hand, at the highest power point 8001 near 980nm, the damage is not as catastrophic, but the spot size appears larger. The larger spot size may be due to the increased scattering at the shorter wavelengths (e.g., 7701 in FIGURE 77). Based on data 8000 such as in FIGURE 80, it may be possible to select the particular wavelength for the laser beam to be used in the non-invasive procedure.

[0412] Even near wavelengths such as described in FIGURE 80, the particular wavelength selected may be more specifically defined based on the target tissue of interest. In one particular embodiment, the vessel lumen may be modeled as water, and for this example assume that wavelengths in the vicinity of 980nm are being selected to create thermal coagulation or occlusion. FIGURE 81 shows the optical absorption or density as a function of wavelength 8100 between approximately 700nm and 1300nm. Curves are shown for the water absorption 8101, hemoglobin Hb absorption 8102, and oxygenated hemoglobin HbO2 8103. In this example, two particular wavelengths are compared: 980nm 8104 and 1075nm 8105. For instance, 980nm may be generated using one or more laser diodes, while 1075nm may be generated using an ytterbium-doped fiber laser. If maximizing the penetration depth is the significant problem, then 1075nm

8105 may be preferred, since it falls near a local minimum in water 8101, hemoglobin 8102, and oxygenated hemoglobin 8103 absorption. On the other hand, if the penetration depth at 980nm 8104 is adequate and the problem is to generate heat through water absorption, then 980nm 8104 may be a preferred wavelength for the light source because of the higher water absorption. This wavelength range is only meant to be exemplary, but other wavelength ranges and particular criteria for selecting the wavelength may be used and are intended to be covered by this disclosure.

[0413] In another embodiment, focused infrared light has been used to preserve the top layer of a tissue while damaging nerves at a deeper level. For instance, FIGURE 82 illustrates the set-up 8200 used for the focused infrared experiments. In this embodiment, a lens 8201 is used to focus the light. Although a single lens is shown, either multiple lenses, GRIN (gradient index) lenses, curved mirrors, or a combination of lenses and mirrors may be used. In this particular example, the tissue 8204 is placed between two microscope slides 8202 and 8203 for in vitro experiments. The tissue 8204 is renal artery wall either from porcine or bovine animals (about 1.2mm thick sample) – i.e., this is the artery leading to the kidneys, and it is the artery where typically renal denervation may be performed to treat hypertension. For this example, the minimum beam waist 8205 falls behind the tissue, and the intensity contrast from the front of the tissue (closest to the lens) to the back of the tissue (furthest from the lens) is about 4:1. These are particular ranges used for this experiment, but other values and locations of minimum beam waist may also be used and intended to be covered by this disclosure.

[0414] For a particular embodiment, histology of the renal artery is shown in FIGURE 83A for no laser exposure 8300 and shown in FIGURE 83B with focused infrared laser exposure 8350. In this experiment, the beam diameter incident on the lens was about 4mm, and the distance from the edge of the flat side of lens to the minimum beam waist was about 3.75mm. The beam diameter on the front side of the renal artery (i.e., the endothelium side) was about 1.6mm, and the beam diameter on the back side of the renal artery was about 0.8mm. In FIGURE 83A with no laser exposure, the layers of the artery wall may be identified: top layer of endothelium 8301 that is about 0.05mm thick, the media comprising smooth muscle cells or tissue 8302 that is about 0.75mm thick, and the adventitia 8303 comprising some of the renal nerves 8304 that is about 1.1mm thick. These are particular values for this experiment, and other layers and thicknesses may also be used and are intended to be covered by this disclosure.

[0415] The histology with focused infrared light exposure 8350 is illustrated in FIGURE 83B. The laser light used is near 1708nm from a cascaded Raman oscillator (described in greater detail herein), and the power incident on the tissue is about 0.8W and the beam is scanned across the tissue at a rate of approximately 0.4mm/sec. The various layers are still observable: the endothelium 8351, the media 8352, and the adventitia 8353. With this type of histology, the non-damaged regions remain darker (similar to FIGURE 83A), while the laser induced damaged regions turn lighter in color. In this example, the endothelium 8351 and top layer of the media 8352 remain undamaged – i.e., the top approximately 0.5mm is the undamaged region 8356. The laser damaged region 8357 extends for about 1mm, and it includes the bottom layer of the media 8352 and much of the adventitia 8353. The renal nerves 8354 that fall within the damage region 8357 are also damaged (i.e., lighter colored). On the other hand, the renal nerves beyond this depth, such as 8355, may remain undamaged.

[0416] Thus, by using focused infrared light near 1708nm in this example, the top approximately 0.5mm of the renal artery is spared from laser damage. It should be noted that when the same experiment is conducted with a collimated laser beam, the entire approximately 1.5mm is damaged (i.e., including regions 8356 and 8357). Therefore, the cone of light with the lower intensity at the top and the higher intensity toward the bottom may, in fact, help preserve the top layer from damage. There should be a Beer's Law attenuation of the light intensity as the light propagates into the tissue. For example, the light intensity should reduce exponentially at a rate determined by the absorption coefficient. In these experiments it appears that the focused light is able to overcome the Beer's law attenuation and still provide contrast in intensity between the front and back surfaces.

[0417] In another embodiment, experiments have also been conducted on dermatology samples with surface cooling, and surface cooling is shown to preserve the top layer of the skin during laser exposure. In this particular example, the experimental set-up 8400 is illustrated in FIGURE 84. The skin sample 8404, or more generally sample under test, is placed in a sample holder 8403. The sample holder 8403 has a cooling side 8401 and a heating side 8402. The heating side 8402 comprises a heater 8405, which may be adjusted to operate around 37 degrees Celsius – i.e., close to body temperature. The cooling side 8401 is coupled to an ice-water bath 8407 (around 2 degrees Celsius) and a warm-water bath 8406 (around 37 degrees Celsius) through a switching

valve 8408. The entire sample holder 8403 is mounted on a linear motor 8409, so the sample can be moved perpendicular 8410 to the incoming light beam.

[0418] In this embodiment, the light is incident on the sample 8404 through a sapphire window 8411. The sapphire material 8411 is selected because it is transparent to the infrared wavelengths, while also being a good thermal conductor. Thus, the top layer of the sample 8404 may be cooled by being approximately in contact with the sapphire window 8411. The laser light 8412 used is near 1708nm from a cascaded Raman oscillator (described in greater detail herein), and one or more collimating lenses 8413 are used to create a beam with a diameter 8414 of approximately 2mm. This is one particular embodiment of the sample surface cooling arrangement, but other apparatuses and methods may be used and are intended to be covered by this disclosure.

[0419] Experimental results obtained using the set-up of FIGURE 84 are included in FIGURE 18. In this example, FIGURE 85 shows the MTT histochemistry of human skin 8500 treated with ~1708 nm laser (5 seconds pre-cool; 2mm diameter spot exposure for 3 seconds) at 725 mW (A 8501, B 8502) corresponding to about 70 J/cm2 average fluence, and 830 mW (C 8503, D 8504) corresponding to about 80 J/cm2 average fluence. The images in FIGURE 85 show that the application of a cold window was effective in protecting the epidermis 8505 (darker top layer) and the top approximately 0.4 or 0.5mm of the dermis 8506. As before, the darker regions of the histology correspond to undamaged regions, while the lighter regions correspond to damaged regions. In contrast, when no surface cooling is applied, then thermal damage to the dermis occurs in the epidermis and dermis where the laser exposure occurs, and the thermal damage extends to about 1.3 or 1.4 mm or more from the skin surface. Thus, surface cooling applied to the skin may help to reduce or eliminate damage to the top layer of the skin under laser exposure.

[0420] In summary, experiments verify that infrared light, such as near 980nm, 1210nm, or 1700nm, may achieve penetration depths between approximately 2mm to 4mm or more. The top layer of skin or tissue may be spared damage under laser exposure by focusing the light beyond the top layer, applying surface cooling, or some combination of the two. These are particular experimental results, but other wavelengths, methods and apparatuses may be used for achieving

the penetration and minimizing damage to the top layer and are intended to be covered by this disclosure. In an alternate embodiment, it may be beneficial to use wavelengths near 1310nm if the absorption from skin constituents (FIGURE 77), such as collagen 7703, adipose 7702 and elastin 7704, are to be minimized. The water absorption 7701 near 1310nm may still permit a penetration depth of approximately 1cm, or perhaps less. In yet another embodiment, wavelengths near 1210nm may be beneficial, if penetration depths on the order of 3mm are adequate and less scattering loss (e.g. 7701 in FIGURE 77) is desired. Any of FIGURES 68, 73, 75, 77, or 78 may be used to select these or other wavelengths to achieve the desired penetration depth and to also perhaps target particular tissue of interest, and these alternate embodiments are also intended to be covered by this disclosure.

[0421] LASER SYSTEMS FOR THERAPEUTICS OR DIAGNOSTICS

[0422] Infrared light sources can be used for diagnostics and therapeutics in a number of medical applications. For example, broadband light sources can advantageously be used for diagnostics, while narrower band light sources can advantageously be used for therapeutics. In one embodiment, selective absorption or damage can be achieved by choosing the laser wavelength to lie approximately at an absorption peak of particular tissue types. Also, by using infrared wavelengths that minimize water absorption peaks and longer wavelengths that have lower tissue scattering, larger penetration depths into the biological tissue can be obtained. In this disclosure, infrared wavelengths include wavelengths in the range of approximately 0.9 microns to 10 microns, with wavelengths between about 0.98 microns and 2.5 microns more suitable for certain applications.

[0423] As used throughout this document, the term “couple” and or “coupled” refers to any direct or indirect communication between two or more elements, whether or not those elements are physically connected to one another. In this disclosure, the term “damage” refers to affecting a tissue or sample so as to render the tissue or sample inoperable. For instance, if a particular tissue normally emits certain signaling chemicals, then by “damaging” the tissue is meant that the tissue reduces or no longer emits that certain signaling chemical. The term “damage” and or “damaged” may include ablation, melting, charring, killing, or simply incapacitating the chemical

emissions from the particular tissue or sample. In one embodiment, histology or histochemical analysis may be used to determine whether a tissue or sample has been damaged.

[0424] As used throughout this disclosure, the term "spectroscopy" means that a tissue or sample is inspected by comparing different features, such as wavelength (or frequency), spatial location, transmission, absorption, reflectivity, scattering, refractive index, or opacity. In one embodiment, "spectroscopy" may mean that the wavelength of the light source is varied, and the transmission, absorption or reflectivity of the tissue or sample is measured as a function of wavelength. In another embodiment, "spectroscopy" may mean that the wavelength dependence of the transmission, absorption or reflectivity is compared between different spatial locations on a tissue or sample. As an illustration, the "spectroscopy" may be performed by varying the wavelength of the light source, or by using a broadband light source and analyzing the signal using a spectrometer, wavemeter, or optical spectrum analyzer.

[0425] As used throughout this document, the term "fiber laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein at least a part of the laser comprises an optical fiber. For instance, the fiber in the "fiber laser" may comprise one of or a combination of a single mode fiber, a multi-mode fiber, a mid-infrared fiber, a photonic crystal fiber, a doped fiber, a gain fiber, or, more generally, an approximately cylindrically shaped waveguide or light-pipe. In one embodiment, the gain fiber may be doped with rare earth material, such as ytterbium, erbium, and/or thulium. In another embodiment, the infrared fiber may comprise one or a combination of fluoride fiber, ZBLAN fiber, chalcogenide fiber, tellurite fiber, or germanium doped fiber. In yet another embodiment, the single mode fiber may include standard single-mode fiber, dispersion shifted fiber, non-zero dispersion shifted fiber, high-nonlinearity fiber, and small core size fibers.

[0426] As used throughout this disclosure, the term "pump laser" refers to a laser or oscillator that has as an output light or an optical beam, wherein the output light or optical beam may be coupled to a gain medium to excite the gain medium, which in turn may amplify another input optical signal or beam. In one particular example, the gain medium may be a doped fiber, such as a fiber doped with ytterbium, erbium, and/or thulium. In another embodiment, the gain medium may be a fused silica fiber or a fiber with a Raman effect from the glass. In one

embodiment, the "pump laser" may be a fiber laser, a solid state laser, a laser involving a nonlinear crystal, an optical parametric oscillator, a semiconductor laser, or a plurality of semiconductor lasers that may be multiplexed together. In another embodiment, the "pump laser" may be coupled to the gain medium by using a fiber coupler, a dichroic mirror, a multiplexer, a wavelength division multiplexer, a grating, or a fused fiber coupler.

[0427] As used throughout this document, the term "super-continuum" and/or "supercontinuum" and/or "SC" refers to a broadband light beam or output that comprises a plurality of wavelengths. In a particular example, the plurality of wavelengths may be adjacent to one-another, so that the spectrum of the light beam or output appears as a continuous band when measured with a spectrometer. In one embodiment, the broadband light beam may have a bandwidth of at least 10nm. In another embodiment, the "super-continuum" may be generated through nonlinear optical interactions in a medium, such as an optical fiber or nonlinear crystal. For example, the "super-continuum" may be generated through one or a combination of nonlinear activities such as four-wave mixing, the Raman effect, modulational instability, and self-phase modulation.

[0428] As used throughout this disclosure, the terms "optical light" and/or "optical beam" and or "light beam" refer to photons or light transmitted to a particular location in space. The "optical light" and or "optical beam" and/or "light beam" may be modulated or unmodulated, which also means that they may or may not contain information. In one embodiment, the "optical light" and/or "optical beam" and/or "light beam" may originate from a fiber, a fiber laser, a laser, a light emitting diode, a lamp, a pump laser, or a light source.

[0429] As used throughout this document, the terms "near" or "about" or the symbol "~" refer to one or more wavelengths of light with wavelengths around the stated wavelength to accomplish the function described. For example, "near 1720nm" may include wavelengths of between about 1680nm and 1760nm. In one embodiment, the term "near 1720nm" refers to one or more wavelengths of light with a wavelength value anywhere between approximately 1700nm and 1740nm. Similarly, as used throughout this document, the term "near 1210nm" refers to one or wavelengths of light with a wavelength value anywhere between approximately 1170nm and

1250nm. In one embodiment, the term "near 1210nm" refers to one or more wavelengths of light with a wavelength value anywhere between approximately 1190nm and 1230nm.

[0430] While exemplary embodiments are described above, it is not intended that these embodiments describe all possible forms of the disclosure. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the spirit and scope of the disclosure. Additionally, the features of various implementing embodiments may be combined to form further embodiments of the disclosure. While various embodiments may have been described as providing advantages or being preferred over other embodiments with respect to one or more desired characteristics, as one skilled in the art is aware, one or more characteristics may be compromised to achieve desired system attributes, which depend on the specific application and implementation. These attributes include, but are not limited to: cost, strength, durability, life cycle cost, marketability, appearance, packaging, size, serviceability, weight, manufacturability, ease of assembly, etc. The embodiments described herein that are described as less desirable than other embodiments or prior art implementations with respect to one or more characteristics are not outside the scope of the disclosure and may be desirable for particular applications.

WHAT IS CLAIMED IS:

1. An optical system, comprising:

a wearable device for measuring one or more physiological parameters, the wearable device adapted to be placed on a wrist or a hand dorsal of a user, wherein the measuring of the one or more physiological parameters is configured to change in response to stretching of a hand, movement of fingers or a thumb of the user;

the wearable device including a light source comprising a plurality of light emitting diodes that are configured to generate an output optical light having one or more optical wavelengths;

the wearable device comprising one or more lenses configured to receive at least a portion of the output optical light and to deliver a lens output light to tissue comprising skin;

the wearable device further comprising a detection system configured to receive at least a portion of the lens output light reflected from the tissue and to generate an output signal having a signal-to-noise ratio, wherein the detection system is configured to be synchronized to the light source;

wherein the detection system comprises a plurality of detectors that are spatially separated from each other, and wherein at least one analog to digital converter is coupled to at least one of the plurality of detectors;

wherein the output signal is indicative of the one or more physiological parameters that change in response to the stretching of the hand or movement of the fingers or the thumb of the user;

the wearable device configured to increase the signal-to-noise ratio by increasing light intensity of at least one of the plurality of light emitting diodes from an initial light intensity; and

the detection system further configured to:

generate a first signal responsive to light received while the light emitting diodes are off,

generate a second signal responsive to light received while at least one of the light emitting diodes is on, and

increase the signal-to-noise ratio by comparing the first signal and the second signal; and

wherein the wearable device is at least in part configured to identify an object.

2. The optical system of claim 1, wherein the plurality of light emitting diodes comprises six light emitting diodes, and wherein the detection system comprises the plurality of detectors arranged along an arc.

3. The optical system of claim 2, wherein the optical system is configured to use artificial intelligence in making decisions associated with at least a portion of the output signal.

4. The optical system of claim 3, wherein the optical system is further configured to combine at least a part of the output signal with data from other non-invasive devices or biosensors adapted to be placed on the user.

5. The optical system of claim 4, wherein the optical system is further configured to communicate with a smart phone or a tablet, the smart phone or the tablet comprising a wireless receiver, a wireless transmitter, a display, a speaker, a voice input module, one or more buttons or knobs, a microprocessor and a touch screen.

6. The optical system of claim 5, the wearable device further configured to be coupled to an imaging system for remote sensing of the user, the imaging system comprising:

a laser diode configured to be pulsed and to generate laser light having a laser wavelength, wherein the laser wavelength is a near-infrared wavelength between 700 nanometers and 2500 nanometers, and wherein the laser diode comprises one or more Bragg reflectors;

a beam splitter configured to receive at least part of the received laser light from the laser diode and to split the received laser light into a sample arm light and a reference arm light, at least a portion of the sample arm light configured to be directed to the user;

the imaging system further comprising a second plurality of detectors; and

at least one of the second plurality of detectors configured to receive at least a portion of the reference arm light and configured to generate a reference detector output, and at least another of the second plurality of detectors configured to receive from the user at least a portion of reflected sample arm light and configured to generate a sample detector output; and

wherein the imaging system is configured to measure time-of-flight based at least in part on the sample detector output.

7. An optical system, comprising:

a wearable device for measuring one or more physiological parameters, the wearable device adapted to be placed on a wrist of a user;

the wearable device including a light source comprising a plurality of semiconductor diodes that are configured to generate an output optical light having one or more optical wavelengths, wherein at least a portion of the one or more optical wavelengths is a near-infrared wavelength between 700 nanometers and 2500 nanometers;

the wearable device comprising one or more lenses configured to receive at least a portion of the output optical light and to deliver a lens output light to tissue comprising skin;

the wearable device further comprising a detection system configured to receive at least a portion of the lens output light reflected from the tissue and to generate an output signal having a signal-to-noise ratio, wherein the detection system is configured to be synchronized to the light source;

wherein the detection system comprises a plurality of detectors that are spatially separated from each other, and wherein at least one analog to digital converter is coupled to at least one of the plurality of detectors;

wherein the output signal is indicative of the one or more of the physiological parameters;

the wearable device configured to increase the signal-to-noise ratio by increasing light intensity of at least one of the plurality of semiconductor diodes from an initial light intensity; and

the detection system further configured to:

generate a first signal responsive to light received while the semiconductor diodes are off,

generate a second signal responsive to light received while at least one of the semiconductor diodes is on, and

increase the signal-to-noise ratio by comparing the first signal and the second signal; and

wherein the wearable device is at least in part configured to identify an object.

8. The optical system of claim 7, wherein the plurality of semiconductor diodes comprises a plurality of near-infrared laser diodes.

9. The optical system of claim 8, wherein the one or more physiological parameters comprises measurement of a blood constituent or a blood flow.

10. The optical system of claim 9, wherein the blood constituent comprises at least in part glucose or HbA1C.

11. The optical system of claim 10, wherein the optical system is configured to perform optical spectroscopy applied to fluids within the skin.

12. The optical system of claim 11, wherein the one or more optical wavelengths comprise wavelengths corresponding to one or more peaks in a glucose absorption spectrum near 1587 nanometers, 1750 nanometers, 2120 nanometers, 2270 nanometers, or 2320 nanometers.

13. The optical system of claim 12, wherein the wearable device is further configured to communicate with a smart phone or a tablet, the smart phone or the tablet comprising a wireless receiver, a wireless transmitter, a display, a speaker, a voice input module, one or more buttons or knobs, a microprocessor, and a touch screen.

14. The optical system of claim 13, wherein at least some of the plurality of semiconductor diodes are configured to be modulated with a modulation frequency, and the detection system is configured to use a lock-in technique comprising narrow band filtering around the modulation frequency or comprising phase locking to the modulation frequency.

15. The optical system of claim 13, wherein measuring the one or more physiological parameters comprises a differential measurement configured to reduce interference from the skin.

16. A remote sensing system comprising:

an array of laser diodes to generate light having one or more optical wavelengths that includes at least one near-infrared wavelength between 600 nanometers and 1000 nanometers, at least one laser diode of the array comprises one or more Bragg reflectors;

at least one of the laser diodes pulse at a modulation frequency between 10 Megahertz and 1 Gigahertz and to have a phase associated with the modulation frequency;

wherein at least a portion of the light generated by the array of laser diodes is configured to be directed to an object; and

a detection system comprising at least one photo-detector, a lens and a spectral filter at an input to the at least one photo-detector, and a processor processing digitized signals received from the at least one photo-detector, the detection system configured to (i) measure a phase shift of at least a portion of the light from the array of laser diodes reflected from the object relative to the at least a portion of the light generated by the array of laser diodes is configured to be directed to the object, (ii) measure time-of-flight of the at least a portion of the light from the array of laser diodes reflected from the object relative to the at least a portion of the light generated by the array of laser diodes is configured to be directed to the object, and (iii) generate one or more images of the object based at least in part on an amplitude of the at least a portion of the light from the array of laser diodes reflected from the object;

wherein the detection system is configured to synchronize to pulsing of the at least one of the laser diodes, and wherein the processor is configured to generate a time-of-flight measurement; and

a camera system coupled to a lens system and the processor, the camera system configured to capture a second image including at least a part of the object;

wherein the remote sensing system including the processor is configured to combine at least a portion of the second image and at least a portion of the time-of-flight measurement to create a combined portion; and

wherein the remote sensing system including the processor is configured to communicate with a wearable device, a smart phone or a tablet that is further configured to process or display some of the combined portion.

17. The remote sensing system of Claim 16, wherein the detection system is further configured to use a lock-in technique, and wherein the lock-in technique comprises narrow band filtering around the modulation frequency.

18. The remote sensing system of Claim 17, wherein the lock-in technique further comprises phase locking of a first signal associated with the at least a portion of the light from the array of laser diodes reflected from the object relative to a second signal associated with the at least a portion of the light generated by the array configured to be directed to the object.

19. The remote sensing system of Claim 17, wherein at least some of the laser diodes in the array of laser diodes operate at a wavelength near 940 nanometers.

20. The remote sensing system of Claim 19, wherein the remote sensing system including the processor is further configured to use artificial intelligence in making decisions associated with the combined portion.

ABSTRACT

An optical system comprises a wearable device for measuring one or more physiological parameters. The physiological parameters may change in response to stretching of the hand or movement of fingers or thumb of the user, or the parameters may be related to blood constituents or blood flow. The wearable device comprises a light source with a plurality of semiconductor diodes and a detection system that measures reflected light from tissue comprising skin. The semiconductor diodes may be light emitting diodes or laser diodes. The signal to noise ratio for the output signal may be improved by synchronizing the detection system to the light source, increasing light intensity of at least one of the plurality of semiconductor diodes from an initial light intensity, and using change detection that compares light on versus light off for the detection system output. The wearable device is also configured to identify an object.

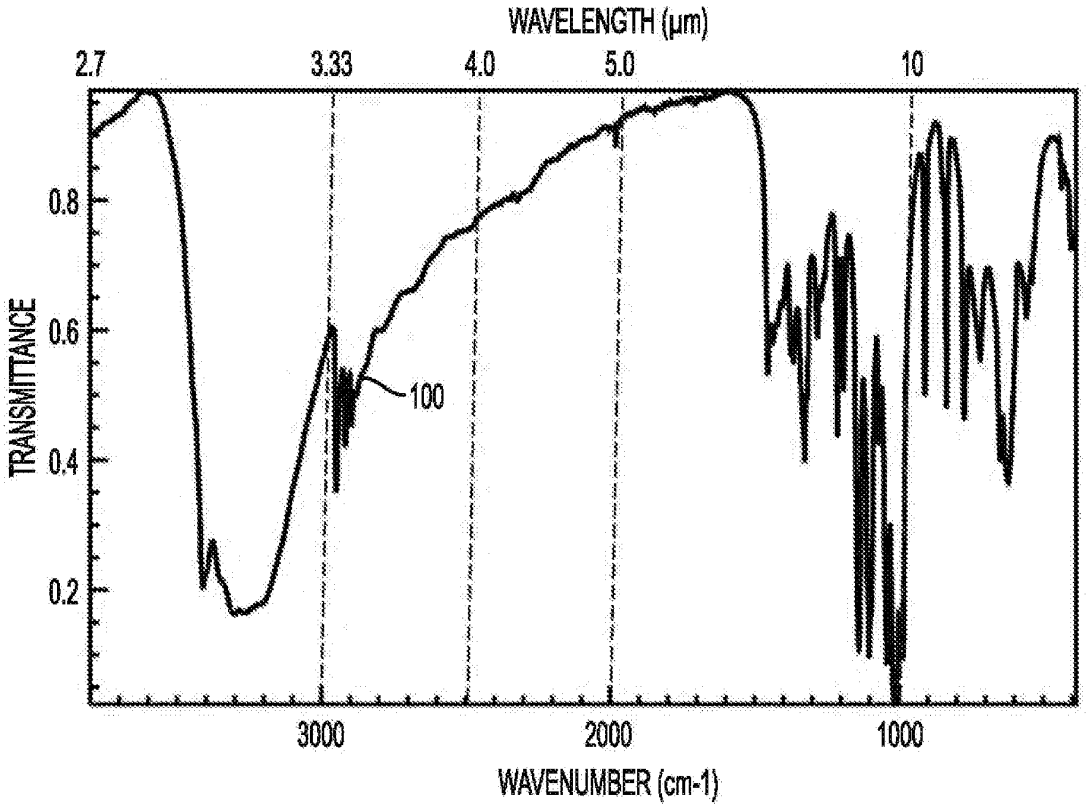

WAVELENGTH (μm)
2.7
3.33
4.0
5.0
10
TRANSMITTANCE
0.8
0.6
0.4
0.2
100
3000
2000
1000
WAVENUMBER (cm-1)

FIG. 1

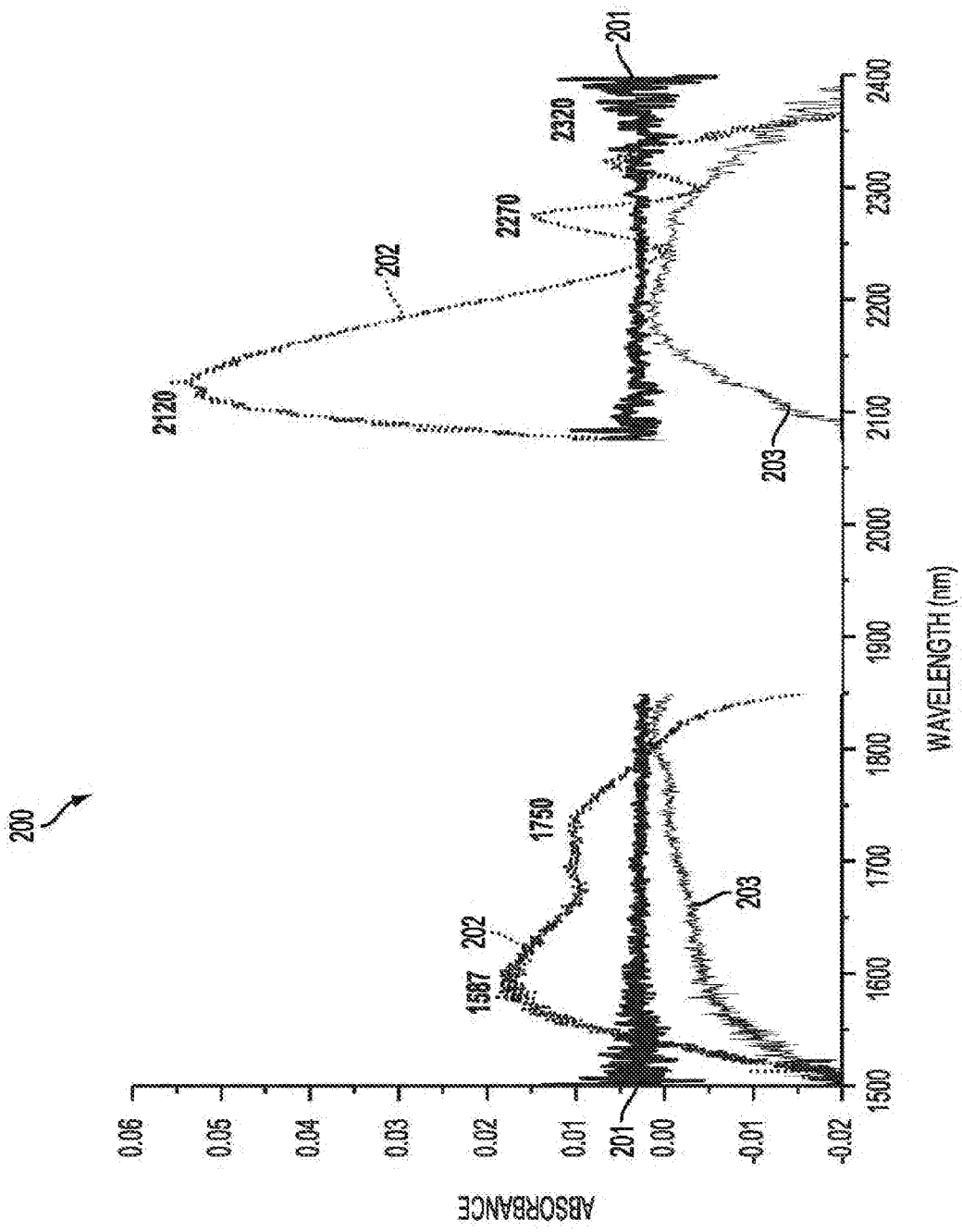

200
201
202
203
1587
1750
2120
2270
2320
ABSORBANCE
0.06
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
-0.02
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
WAVELENGTH (nm)

FIG. 2

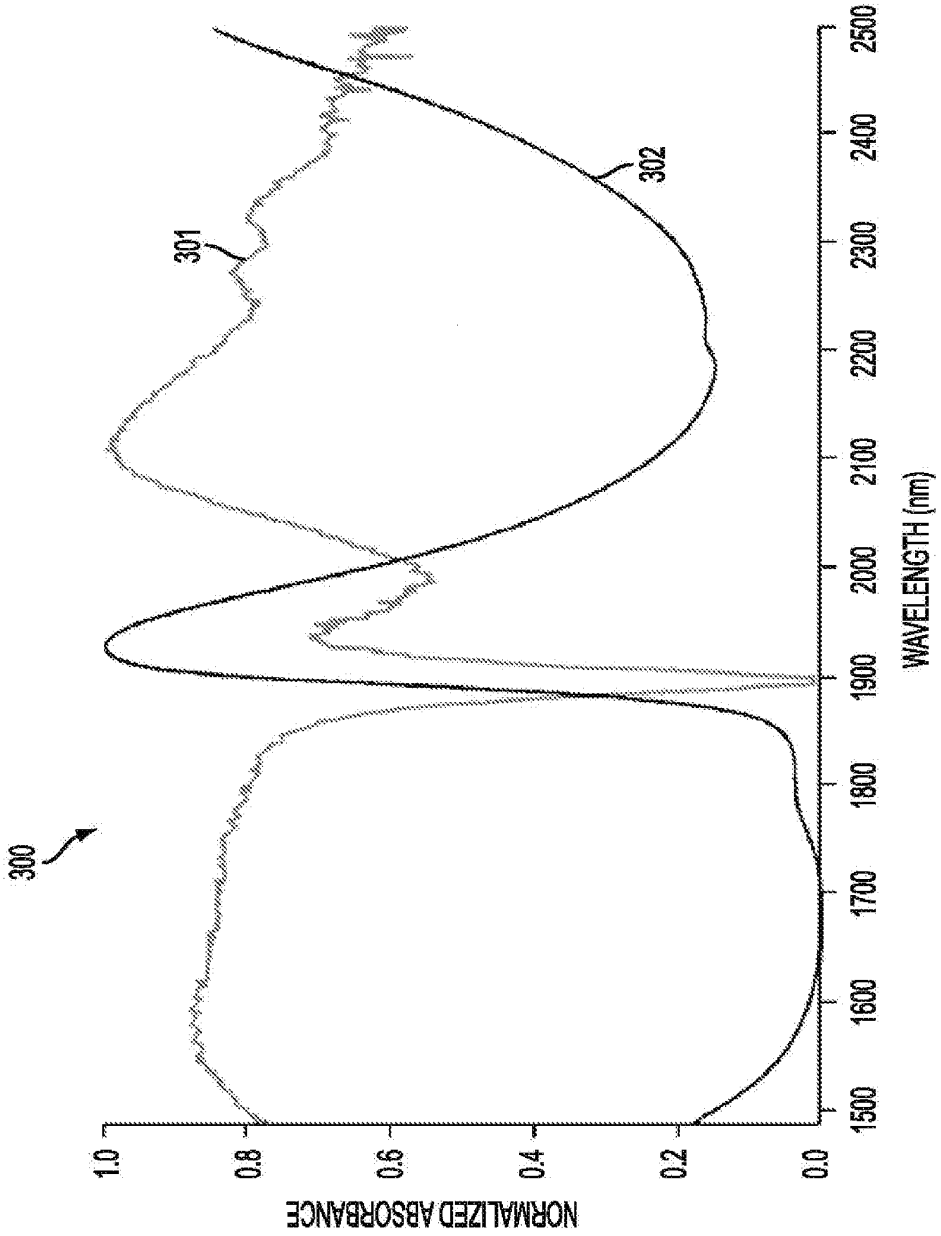

300
301
302
NORMALIZED ABSORBANCE
1.0
0.8
0.6
0.4
0.2
0.0
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
2500
WAVELENGTH (nm)

FIG. 3A

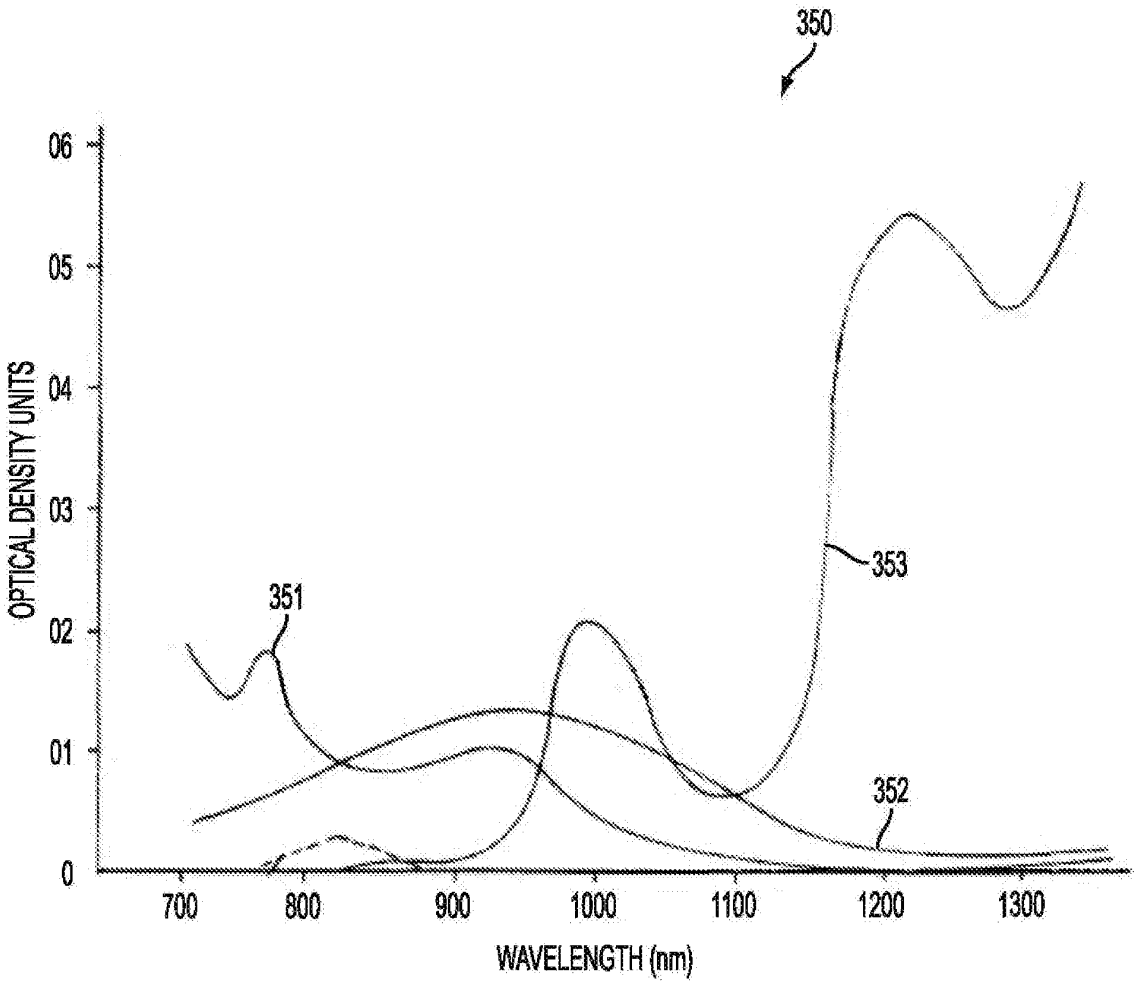

350
06
05
04
03
02
01
0
OPTICAL DENSITY UNITS
351
352
353
700
800
900
1000
1100
1200
1300
WAVELENGTH (nm)

FIG. 3B

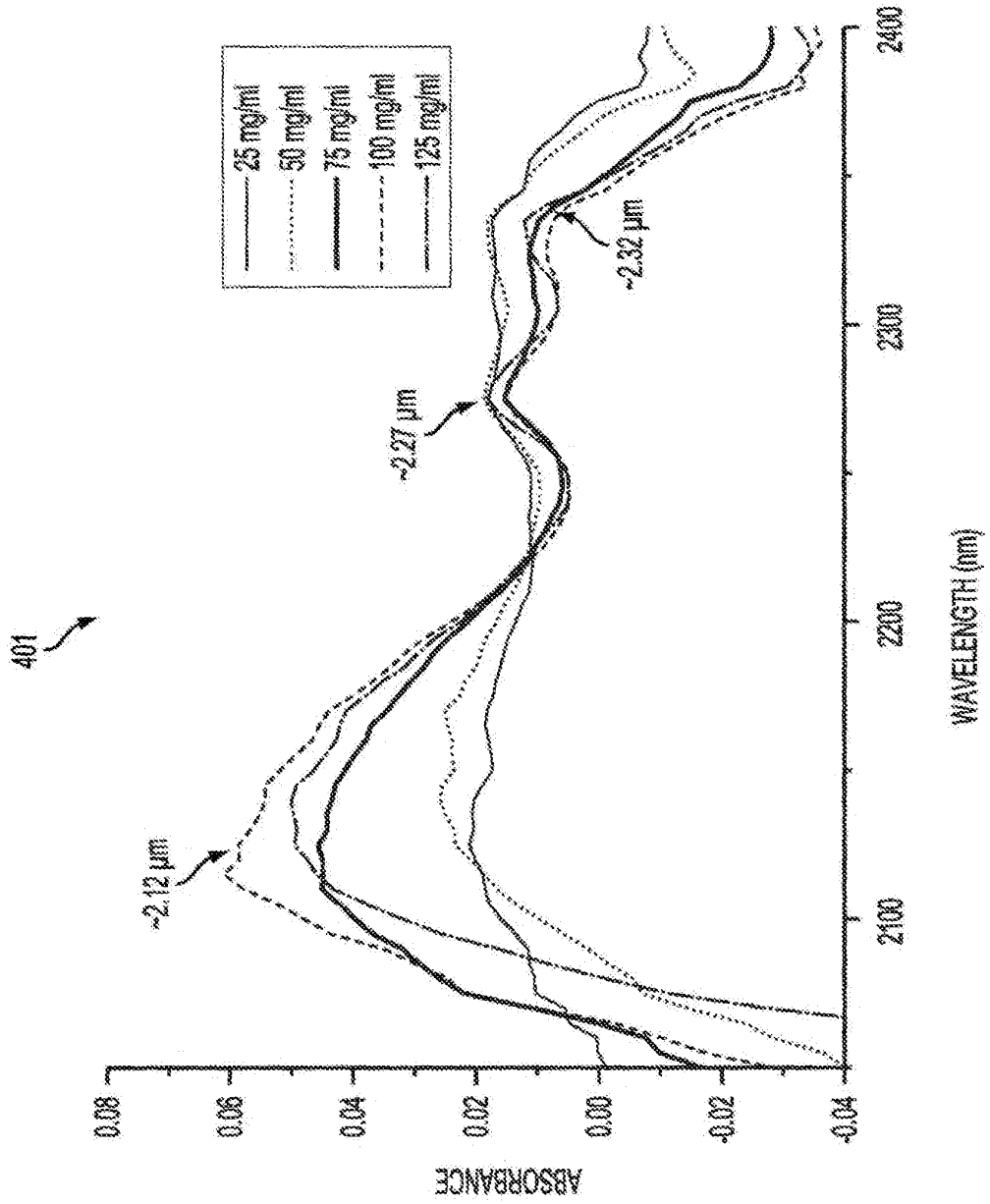

401
25 mg/ml
50 mg/ml
75 mg/ml
100 mg/ml
125 mg/ml
~2.12 µm
~2.27 µm
~2.32 µm
ABSORBANCE
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
2100
2200
2300
2400
WAVELENGTH (nm)

FIG. 4A

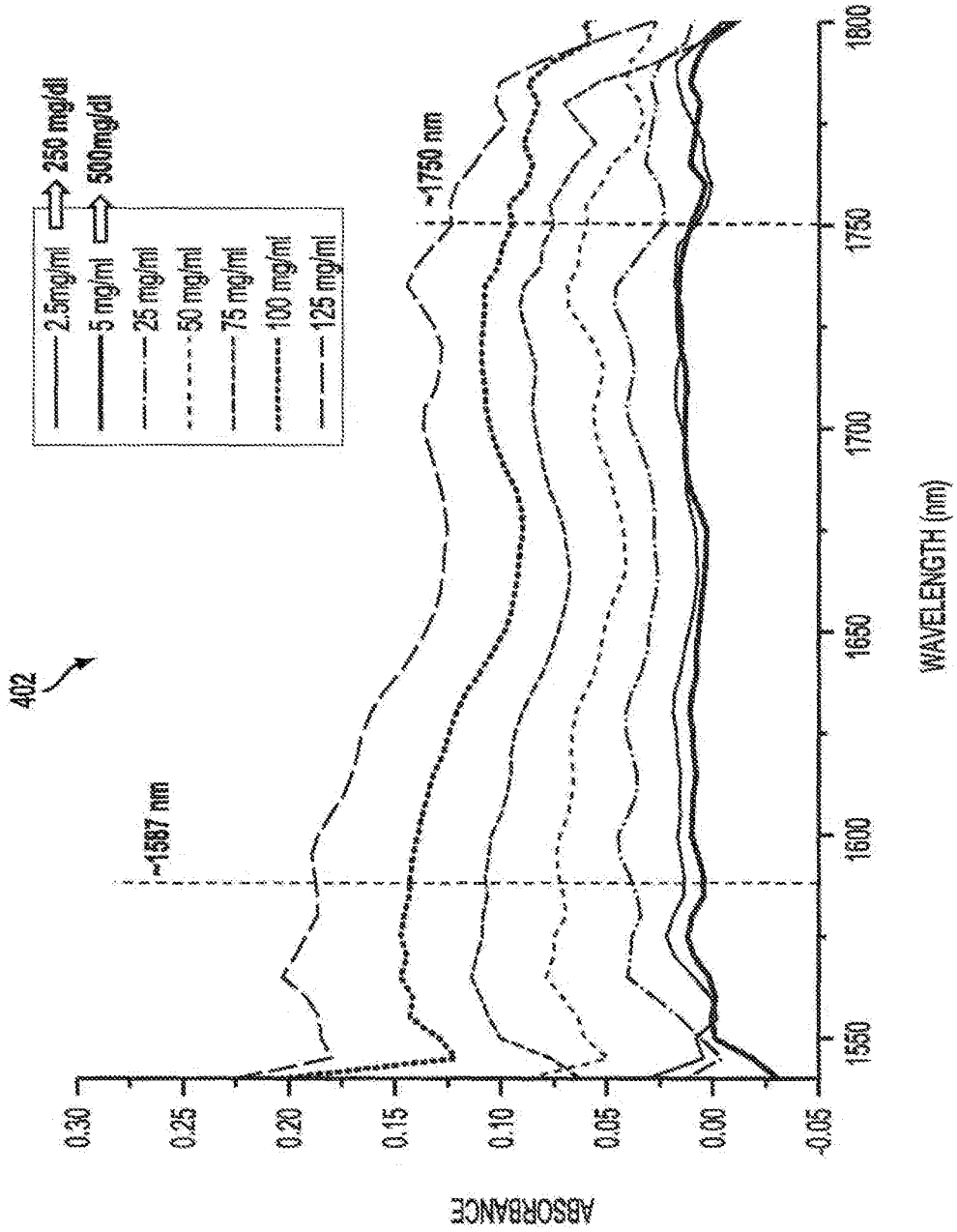

402
2.5mg/ml
250 mg/dl
5 mg/ml
500mg/dl
25 mg/ml
50 mg/ml
75 mg/ml
100 mg/ml
125 mg/ml
~1587 nm
~1750 nm
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
ABSORBANCE
1550
1600
1650
1700
1750
1800
WAVELENGTH (nm)

FIG. 4B

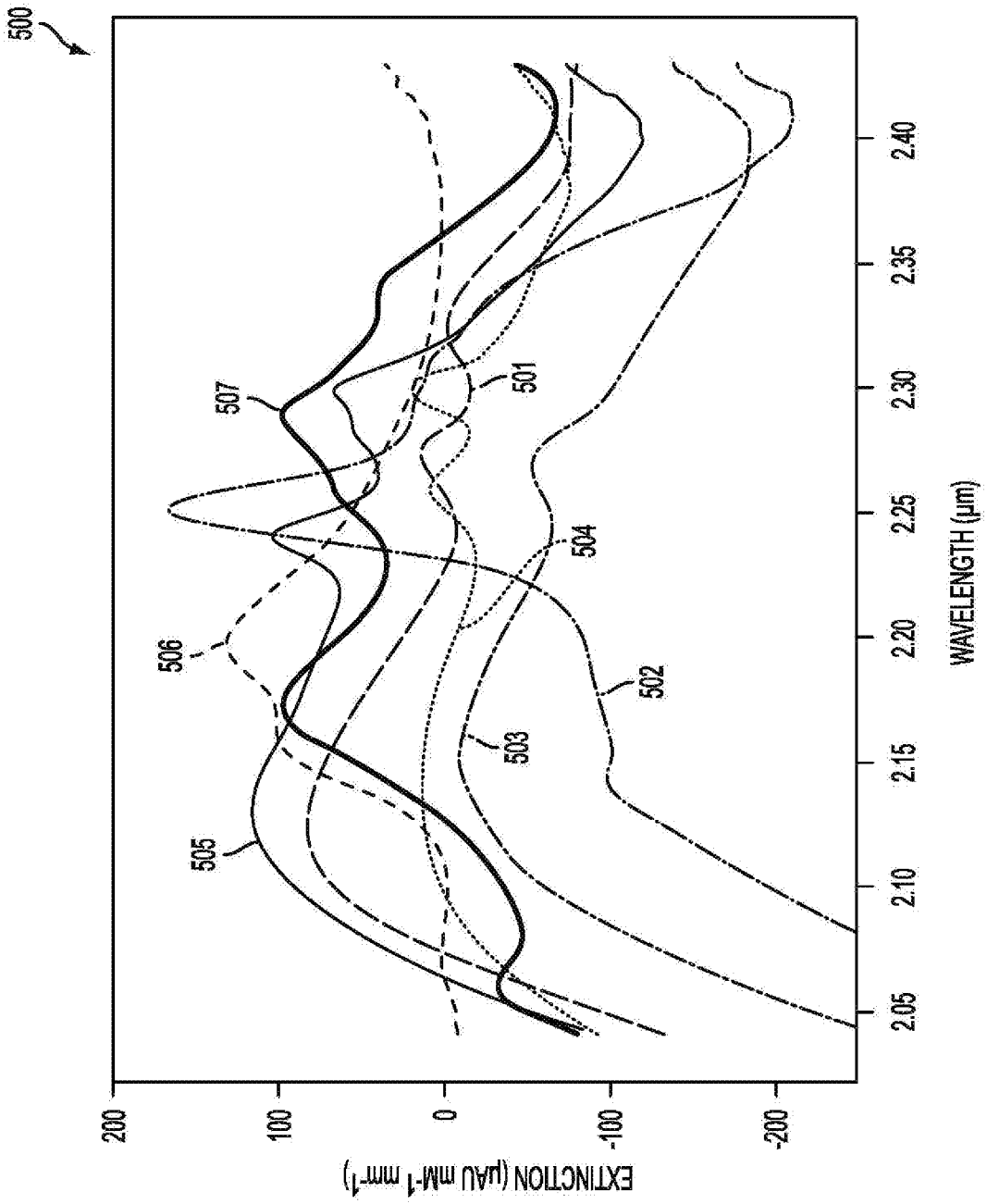

500
200
100
0
-100
-200
EXTINCTION (μAU mM-1 mm-1)
2.05
2.10
2.15
2.20
2.25
2.30
2.35
2.40
WAVELENGTH (μm)
501
502
503
504
505
506
507

FIG. 5

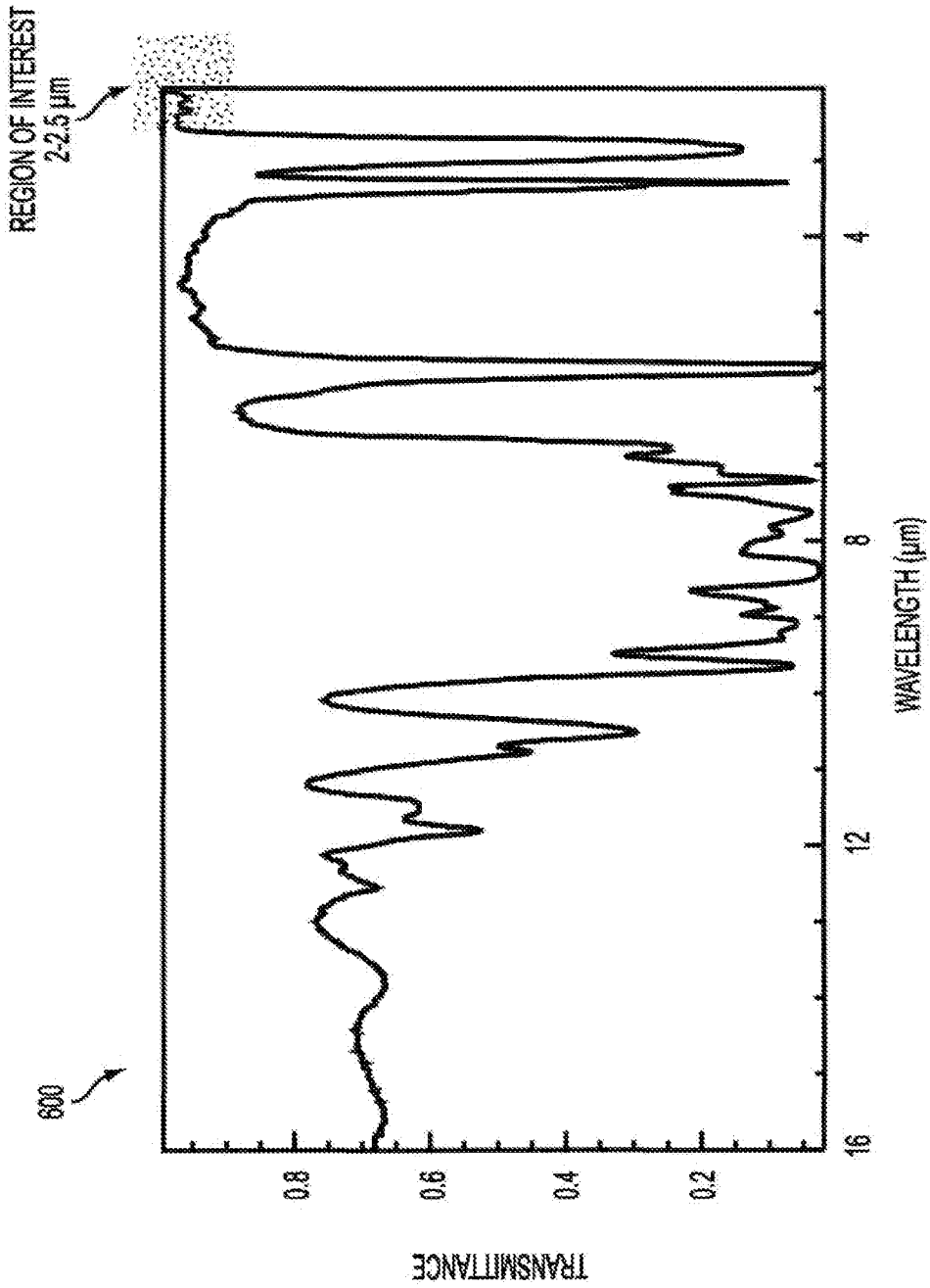

600
REGION OF INTEREST
2-2.5 µm
TRANSMITTANCE
0.8
0.6
0.4
0.2
16
12
8
4
WAVELENGTH (µm)

FIG. 6

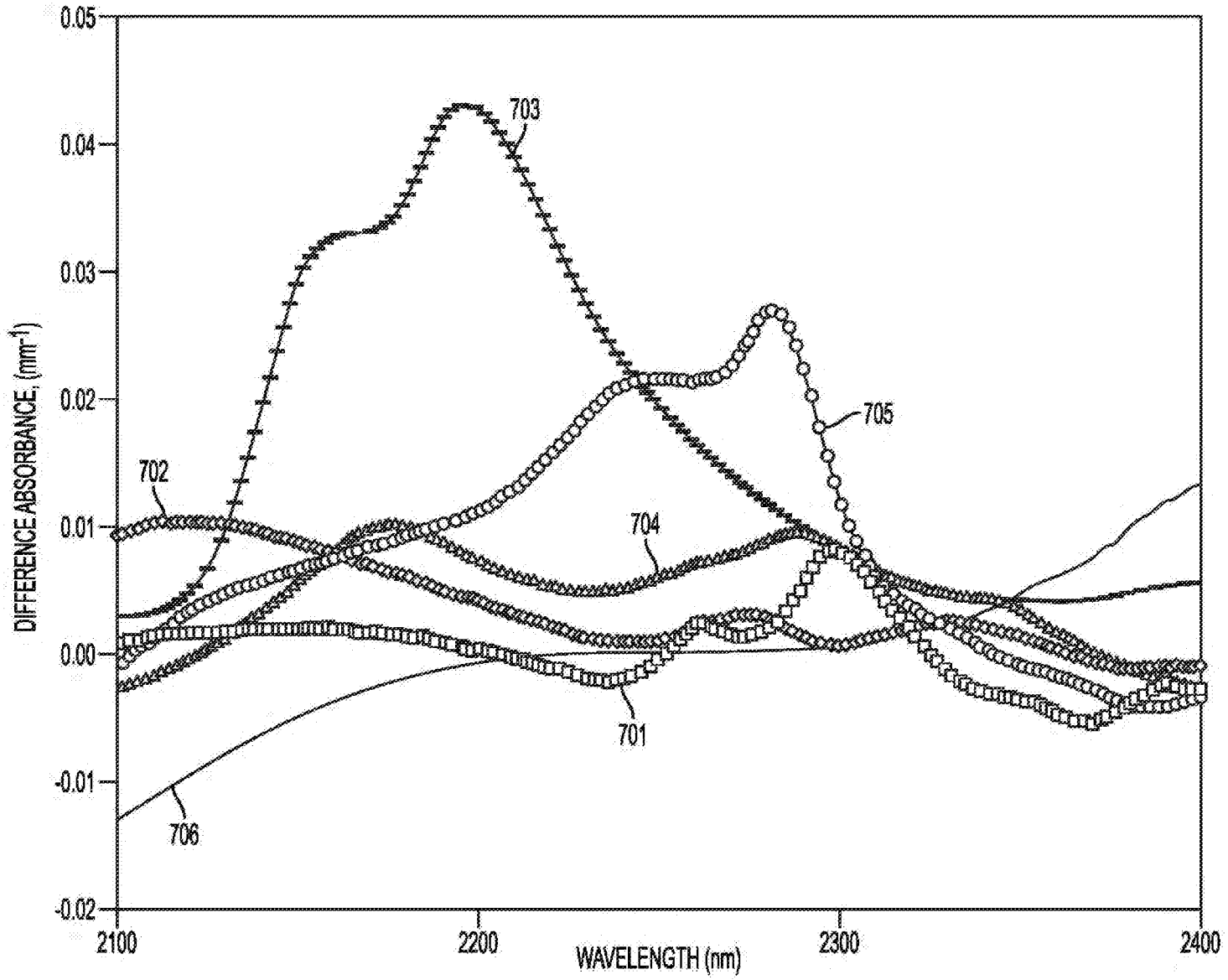
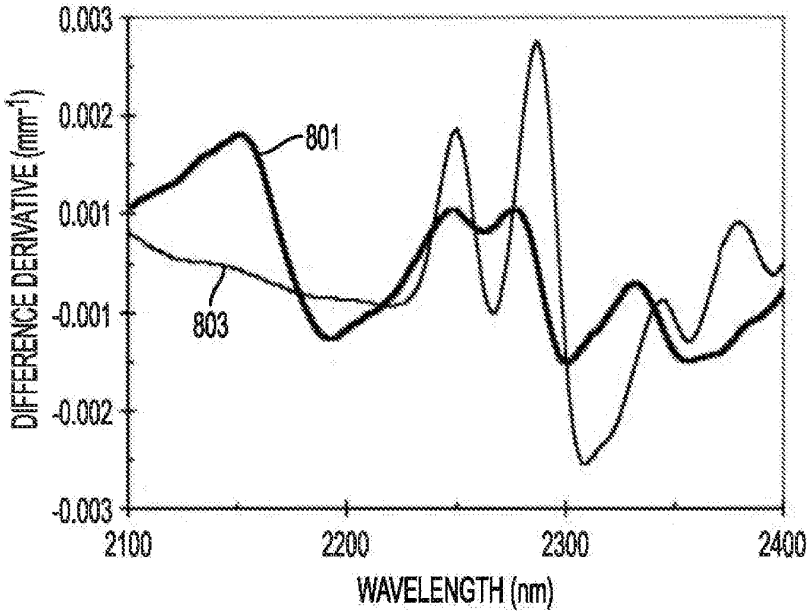

0.05
0.04
0.03
0.02
0.01
0.00
-0.01
-0.02
DIFFERENCE ABSORBANCE, (mm-1)
2100
2200
2300
2400
WAVELENGTH (nm)
701
702
703
704
705
706

FIG. 7

800


0.003
0.002
0.001
-0.001
-0.002
-0.003
DIFFERENCE DERIVATIVE (mm-1)
801
803
2100
2200
2300
2400
WAVELENGTH (nm)

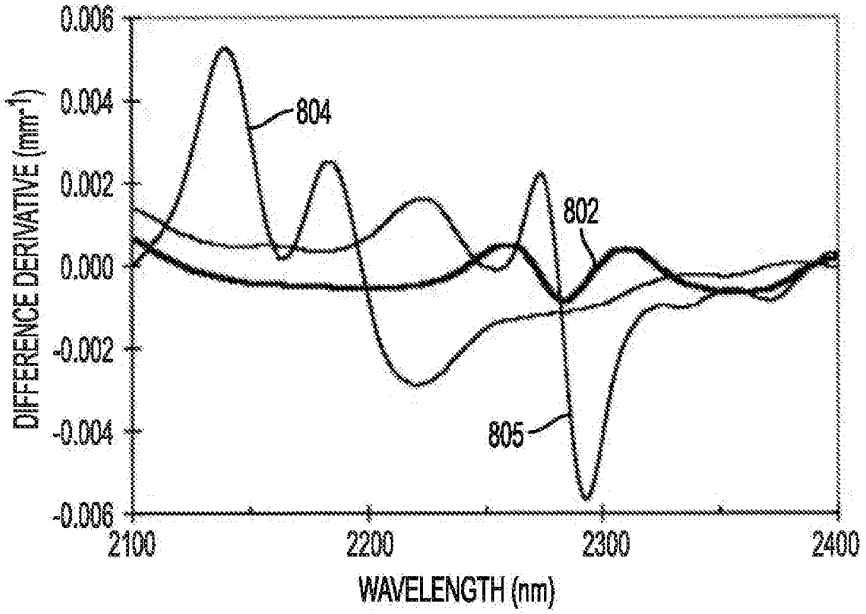

0.006
0.004
0.002
0.000
-0.002
-0.004
-0.006
DIFFERENCE DERIVATIVE (mm-1)
804
802
805
2100
2200
2300
2400
WAVELENGTH (nm)

FIG. 8A

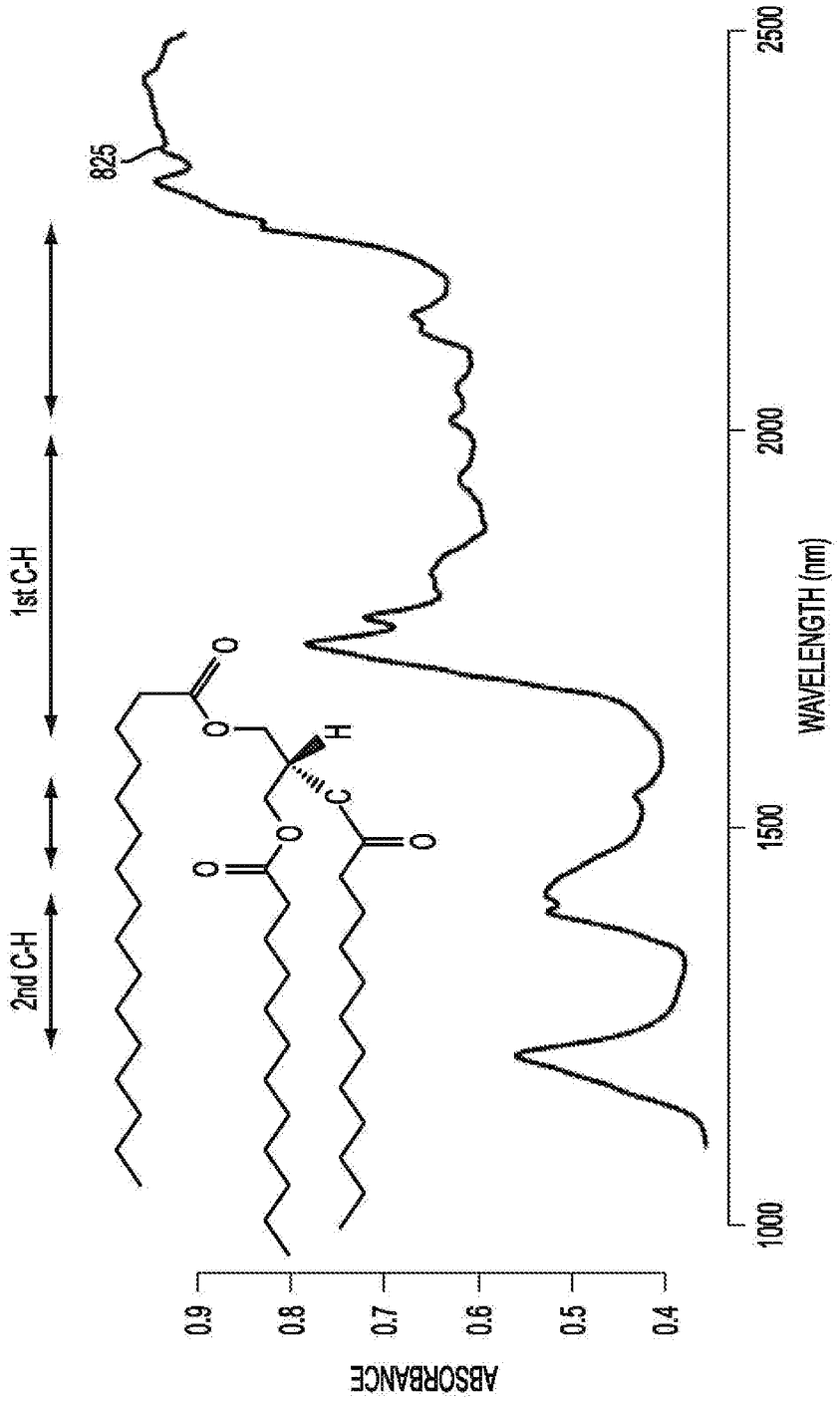

2nd C-H
1st C-H
825
ABSORBANCE
0.9
0.8
0.7
0.6
0.5
0.4
1000
1500
2000
2500
WAVELENGTH (nm)

FIG. 8B

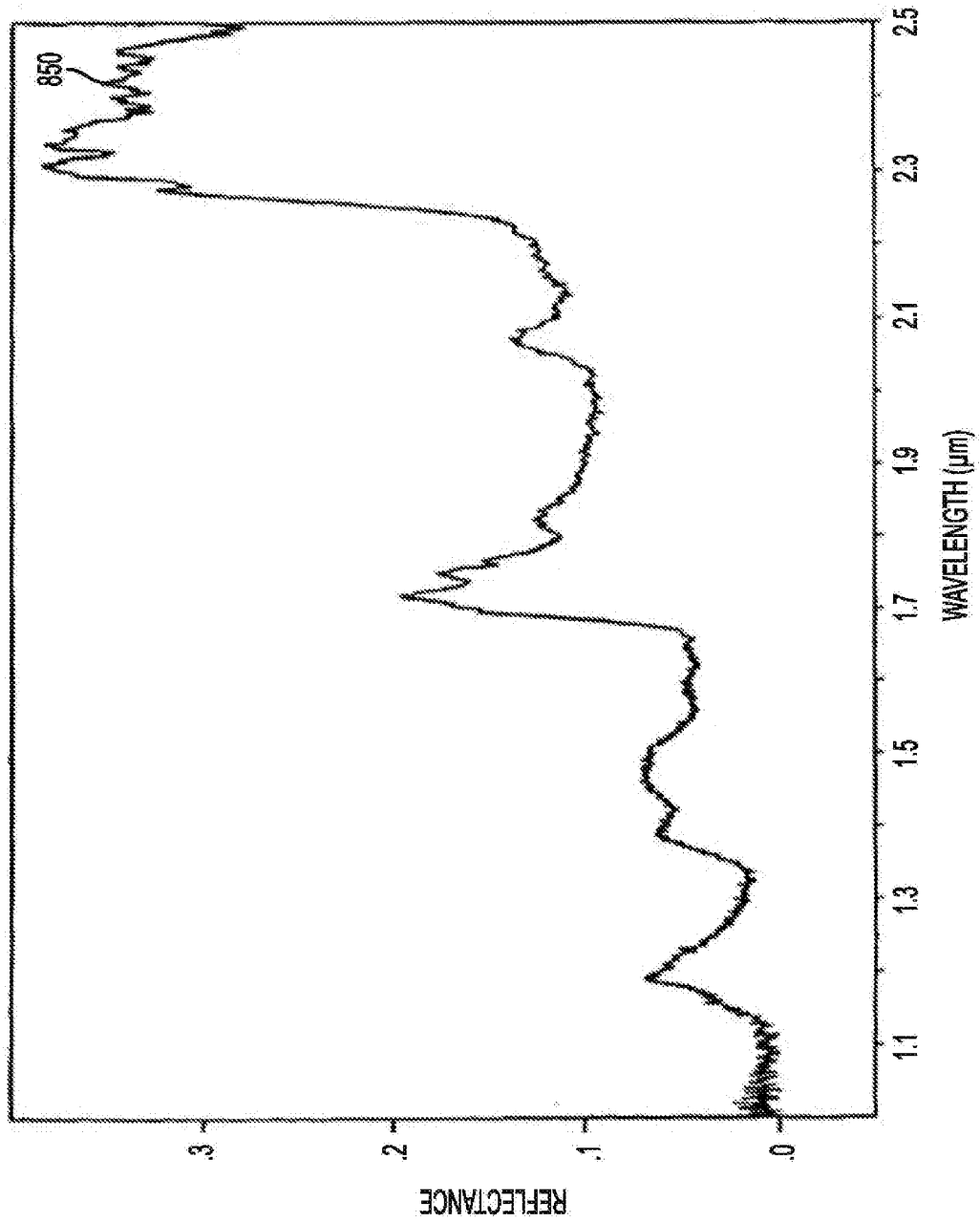


FIG. 8C

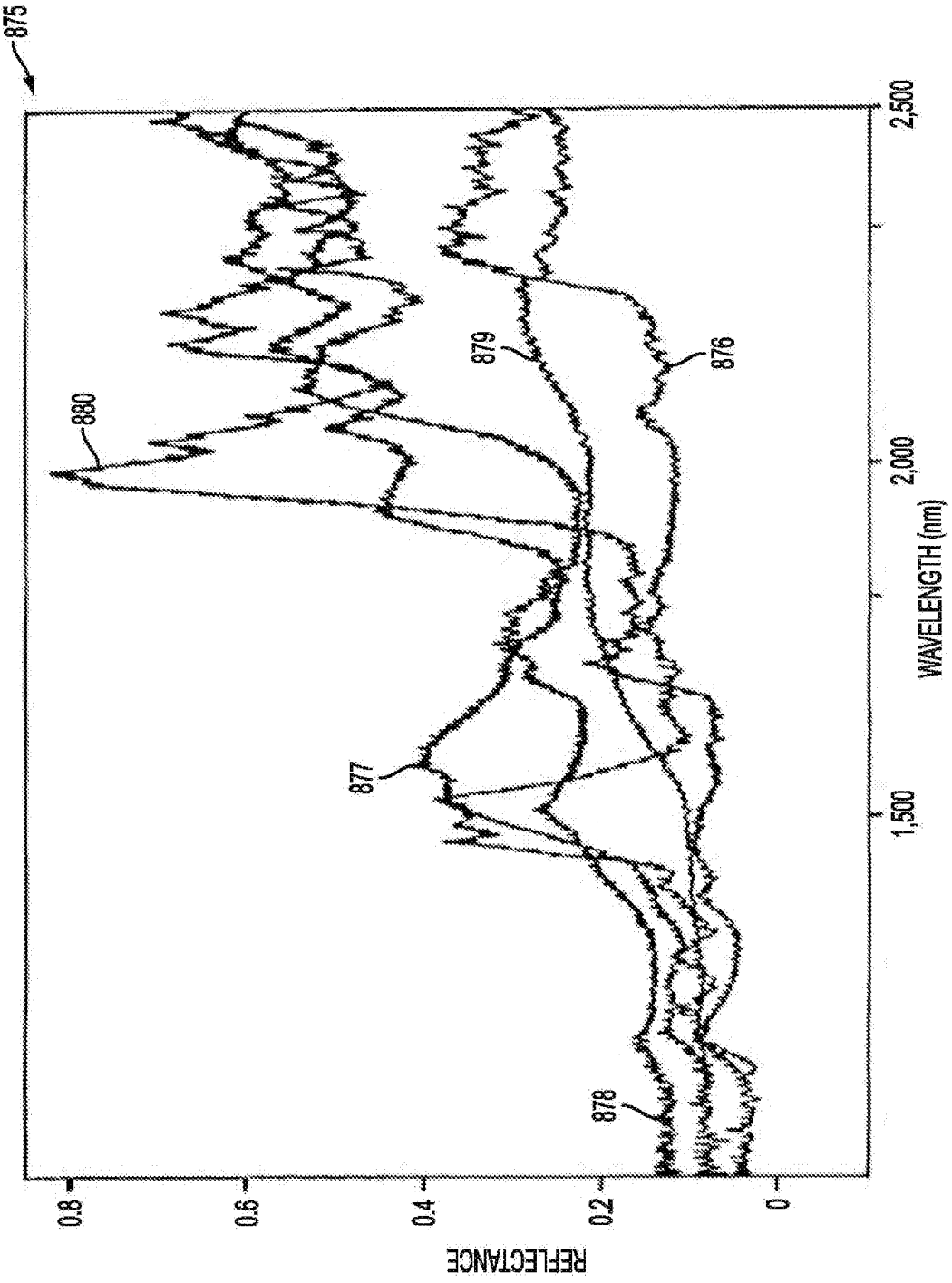

875
880
879
876
877
878
0.8
0.6
0.4
0.2
0
REFLECTANCE
1,500
2,000
2,500
WAVELENGTH (nm)

FIG. 8D

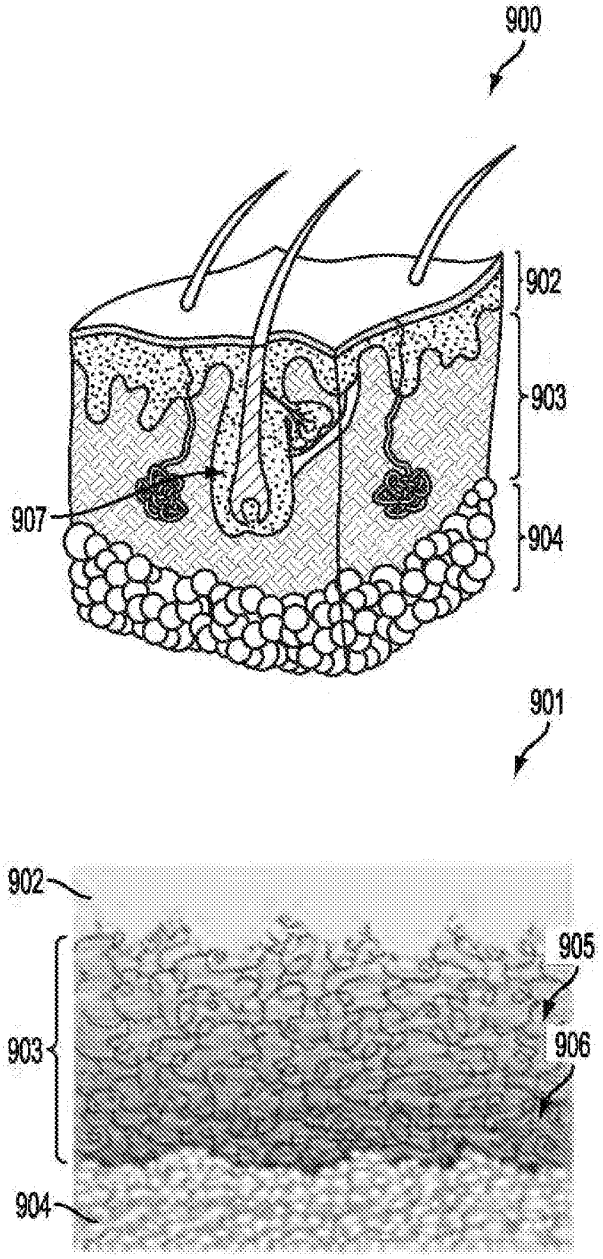


FIG. 9

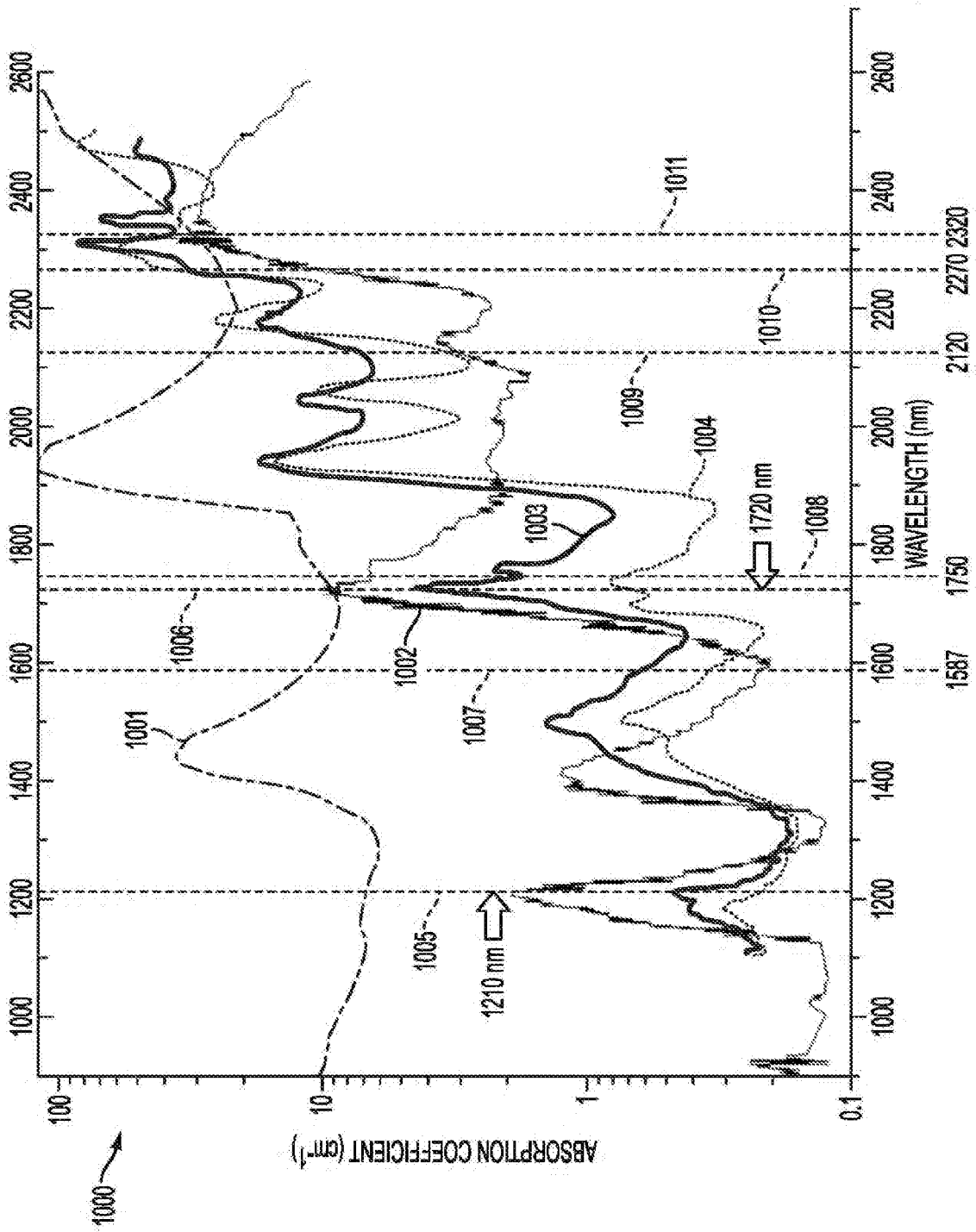

1000
ABSORPTION COEFFICIENT (cm-1)
100
10
1
0.1
WAVELENGTH (nm)
1000
1200
1400
1600
1800
2000
2200
2400
2600
1587
1750
2120
2270
2320
1210 nm
1720 nm
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011

FIG. 10

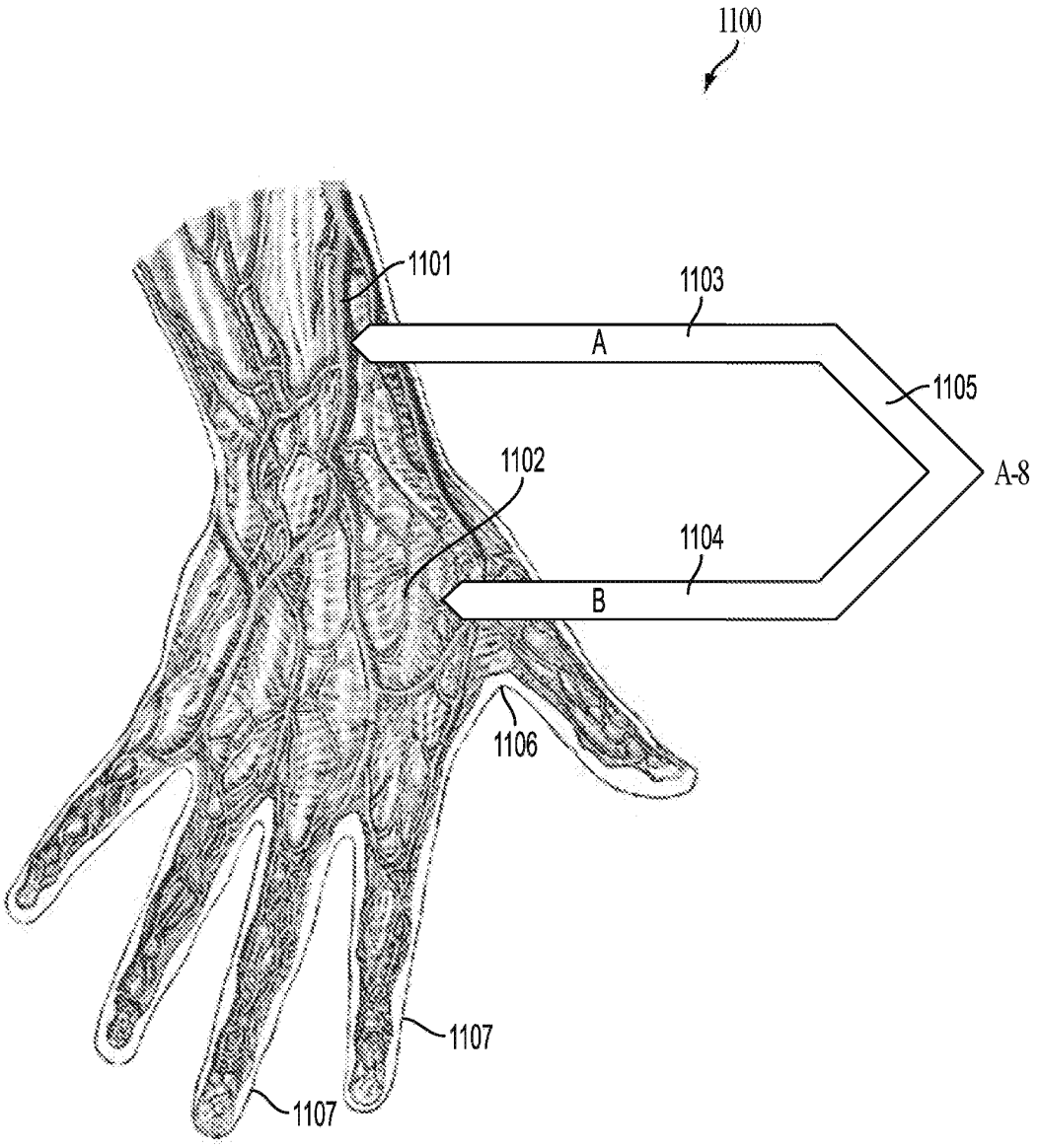


FIG. 11

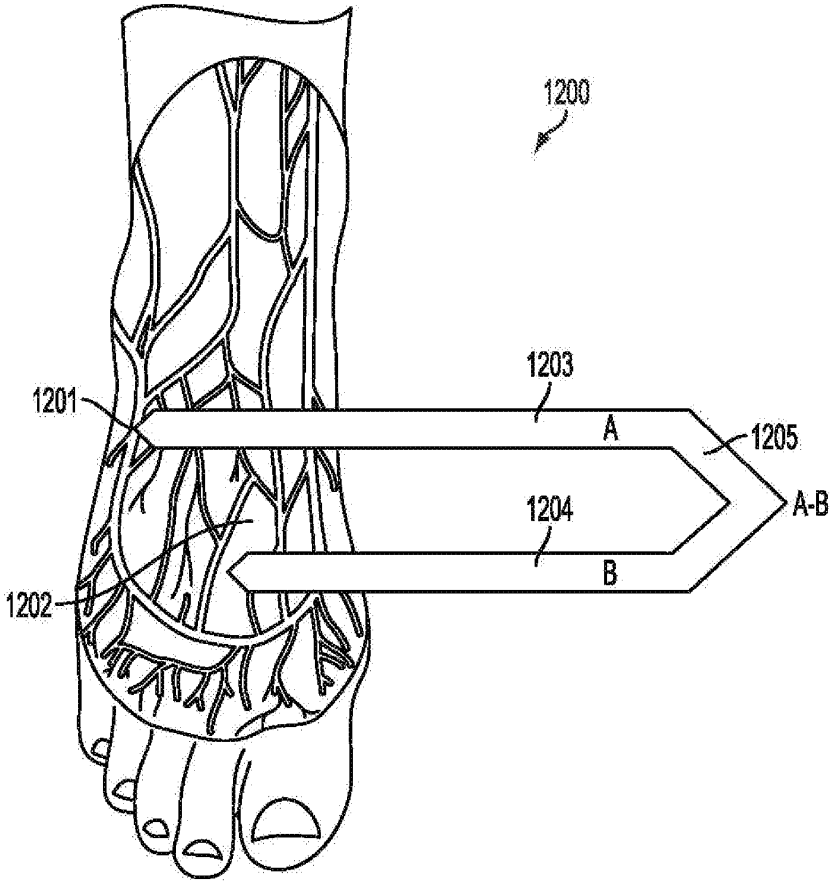


FIG. 12

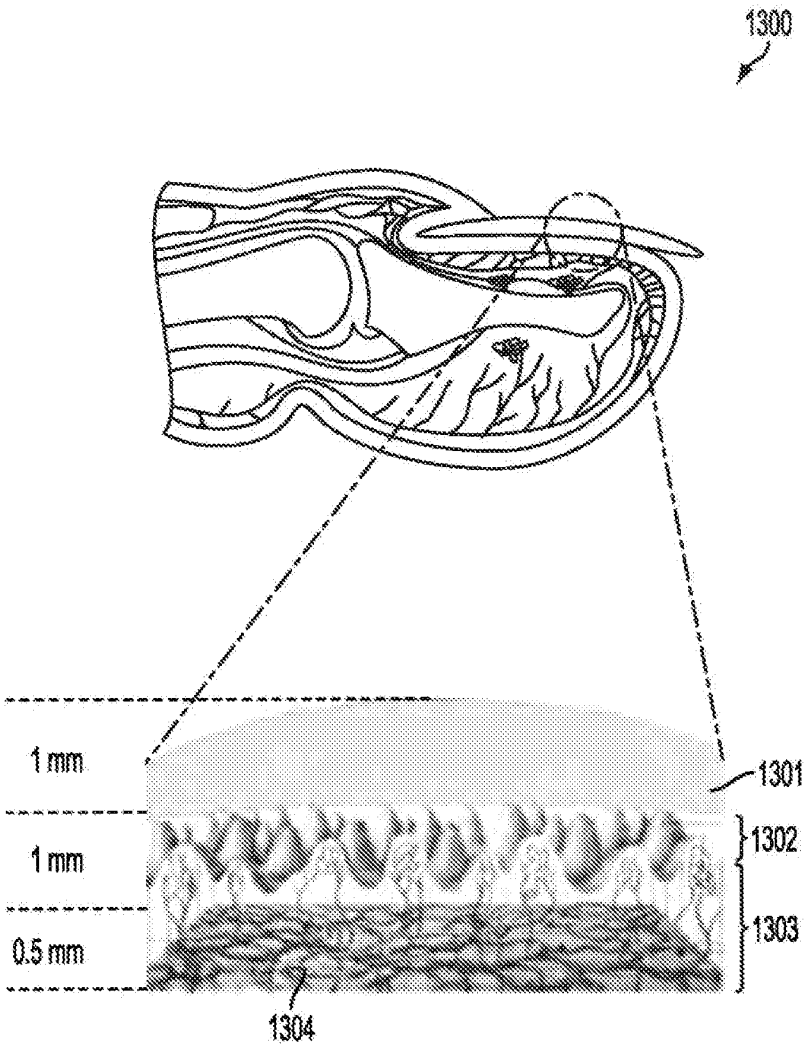


FIG. 13

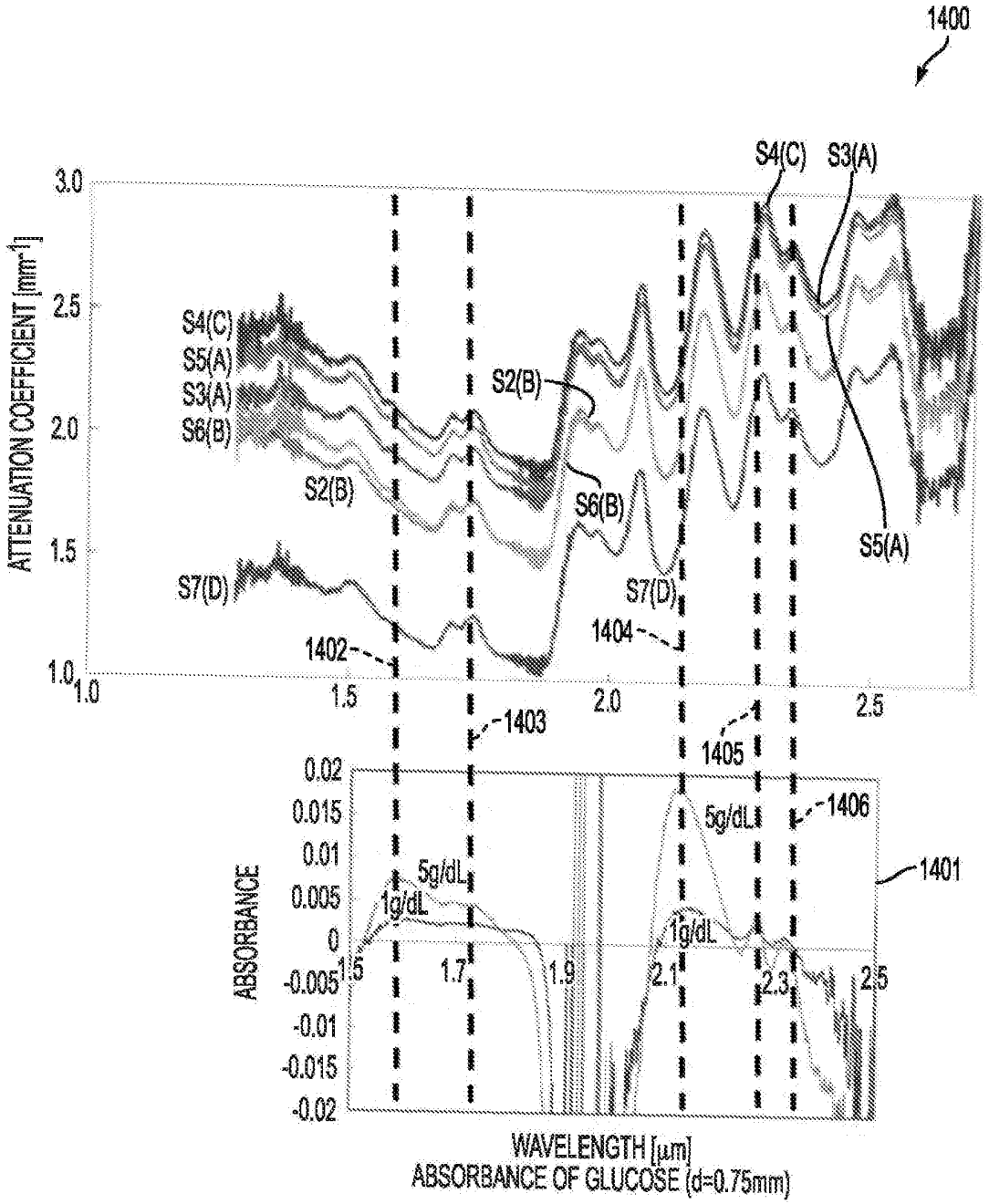

1400
ATTENUATION COEFFICIENT [mm⁻¹]
3.0
2.5
2.0
1.5
1.0
1.0
1.5
2.0
2.5
S4(C)
S5(A)
S3(A)
S6(B)
S2(B)
S7(D)
1402
1403
1404
1405
1406
1401
ABSORBANCE
0.02
0.015
0.01
0.005
0
-0.005
-0.01
-0.015
-0.02
5g/dL
1g/dL
1.5
1.7
1.9
2.1
2.3
2.5
WAVELENGTH [μm]
ABSORBANCE OF GLUCOSE (d=0.75mm)

FIG. 14

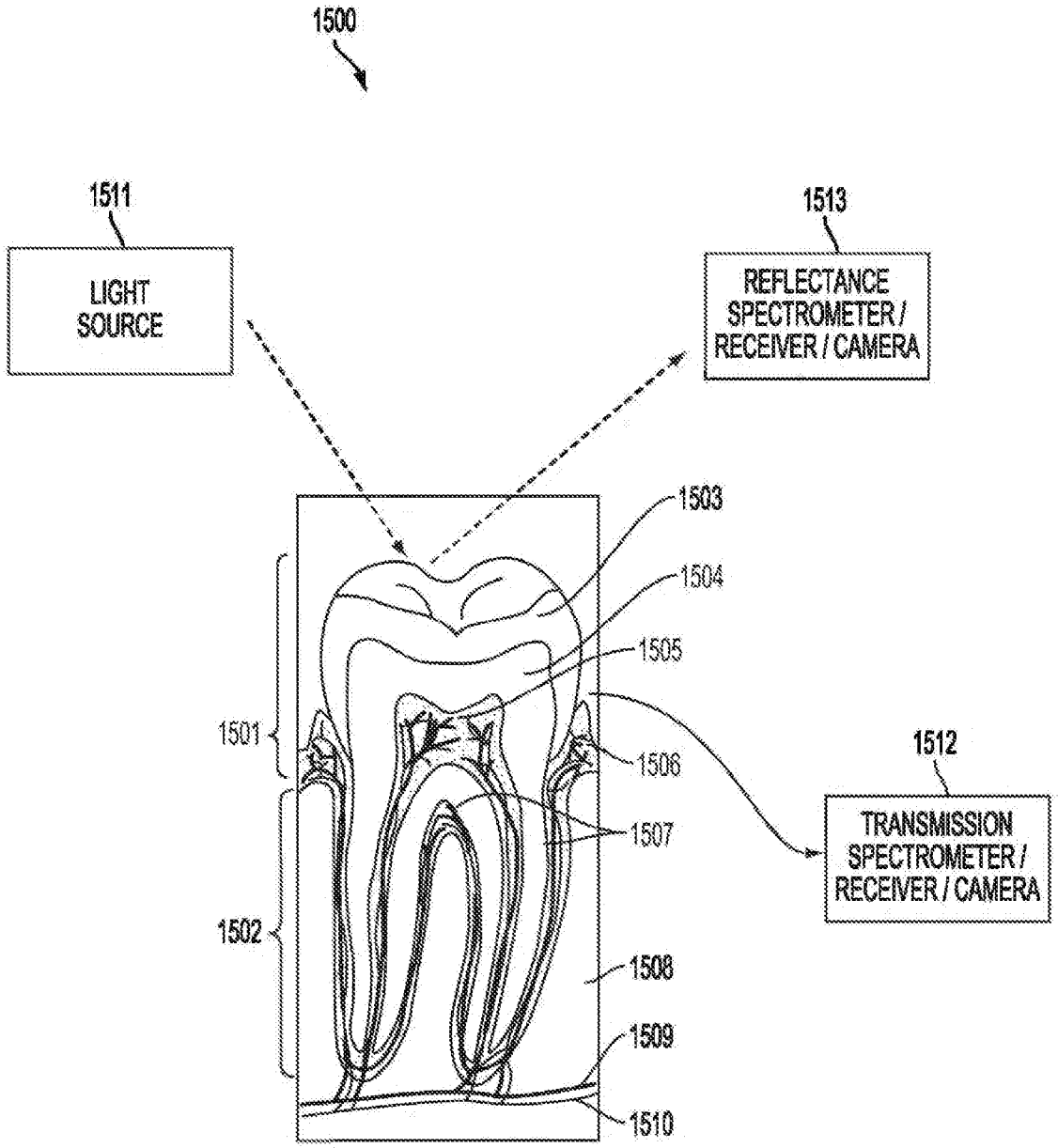

1500
1511
LIGHT SOURCE
1513
REFLECTANCE SPECTROMETER / RECEIVER / CAMERA
1503
1504
1505
1501
1506
1512
TRANSMISSION SPECTROMETER / RECEIVER / CAMERA
1507
1502
1508
1509
1510

FIG. 15

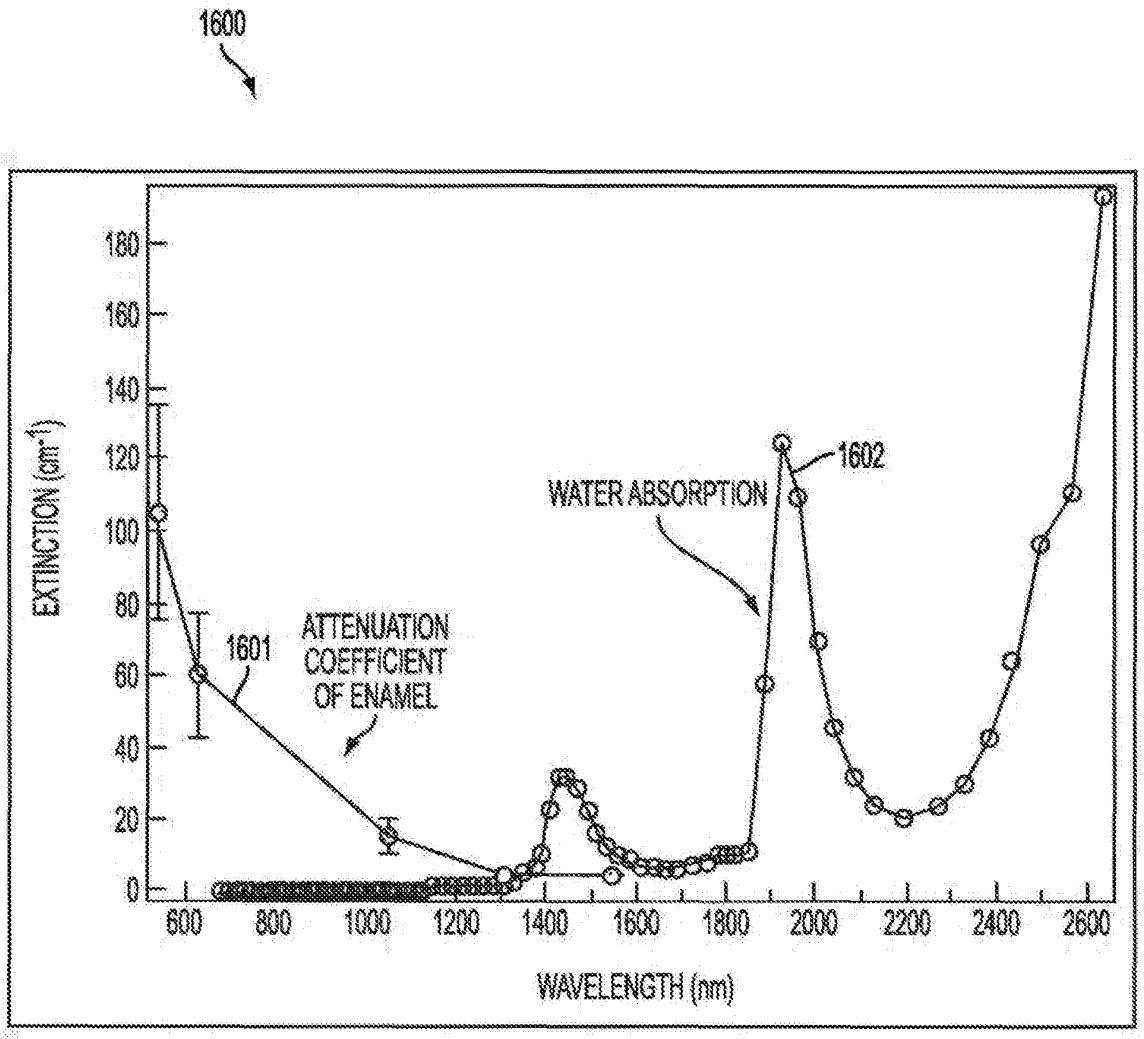

1600
EXTINCTION (cm-1)
180
160
140
120
100
80
60
40
20
0
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
WAVELENGTH (nm)
1601
ATTENUATION COEFFICIENT OF ENAMEL
WATER ABSORPTION
1602

FIG. 16A

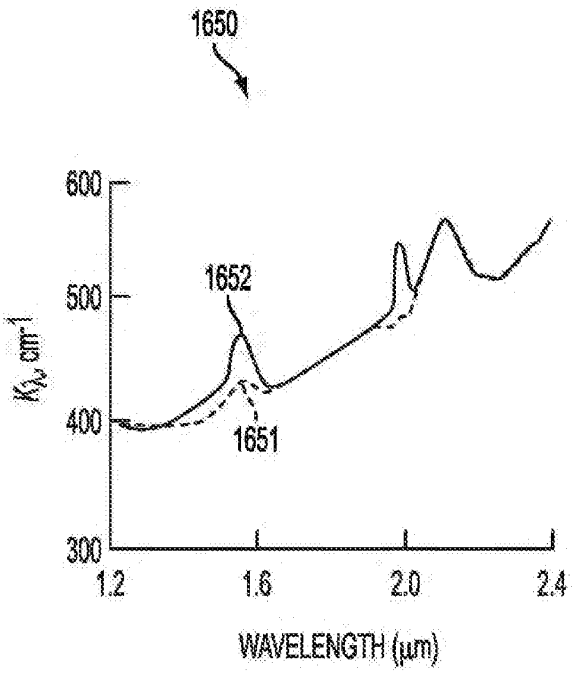

1650
600
500
400
300
1652
1651
K_λ cm^{-1}
1.2
1.6
2.0
2.4
WAVELENGTH (μm)

FIG. 16B

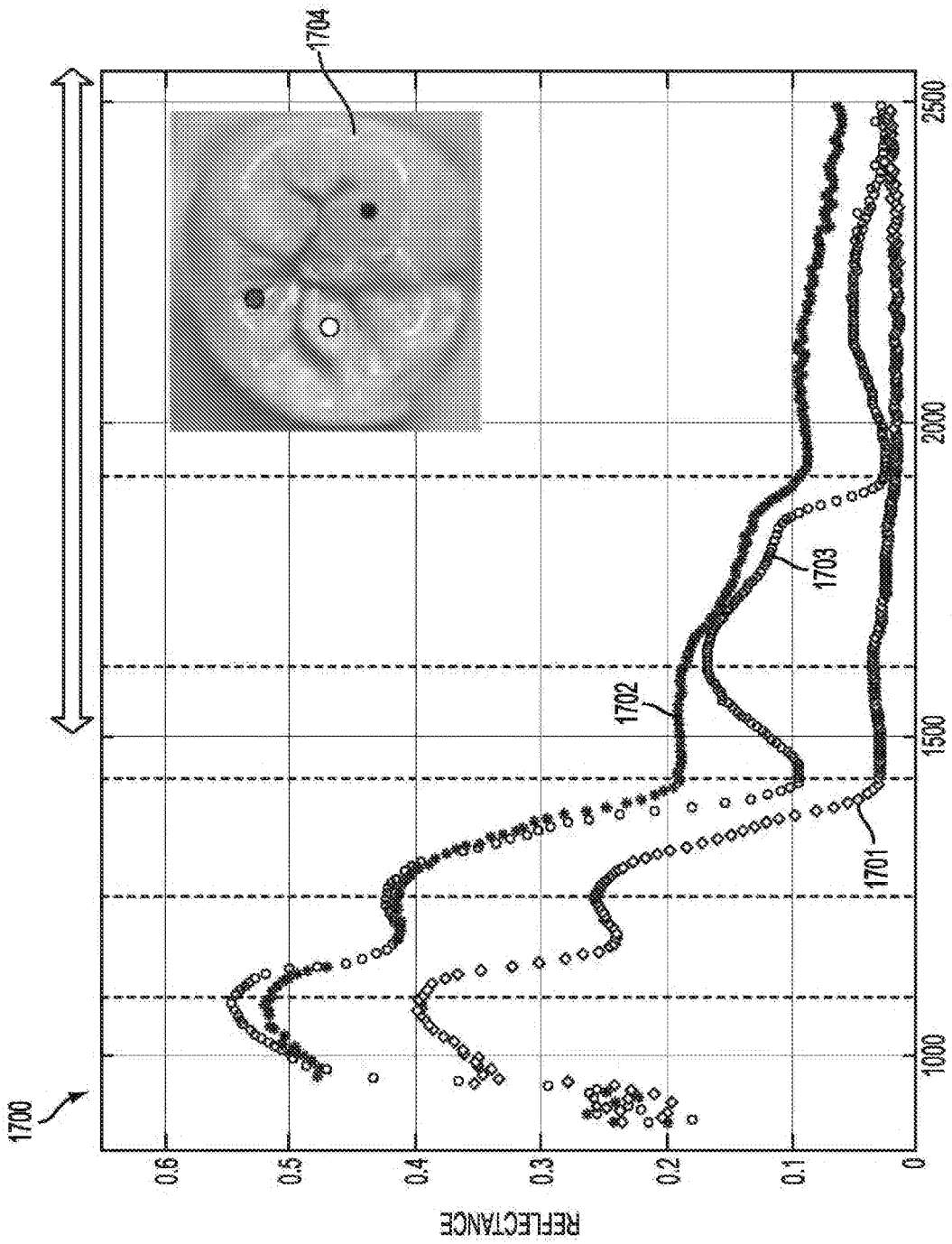

1700
1704
1701
1702
1703
REFLECTANCE
0.6
0.5
0.4
0.3
0.2
0.1
0
1000
1500
2000
2500
WAVELENGTH (nm)

FIG. 17

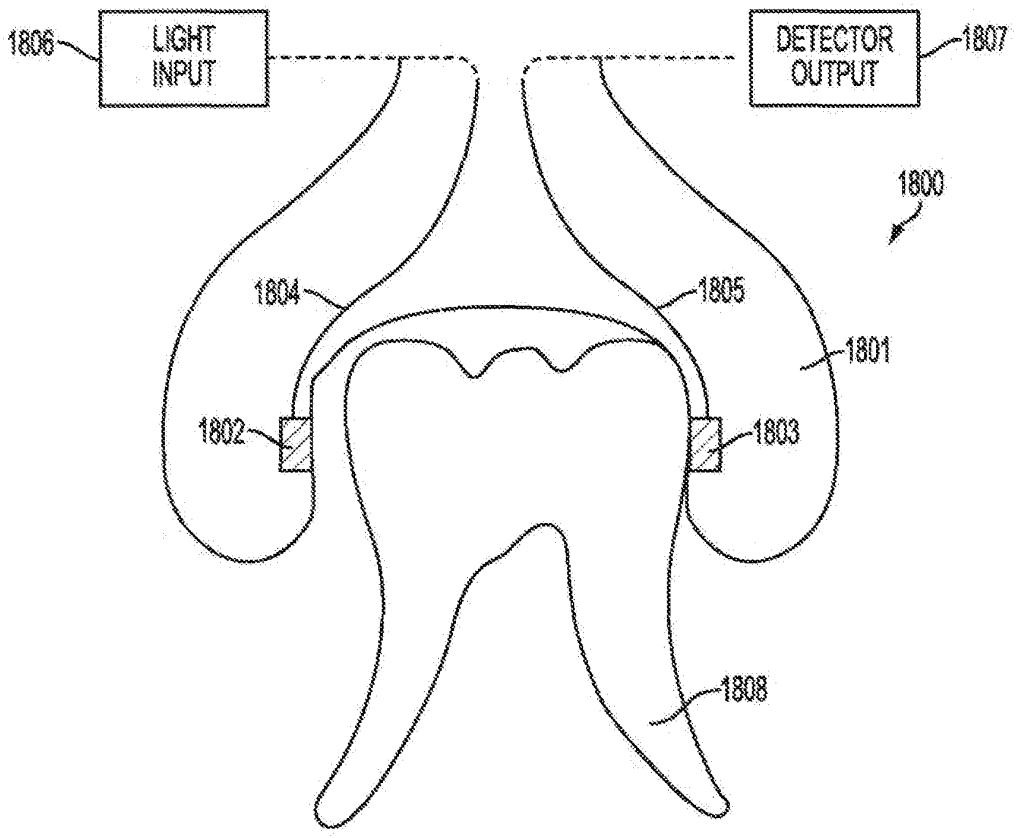

1806
LIGHT INPUT
DETECTOR OUTPUT
1807
1800
1804
1805
1801
1802
1803
1808

FIG. 18A

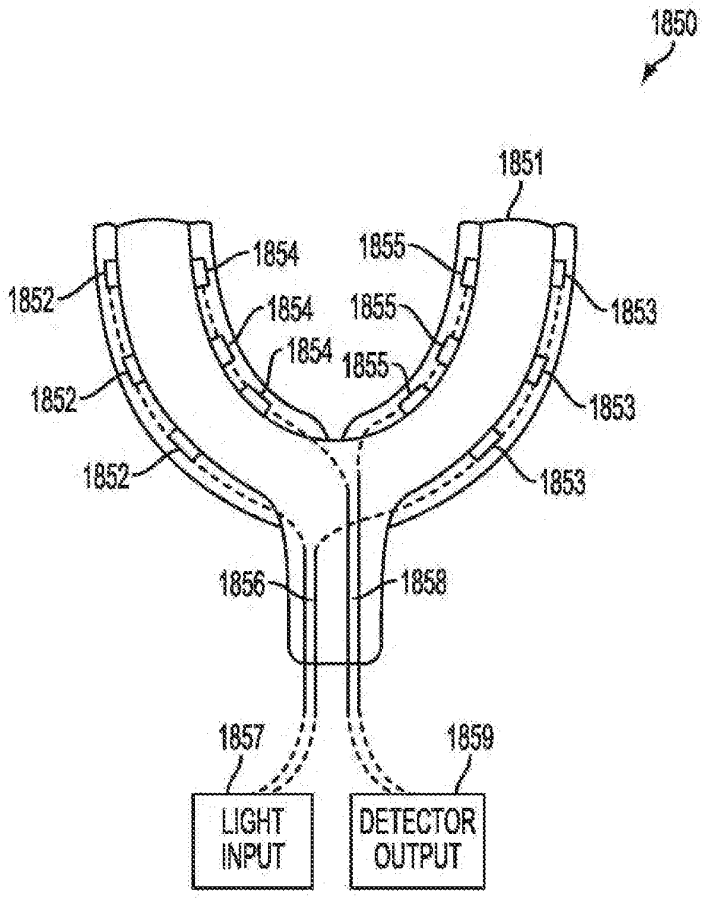

1850
1851
1852
1852
1852
1853
1853
1853
1854
1854
1854
1855
1855
1855
1856
1858
1857
1859
LIGHT INPUT
DETECTOR OUTPUT

FIG. 18B

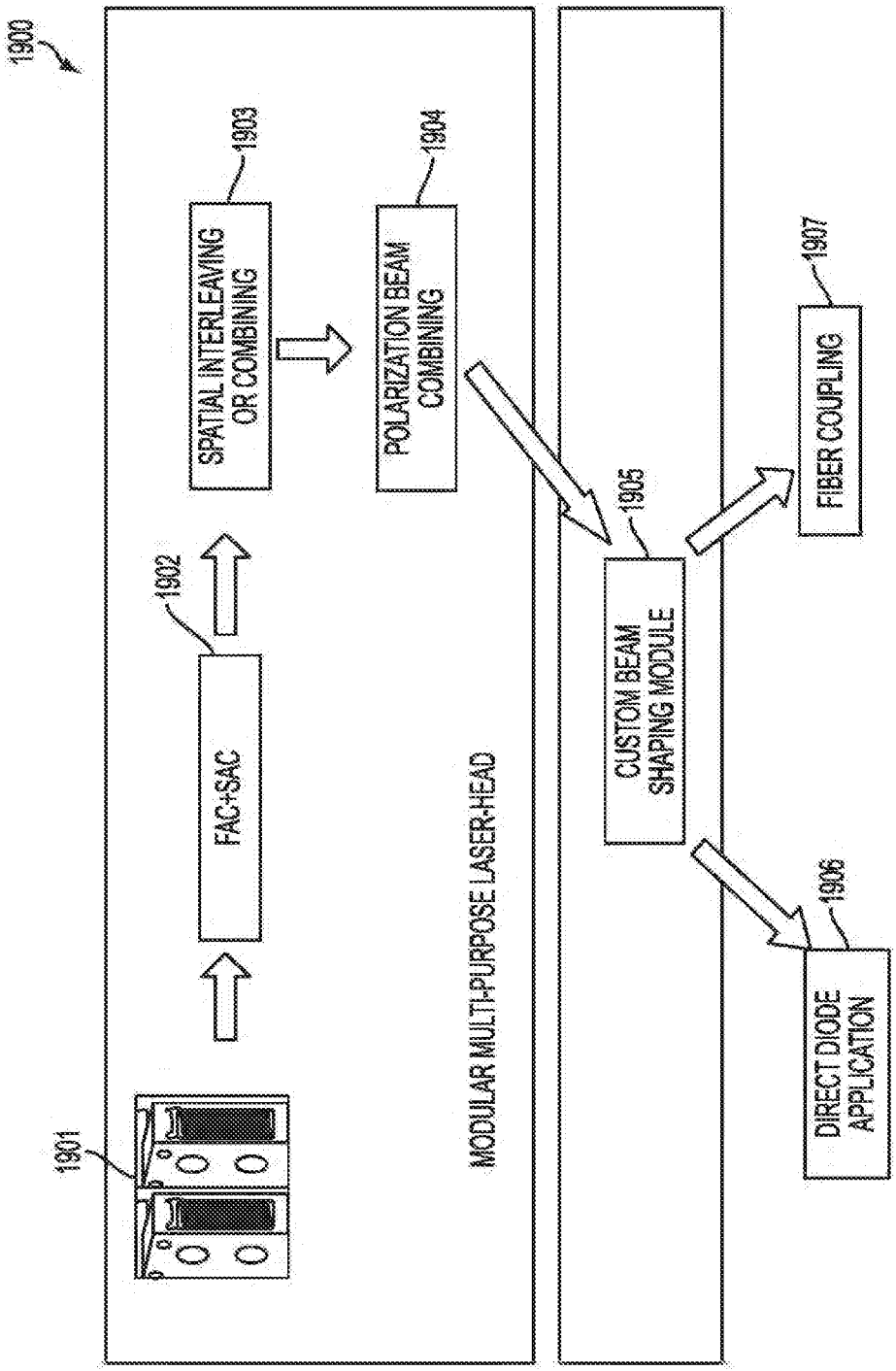

1900
1901
1902
FAC+SAC
1903
SPATIAL INTERLEAVING OR COMBINING
1904
POLARIZATION BEAM COMBINING
MODULAR MULTI-PURPOSE LASER-HEAD
1905
CUSTOM BEAM SHAPING MODULE
1906
DIRECT DIODE APPLICATION
1907
FIBER COUPLING

FIG. 19

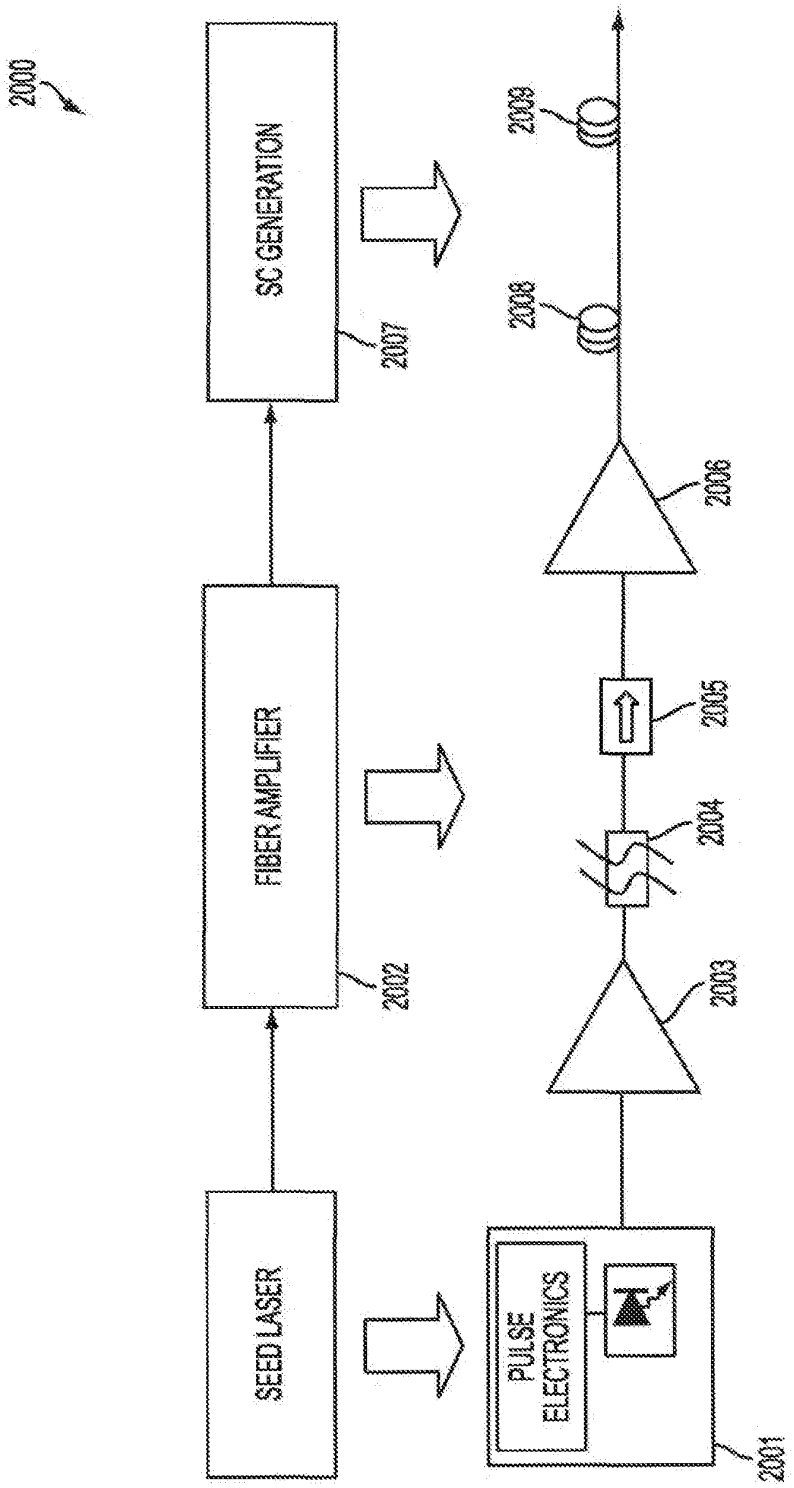

2000
SEED LASER
FIBER AMPLIFIER
SC GENERATION
PULSE ELECTRONICS
2001
2002
2003
2004
2005
2006
2007
2008
2009

FIG. 20

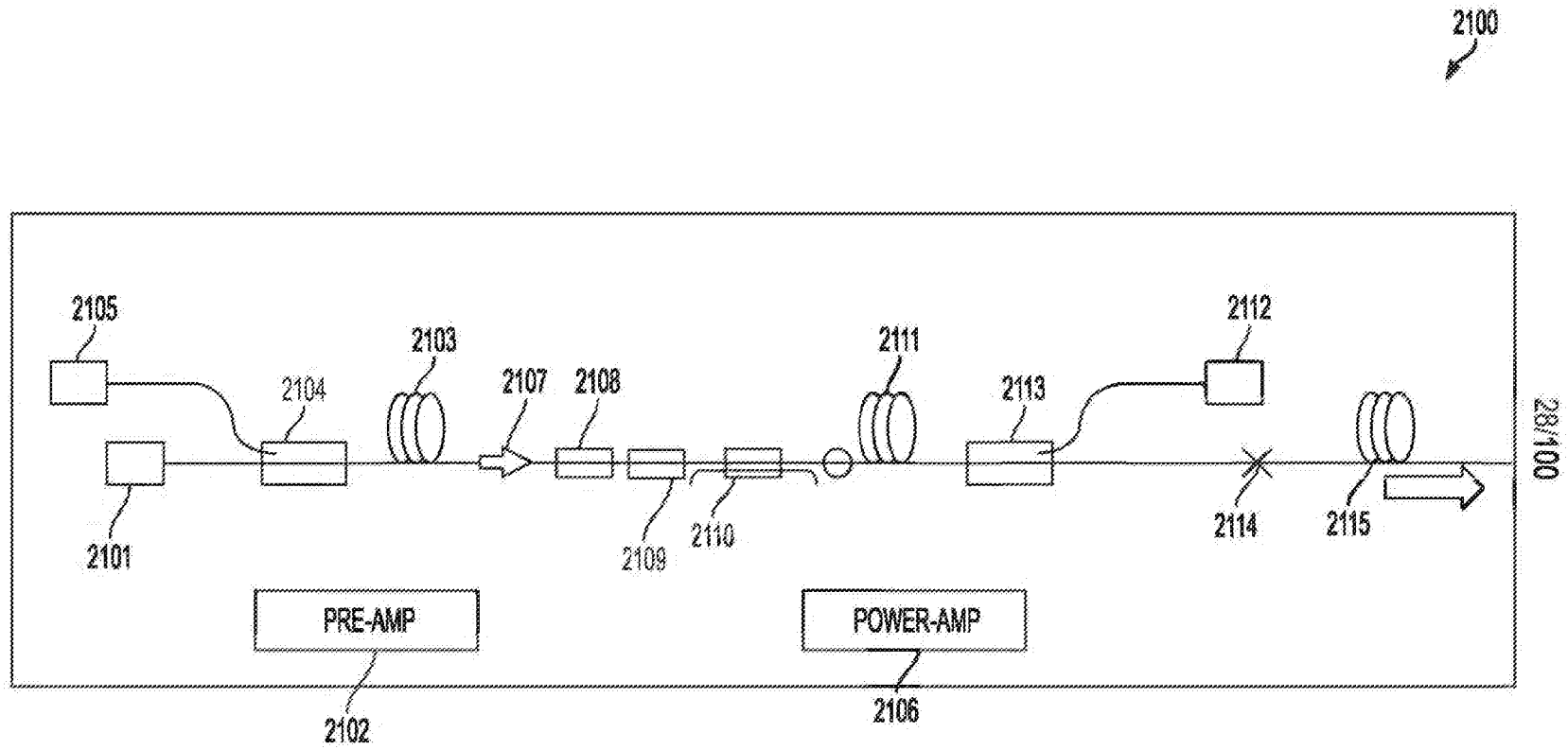

2100
2105
2104
2103
2107
2108
2111
2113
2112
2101
2109
2110
2114
2115
PRE-AMP
POWER-AMP
2102
2106

FIG. 21

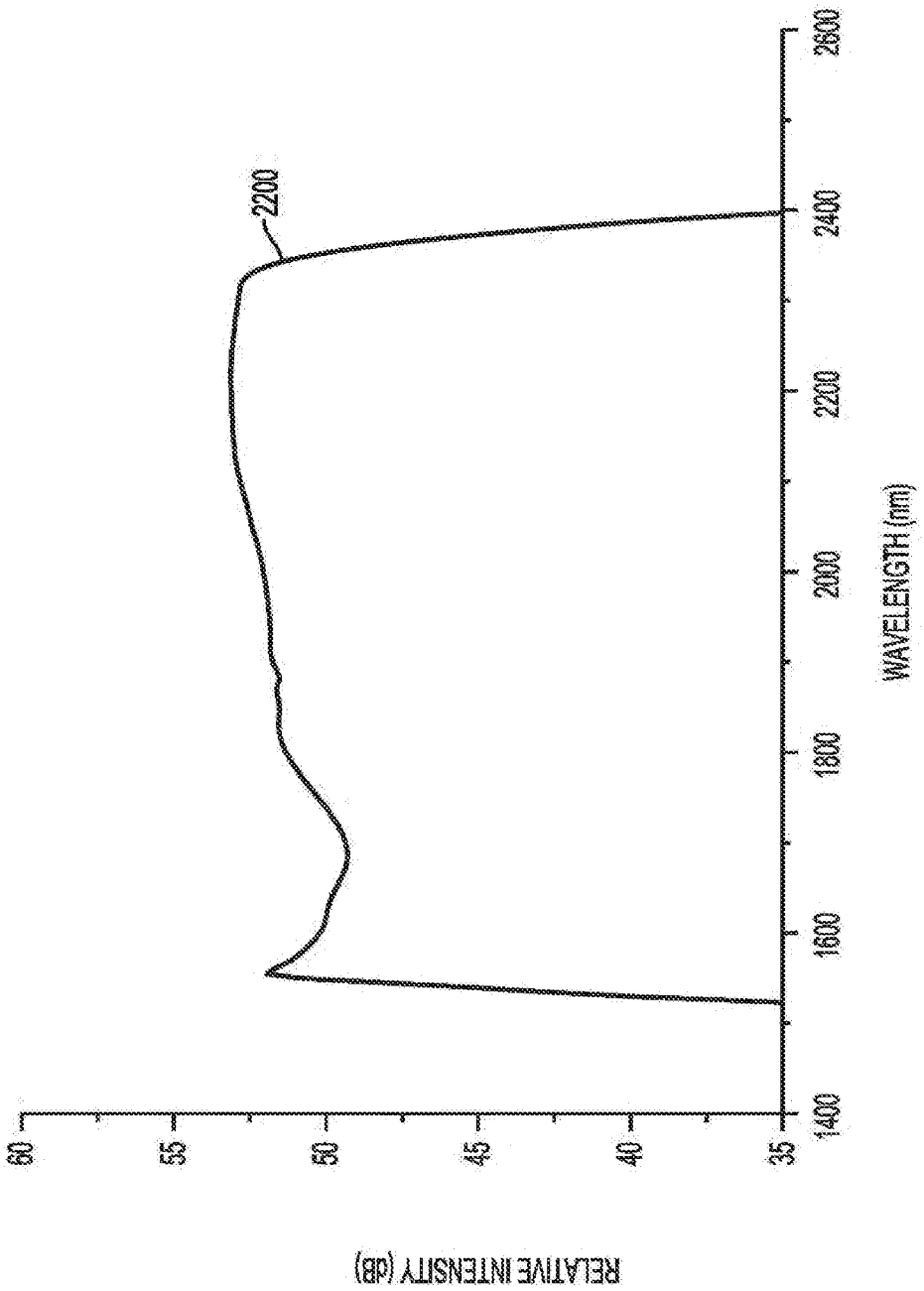

2200
60
55
50
45
40
35
1400
1600
1800
2000
2200
2400
2600
WAVELENGTH (nm)
RELATIVE INTENSITY (dB)

FIG. 22

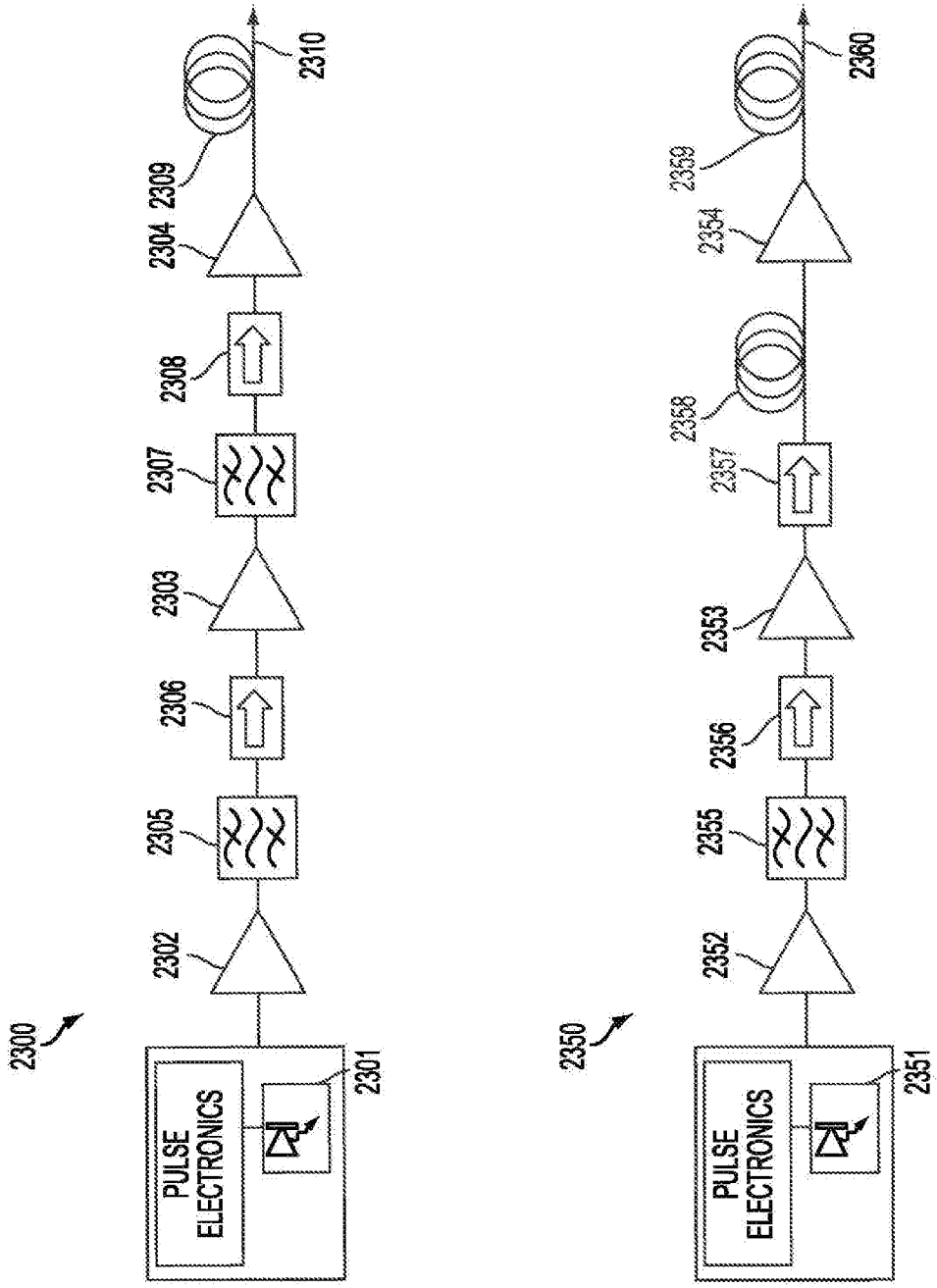

2300
PULSE ELECTRONICS
2301
2302
2305
2306
2303
2307
2308
2304
2309
2310
2350
PULSE ELECTRONICS
2351
2352
2355
2356
2353
2357
2358
2354
2359
2360

FIG. 23

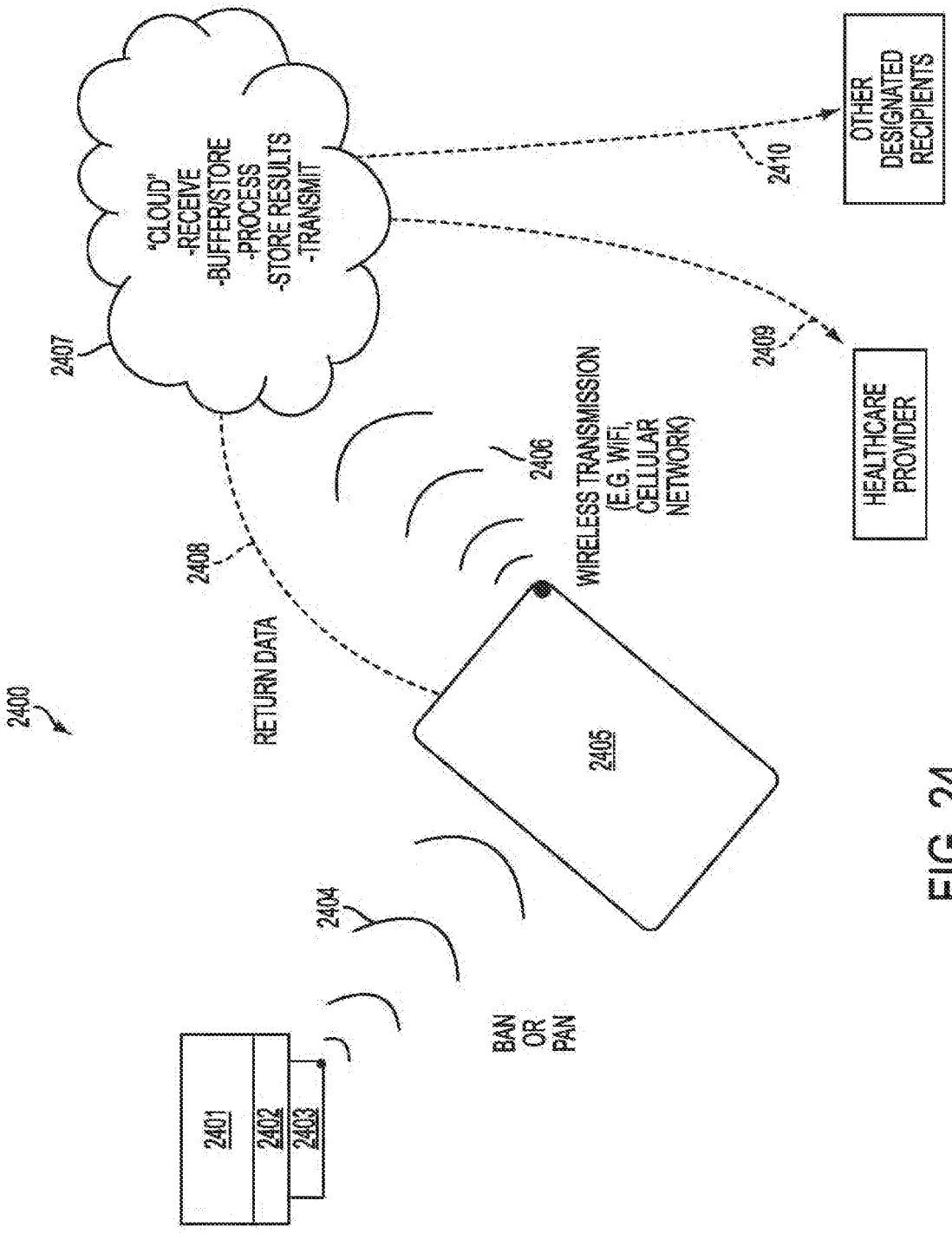

2400
"CLOUD"
-RECEIVE
-BUFFER/STORE
-PROCESS
-STORE RESULTS
-TRANSMIT
2407
2408
RETURN DATA
2406
WIRELESS TRANSMISSION
(E.G. WIFI,
CELLULAR
NETWORK)
2405
2404
BAN
OR
PAN
2401
2402
2403
2409
HEALTHCARE
PROVIDER
2410
OTHER
DESIGNATED
RECIPIENTS

FIG. 24

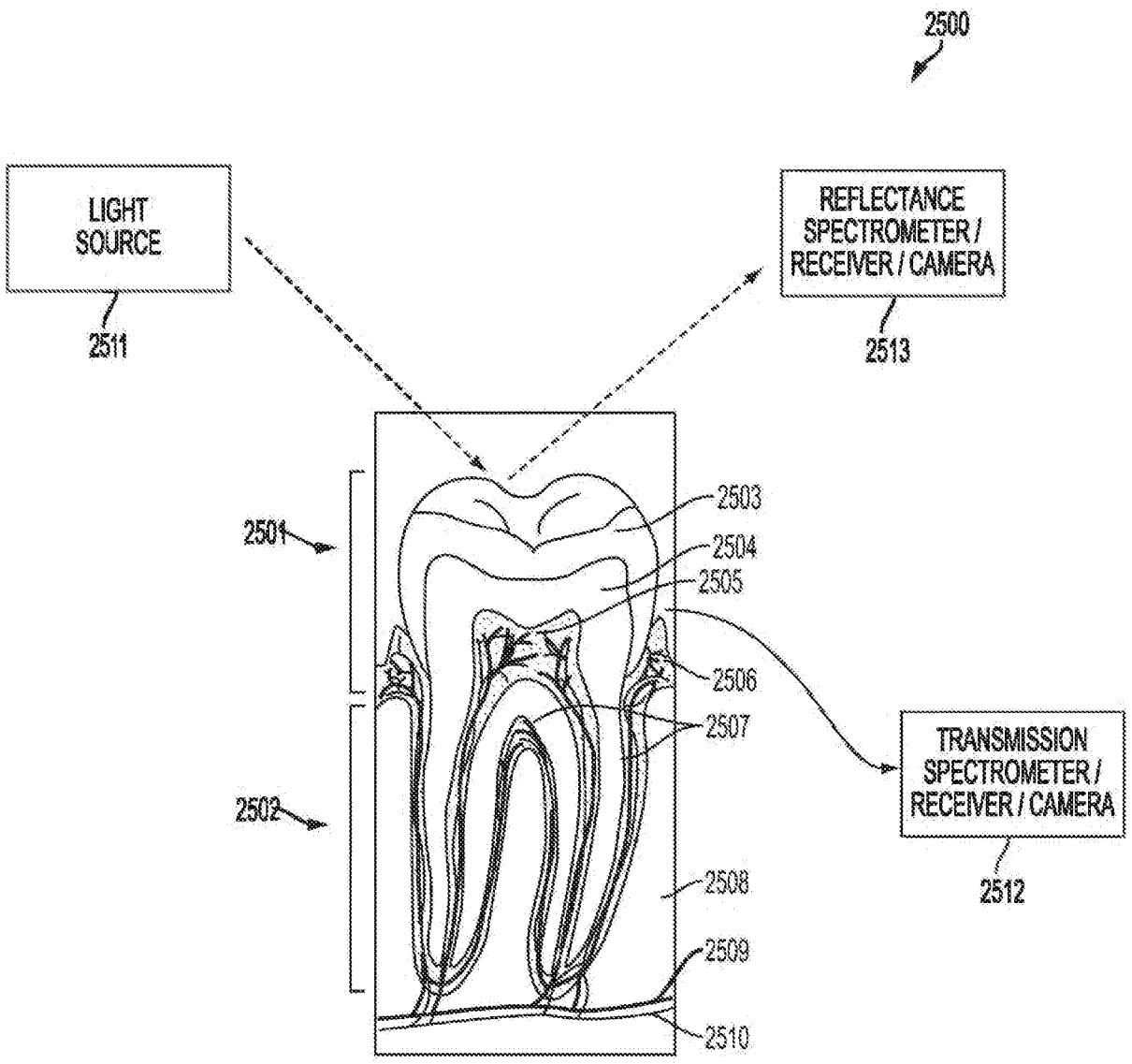

2500
LIGHT SOURCE
2511
REFLECTANCE SPECTROMETER / RECEIVER / CAMERA
2513
2501
2502
2503
2504
2505
2506
2507
2508
2509
2510
TRANSMISSION SPECTROMETER / RECEIVER / CAMERA
2512

FIG. 25

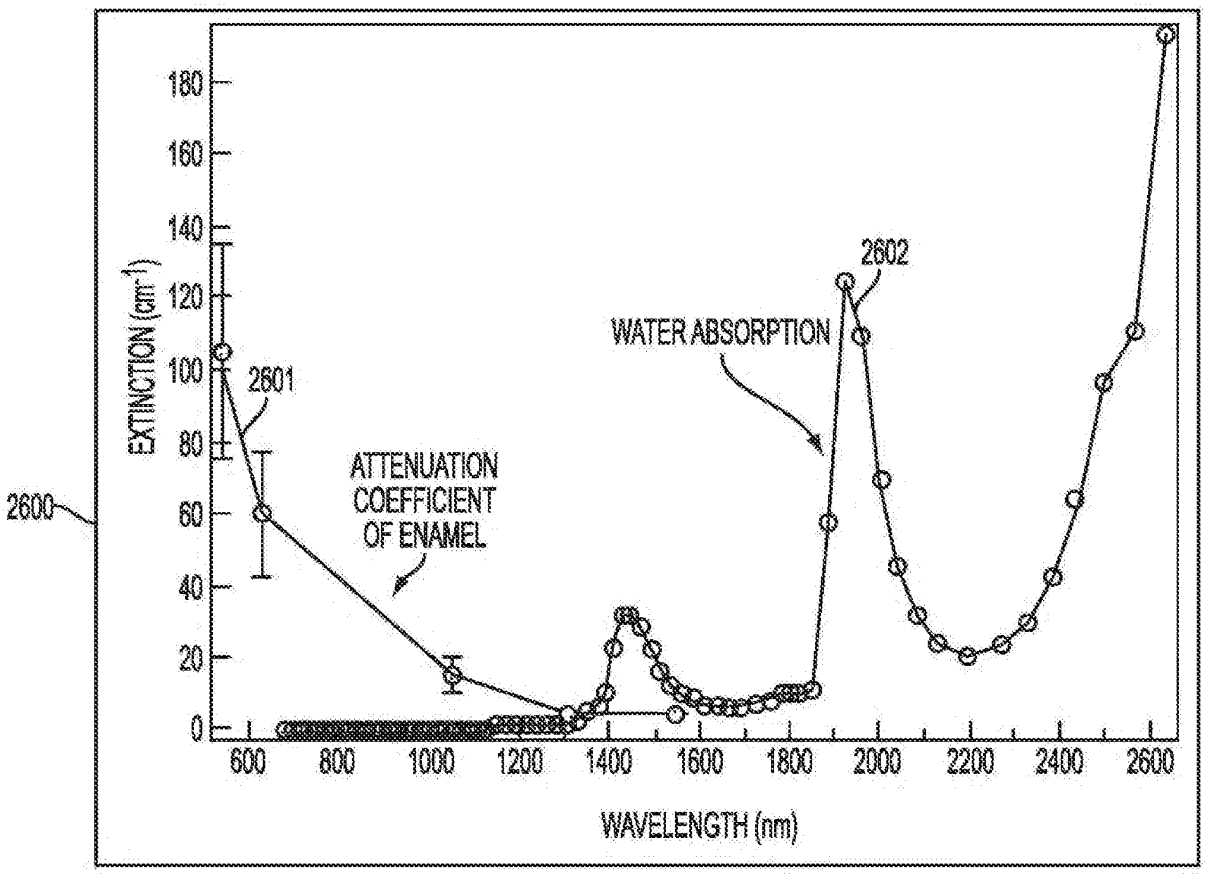

2600
EXTINCTION (cm^{-1})
180
160
140
120
100
80
60
40
20
0
2601
2602
WATER ABSORPTION
ATTENUATION
COEFFICIENT
OF ENAMEL
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
WAVELENGTH (nm)

FIG. 26A

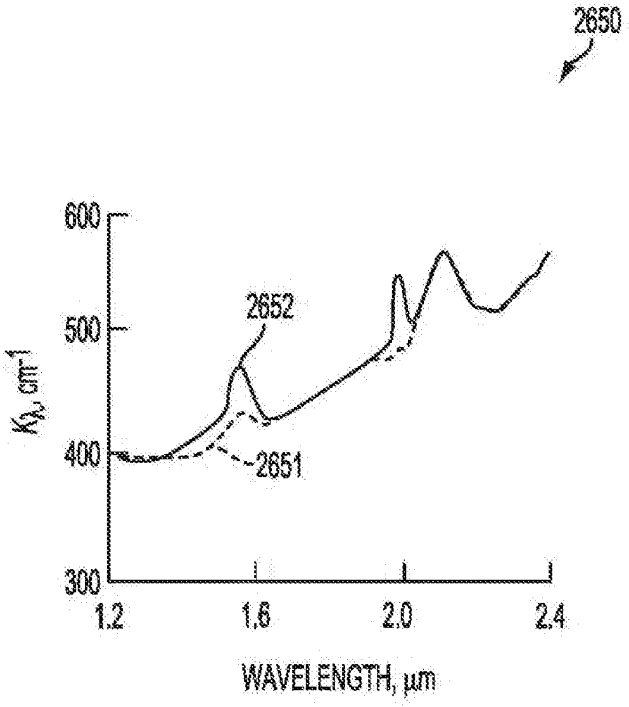

2650
600
500
400
300
K_λ, cm^{-1}
2652
2651
1.2
1.6
2.0
2.4
WAVELENGTH, µm

FIG. 26B

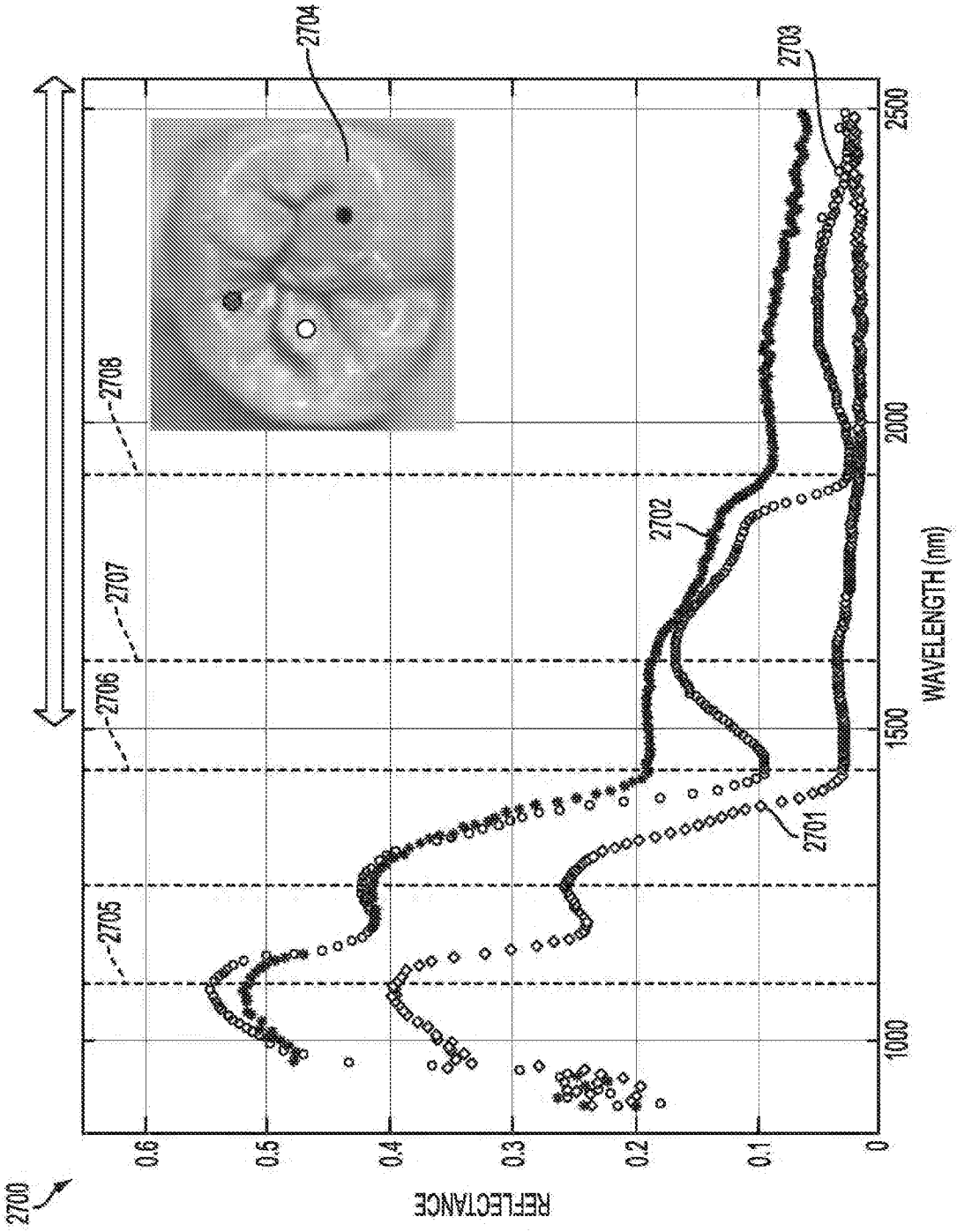

2700
2704
2703
2708
2707
2706
2705
2702
2701
REFLECTANCE
0.6
0.5
0.4
0.3
0.2
0.1
0
1000
1500
2000
2500
WAVELENGTH (nm)

FIG. 27

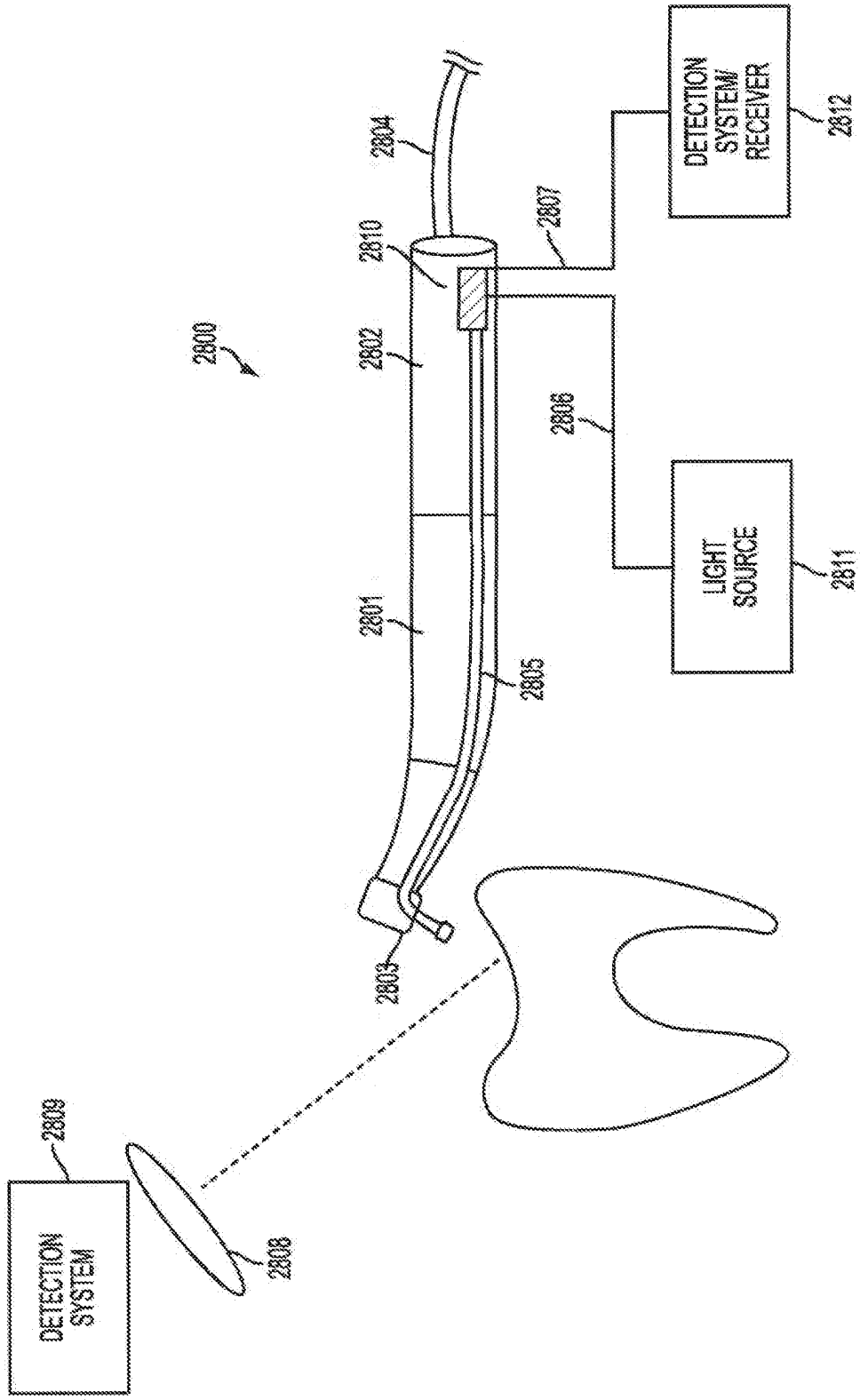

2800
2801
2802
2803
2804
2805
2806
2807
2808
2809
2810
2811
2812
DETECTION SYSTEM
LIGHT SOURCE
DETECTION SYSTEM/ RECEIVER

FIG. 28

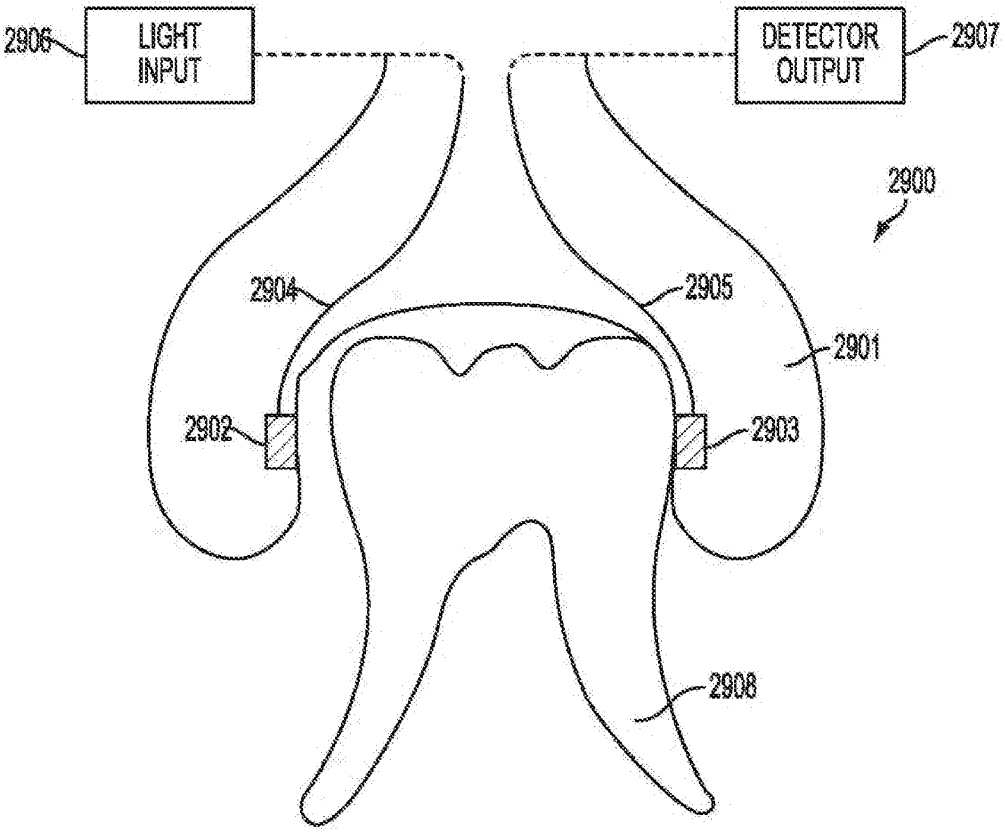

2906
LIGHT INPUT
DETECTOR OUTPUT
2907
2900
2904
2905
2901
2902
2903
2908

FIG. 29

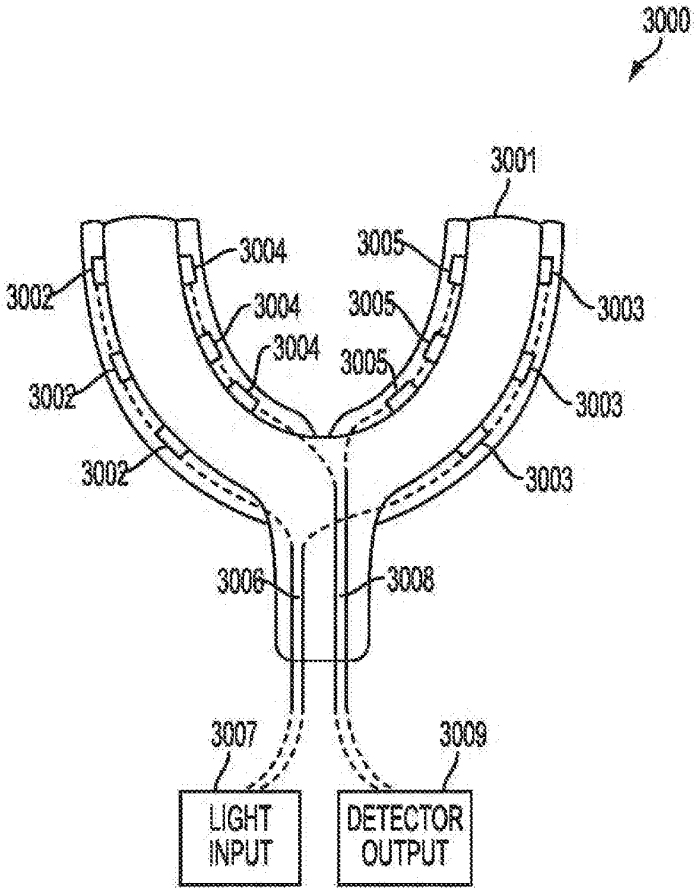

3000
3001
3002
3002
3002
3003
3003
3003
3004
3004
3004
3005
3005
3005
3006
3008
3007
3009
LIGHT INPUT
DETECTOR OUTPUT

FIG. 30

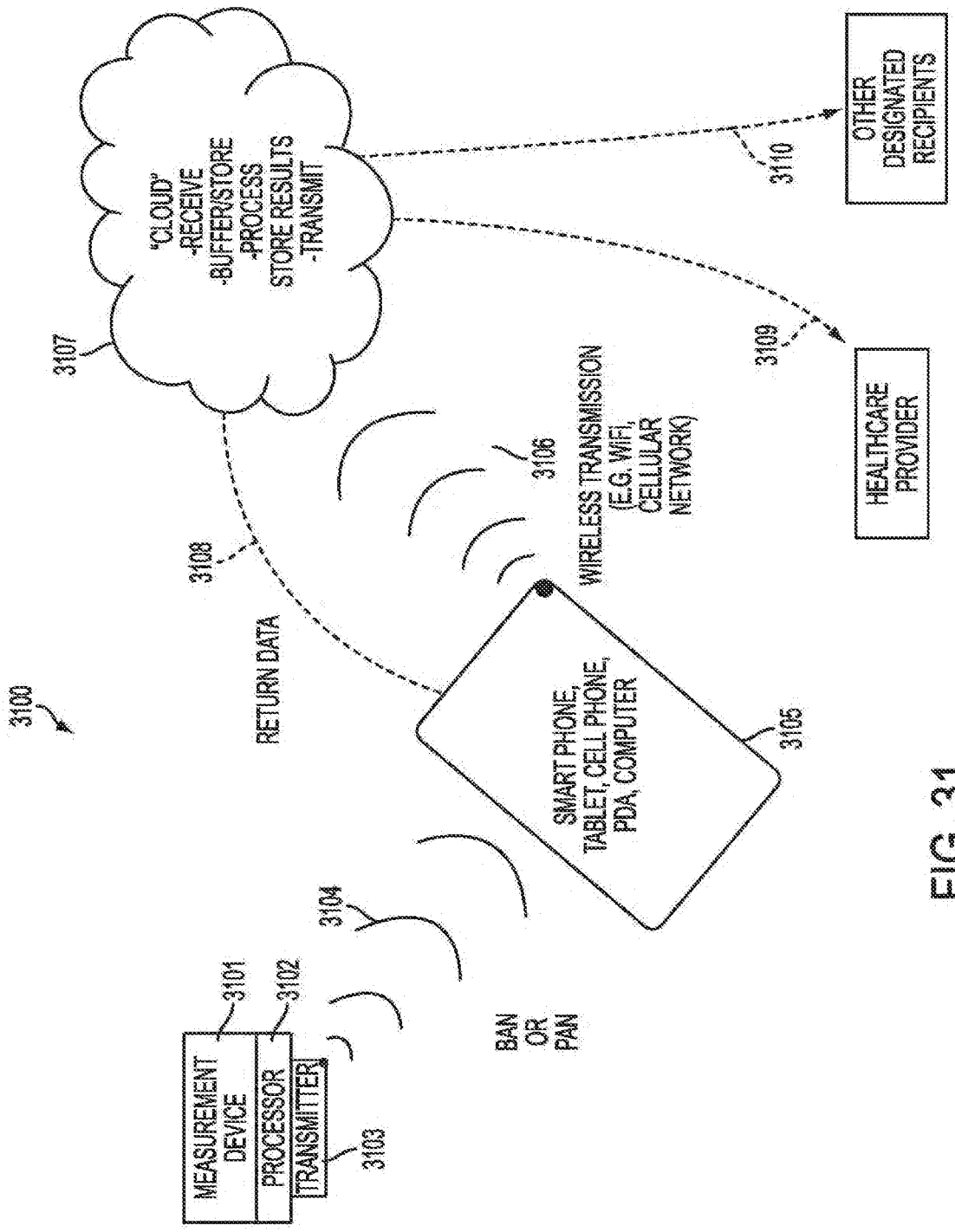

3100
MEASUREMENT DEVICE
PROCESSOR
TRANSMITTER
3101
3102
3103
3104
BAN OR PAN
SMART PHONE, TABLET, CELL PHONE, PDA, COMPUTER
3105
3106
WIRELESS TRANSMISSION (E.G. WIFI, CELLULAR NETWORK)
3107
"CLOUD"
-RECEIVE
-BUFFER/STORE
-PROCESS
STORE RESULTS
-TRANSMIT
3108
RETURN DATA
3109
HEALTHCARE PROVIDER
3110
OTHER DESIGNATED RECIPIENTS

FIG. 31

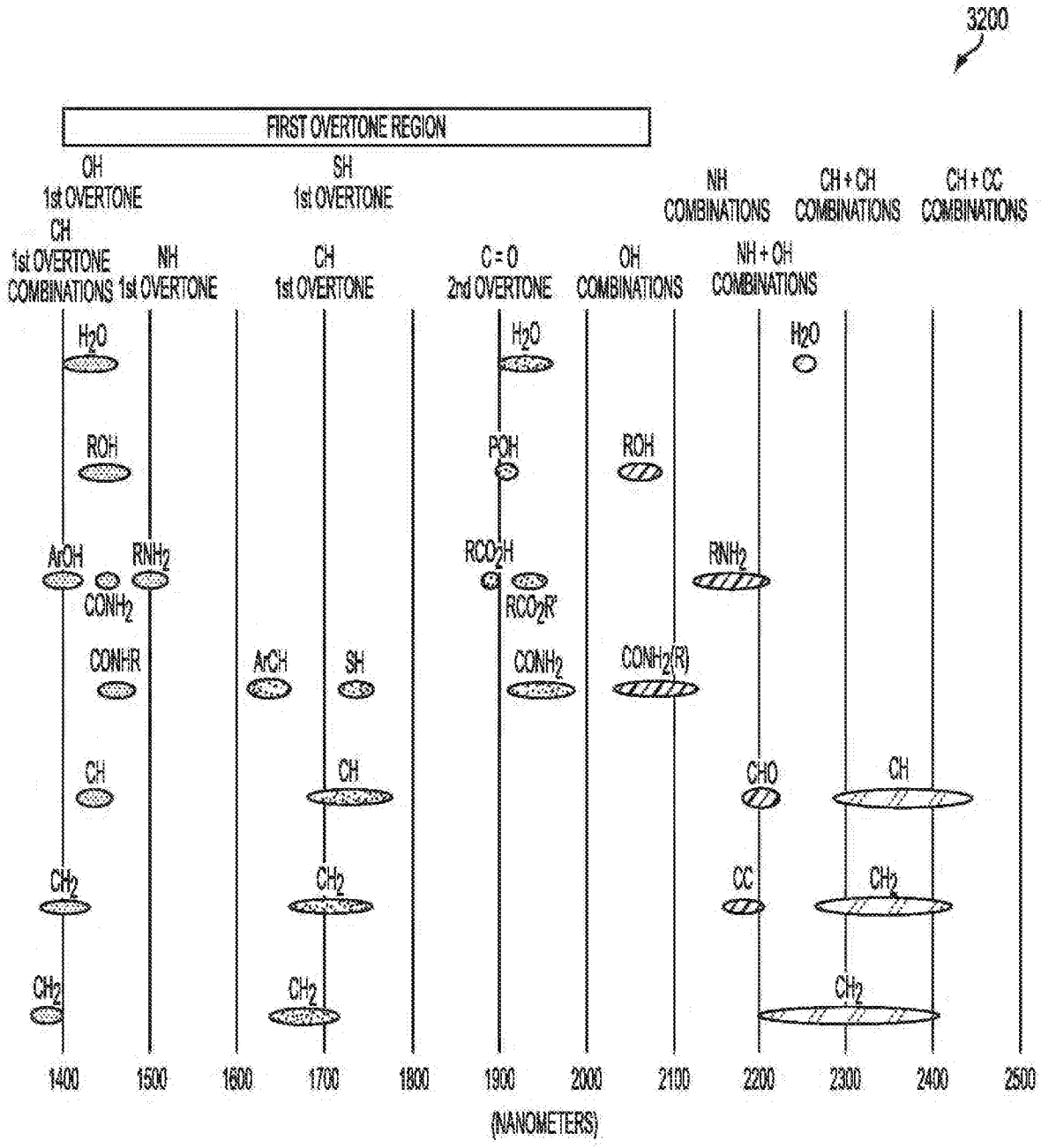

3200
FIRST OVERTONE REGION
CH 1st OVERTONE
CH 1st OVERTONE COMBINATIONS
NH 1st OVERTONE
SH 1st OVERTONE
CH 1st OVERTONE
C = O 2nd OVERTONE
OH COMBINATIONS
NH COMBINATIONS
NH + OH COMBINATIONS
CH + CH COMBINATIONS
CH + CC COMBINATIONS
H2O
ROH
ArOH
RNH2
CONH2
CONHR
ArCH
SH
CH
CH2
RCO2H
RCO2R'
CONH2(R)
CHO
CC
1400
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
2500
(NANOMETERS)

FIG. 32

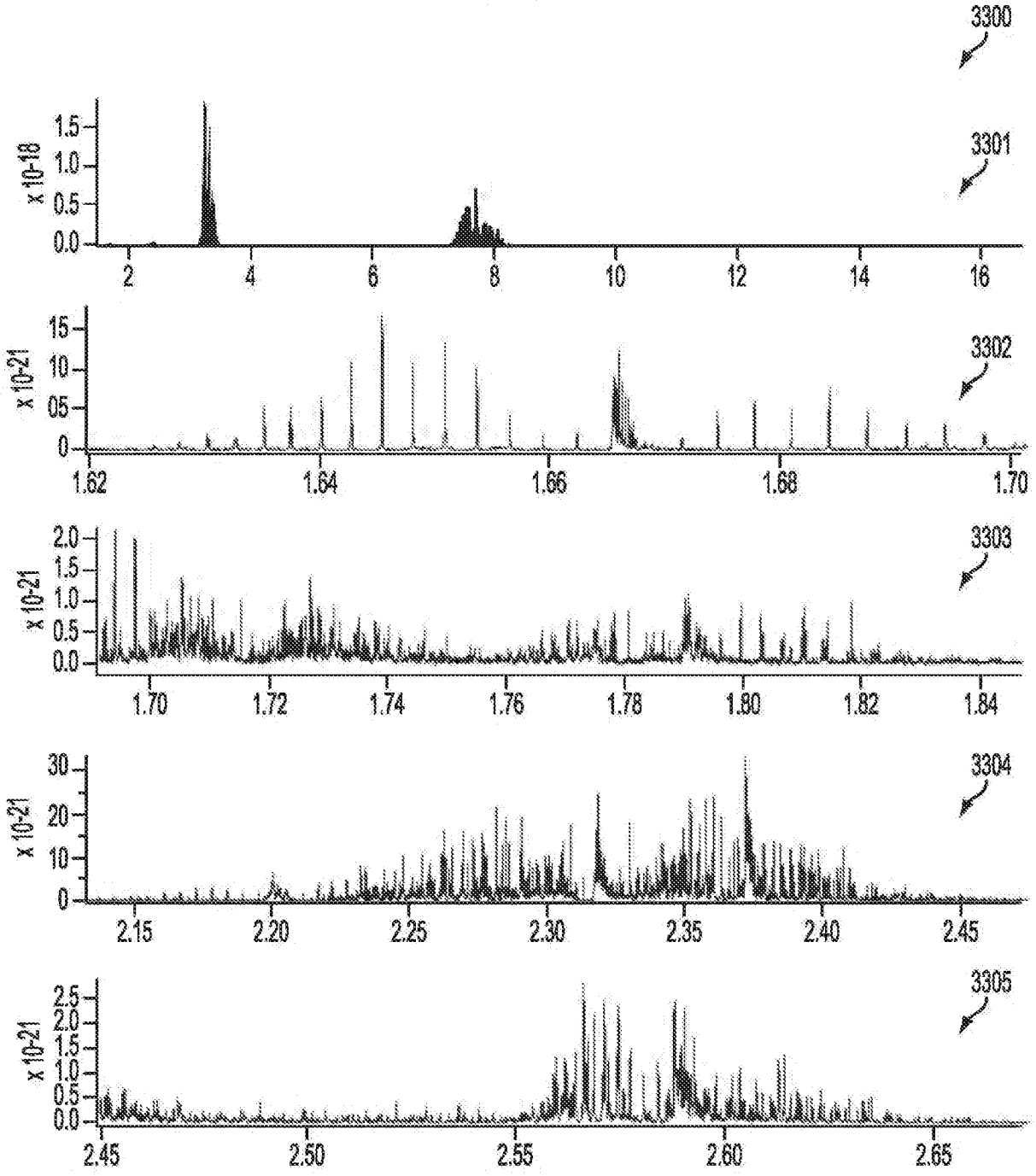

3300
3301
x 10-18
1.5
1.0
0.5
0.0
2
4
6
8
10
12
14
16
3302
x 10-21
15
10
05
0
1.62
1.64
1.66
1.68
1.70
3303
x 10-21
2.0
1.5
1.0
0.5
0.0
1.70
1.72
1.74
1.76
1.78
1.80
1.82
1.84
3304
x 10-21
30
20
10
0
2.15
2.20
2.25
2.30
2.35
2.40
2.45
3305
x 10-21
2.5
2.0
1.5
1.0
0.5
0.0
2.45
2.50
2.55
2.60
2.65

FIG. 33A

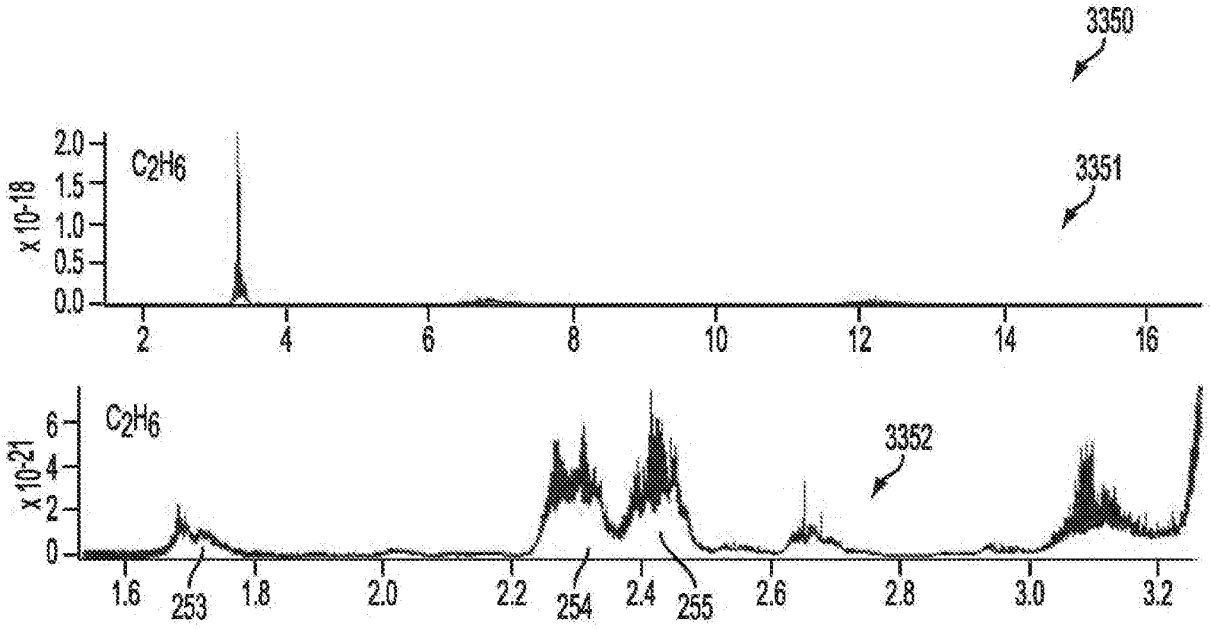

3350
3351
C_2H_6
x 10-18
2.0
1.5
1.0
0.5
0.0
2
4
6
8
10
12
14
16
C_2H_6
x 10-21
6
4
2
0
3352
1.6
253
1.8
2.0
2.2
254
2.4
255
2.6
2.8
3.0
3.2

FIG. 33B

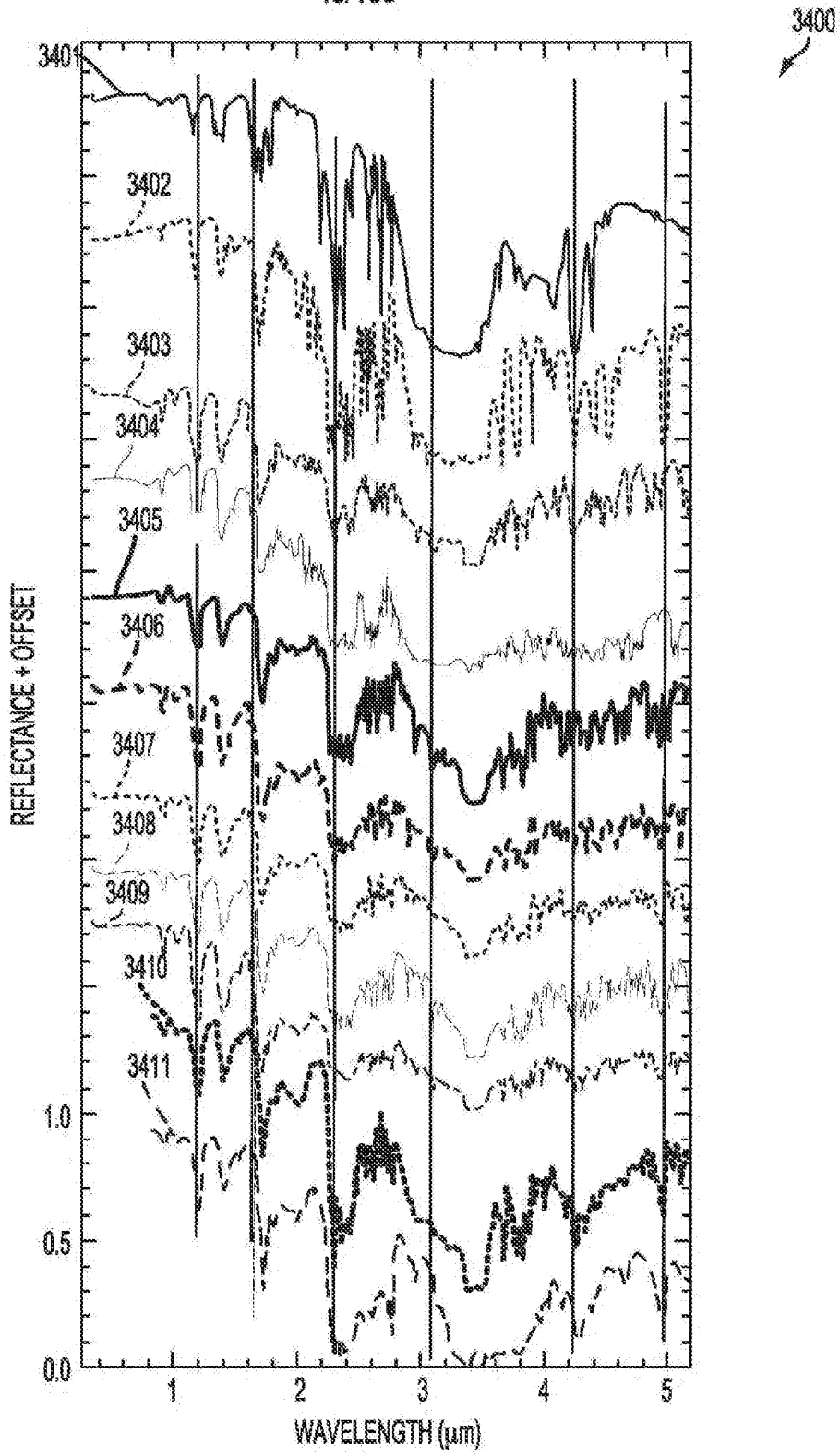

3400
3401
3402
3403
3404
3405
3406
3407
3408
3409
3410
3411
REFLECTANCE + OFFSET
1.0
0.5
0.0
1
2
3
4
5
WAVELENGTH (μm)

FIG.34

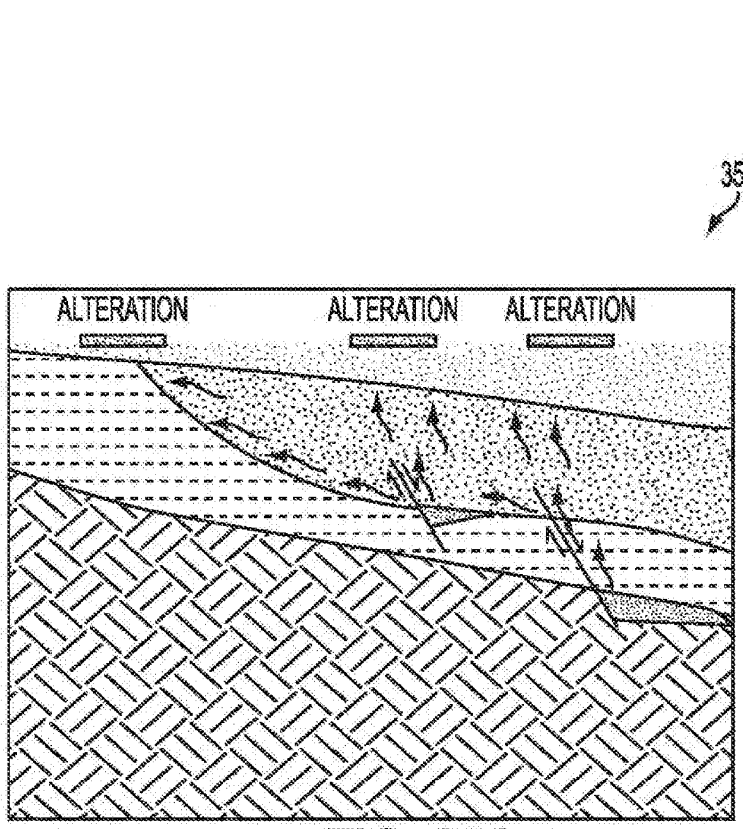


FIG. 35A

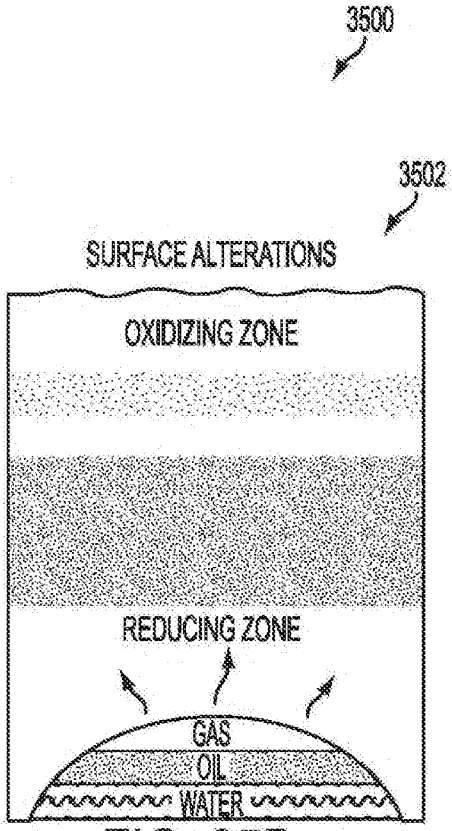


FIG. 35B

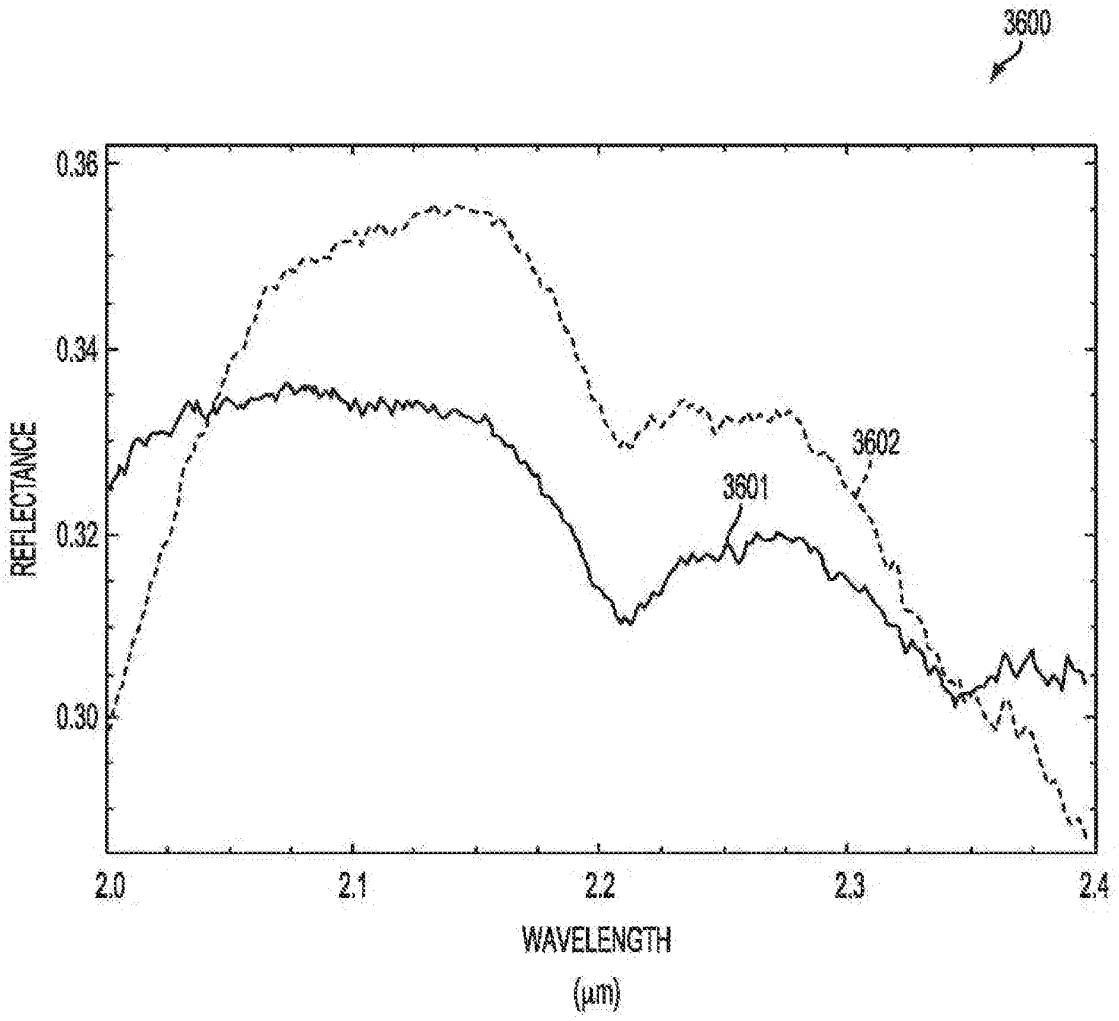

3600
0.36
0.34
0.32
0.30
REFLECTANCE
3602
3601
2.0
2.1
2.2
2.3
2.4
WAVELENGTH
(μm)

FIG. 36A

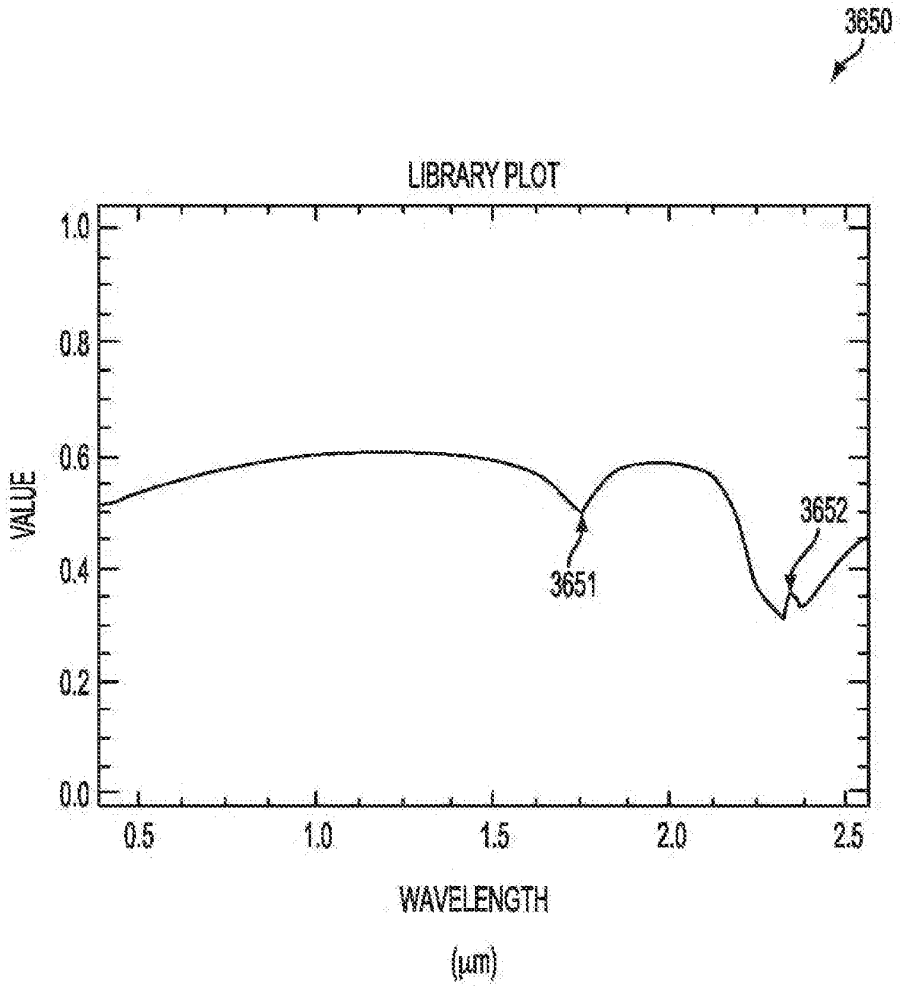

3650
LIBRARY PLOT
1.0
0.8
0.6
0.4
0.2
0.0
VALUE
3651
3652
0.5
1.0
1.5
2.0
2.5
WAVELENGTH
(μm)

FIG. 36B

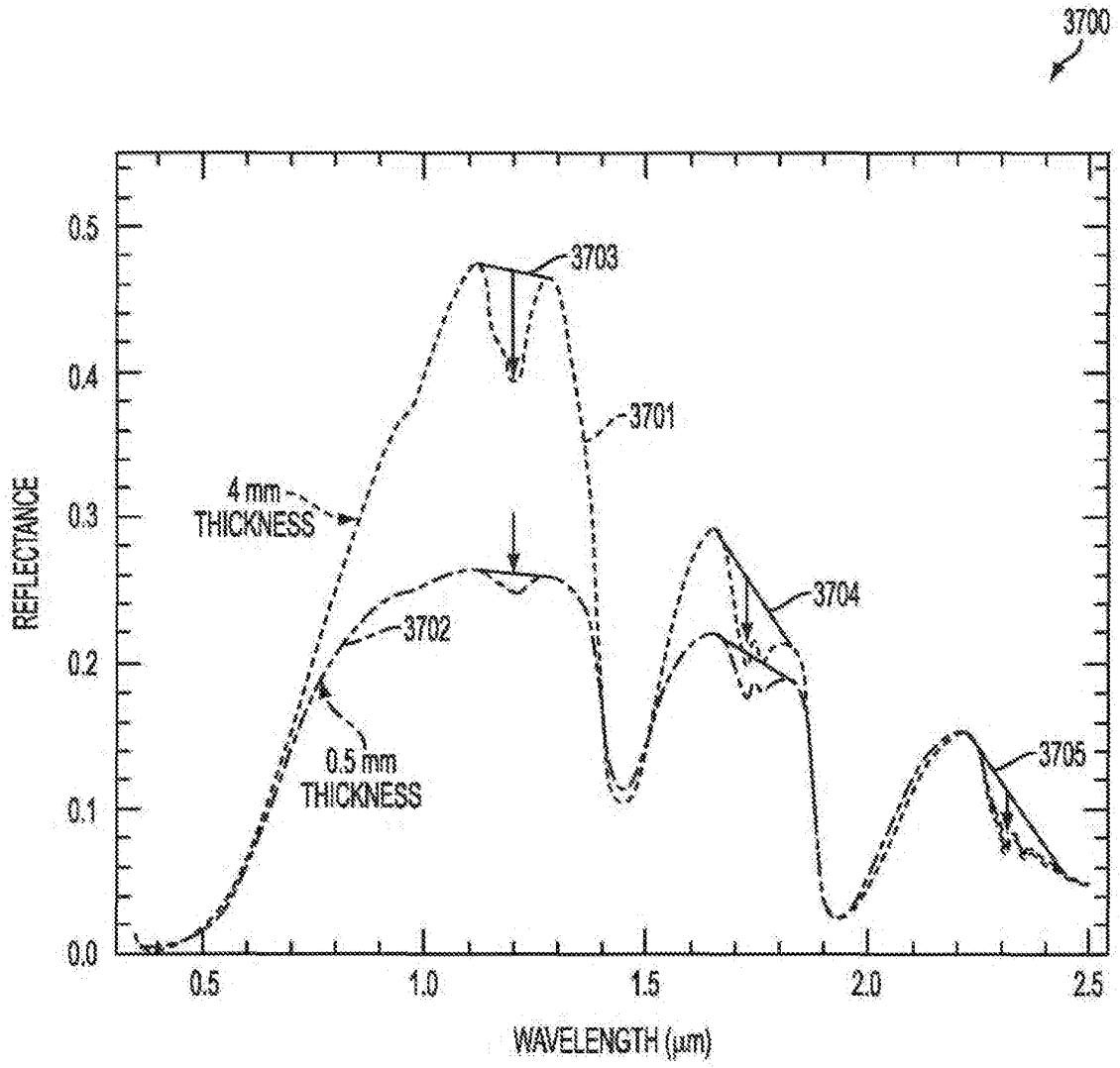

3700
3703
3701
4 mm
THICKNESS
3704
3702
0.5 mm
THICKNESS
3705
REFLECTANCE
0.0
0.1
0.2
0.3
0.4
0.5
0.5
1.0
1.5
2.0
2.5
WAVELENGTH (μm)

FIG. 37

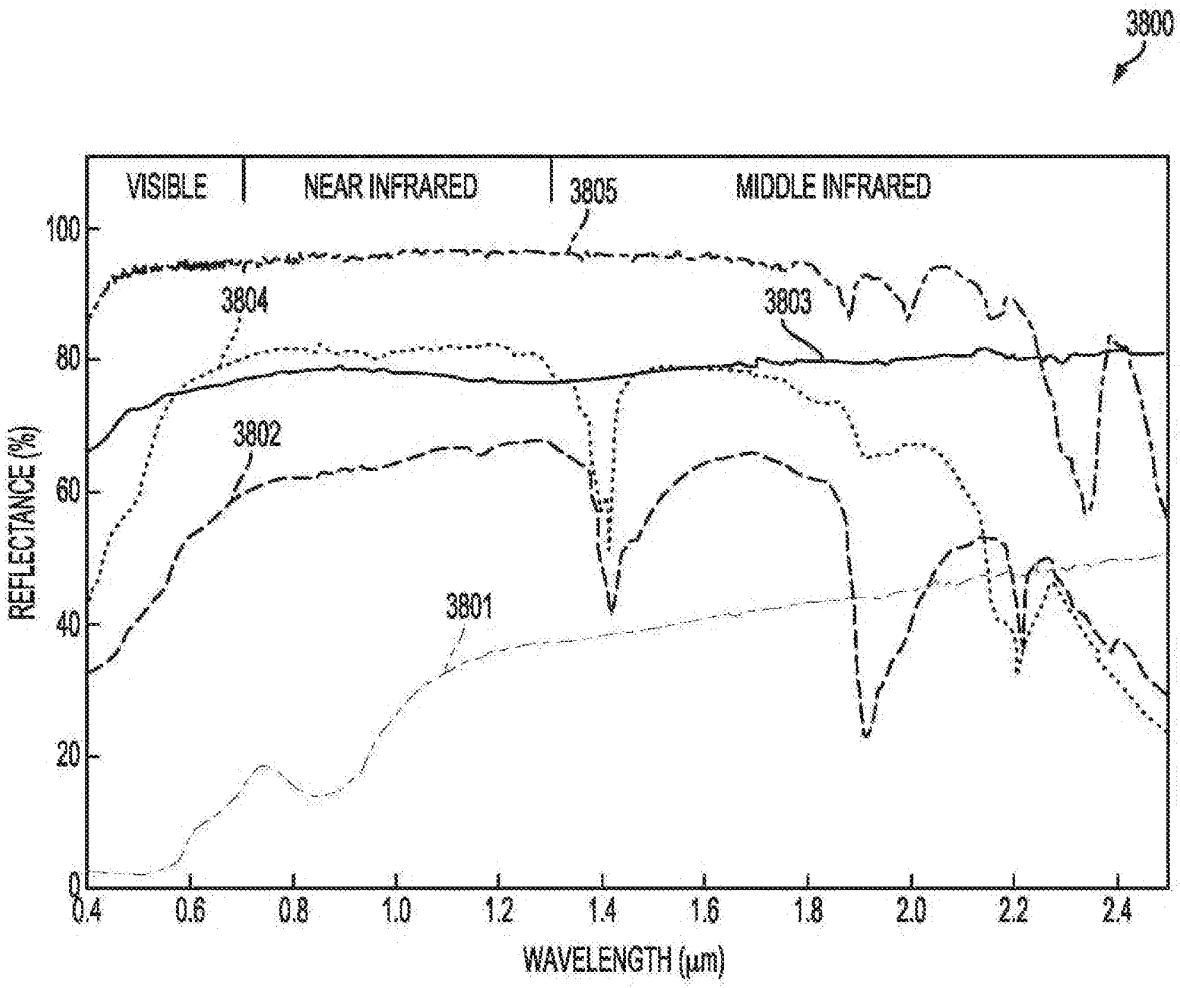

3800
VISIBLE
NEAR INFRARED
MIDDLE INFRARED
3805
3804
3803
3802
3801
REFLECTANCE (%)
100
80
60
40
20
0
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
WAVELENGTH (μm)

FIG. 38

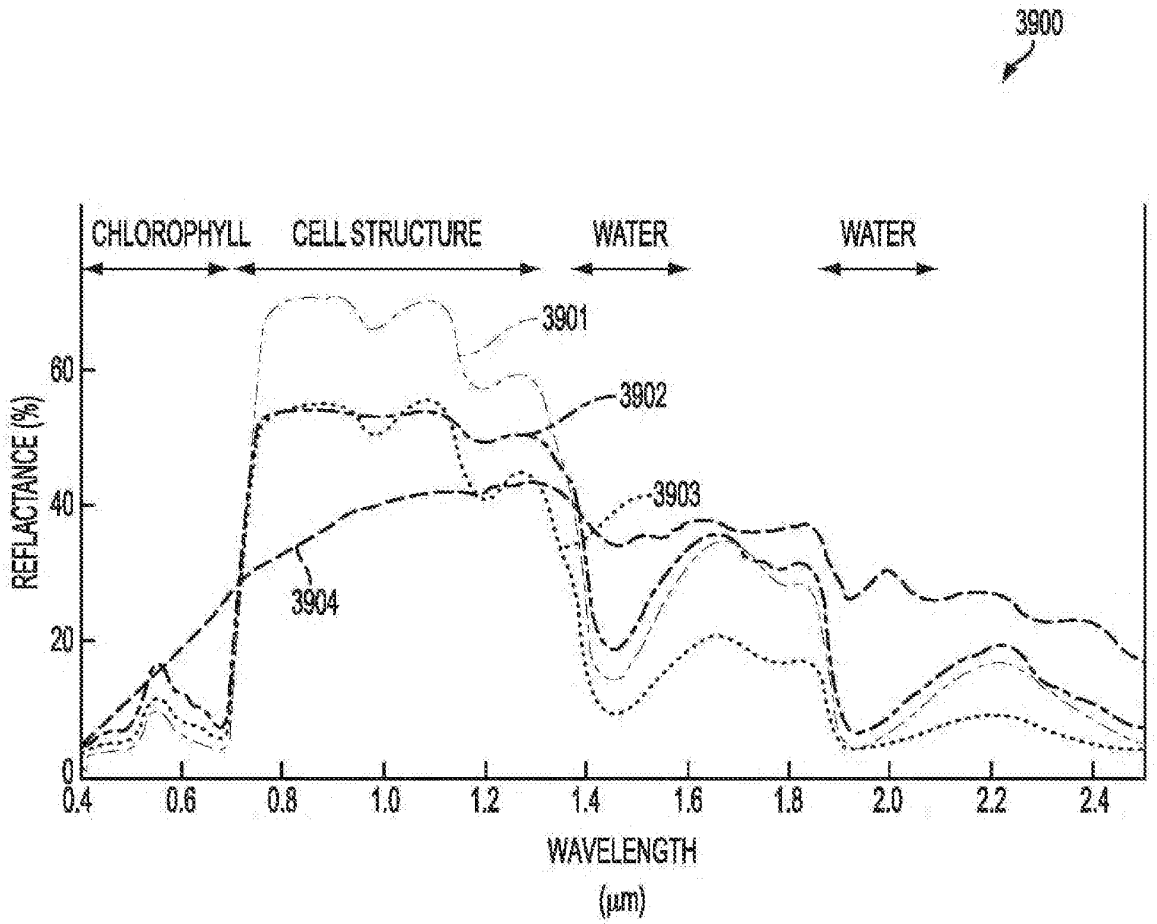

3900
CHLOROPHYLL
CELL STRUCTURE
WATER
WATER
3901
3902
3903
3904
REFLACTANCE (%)
0
20
40
60
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
WAVELENGTH
(μm)

FIG. 39

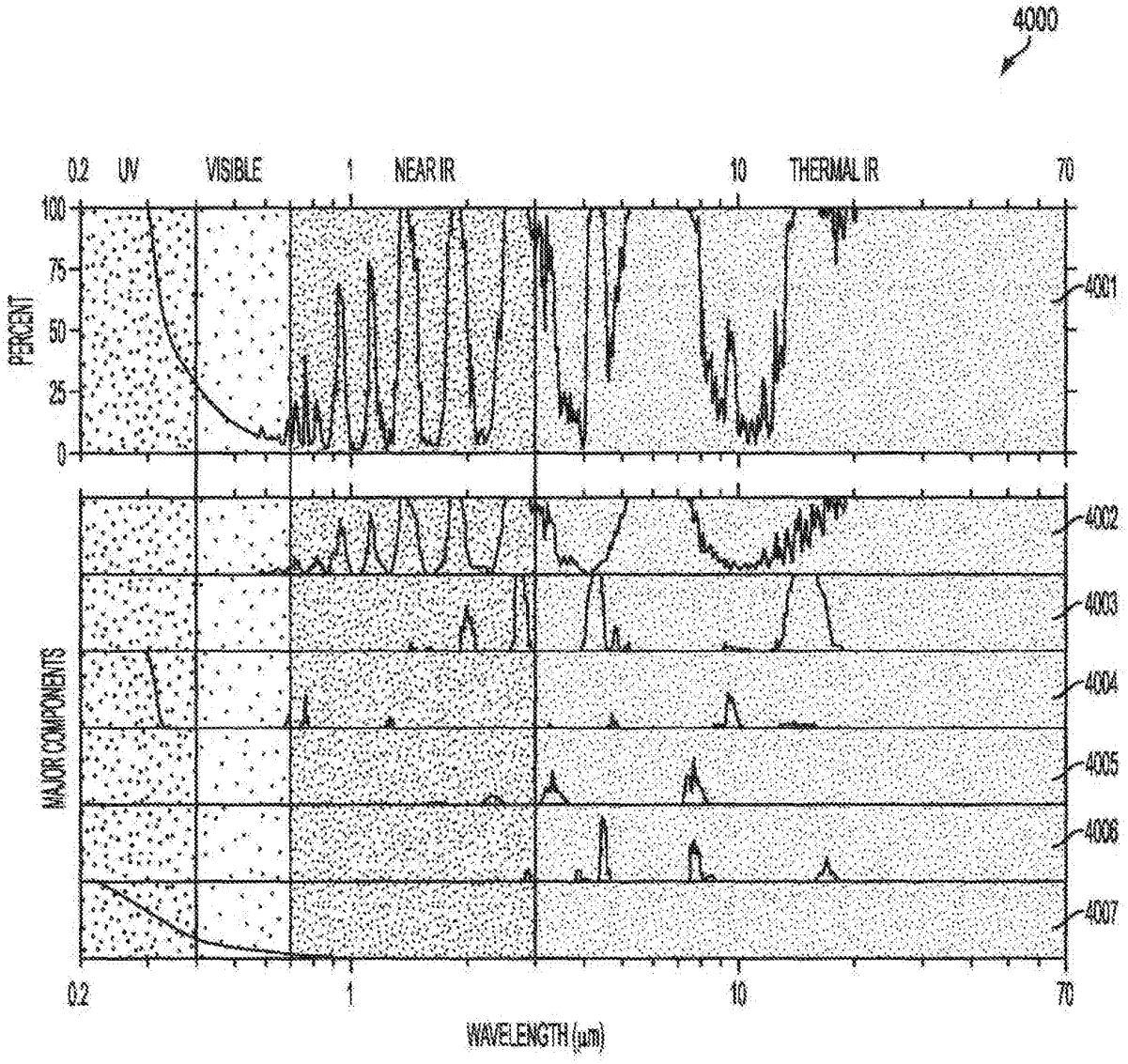

4000
0.2
UV
VISIBLE
1
NEAR IR
10
THERMAL IR
70
100
75
50
25
0
PERCENT
4001
4002
4003
4004
4005
4006
4007
MAJOR COMPONENTS
0.2
1
10
70
WAVELENGTH (μm)

FIG. 40

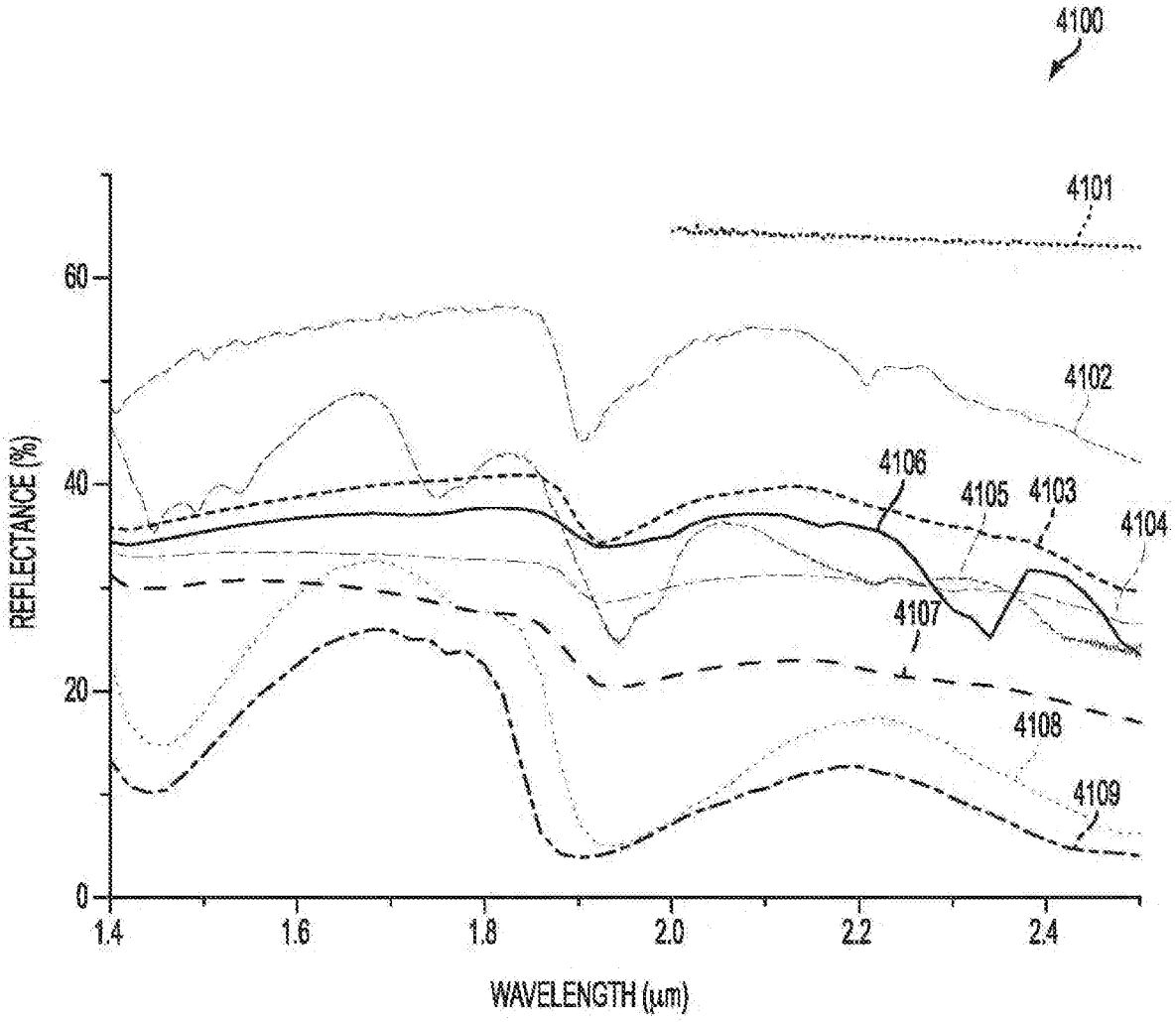

4100
4101
4102
4103
4104
4105
4106
4107
4108
4109
REFLECTANCE (%)
0
20
40
60
1.4
1.6
1.8
2.0
2.2
2.4
WAVELENGTH (μm)

FIG. 41

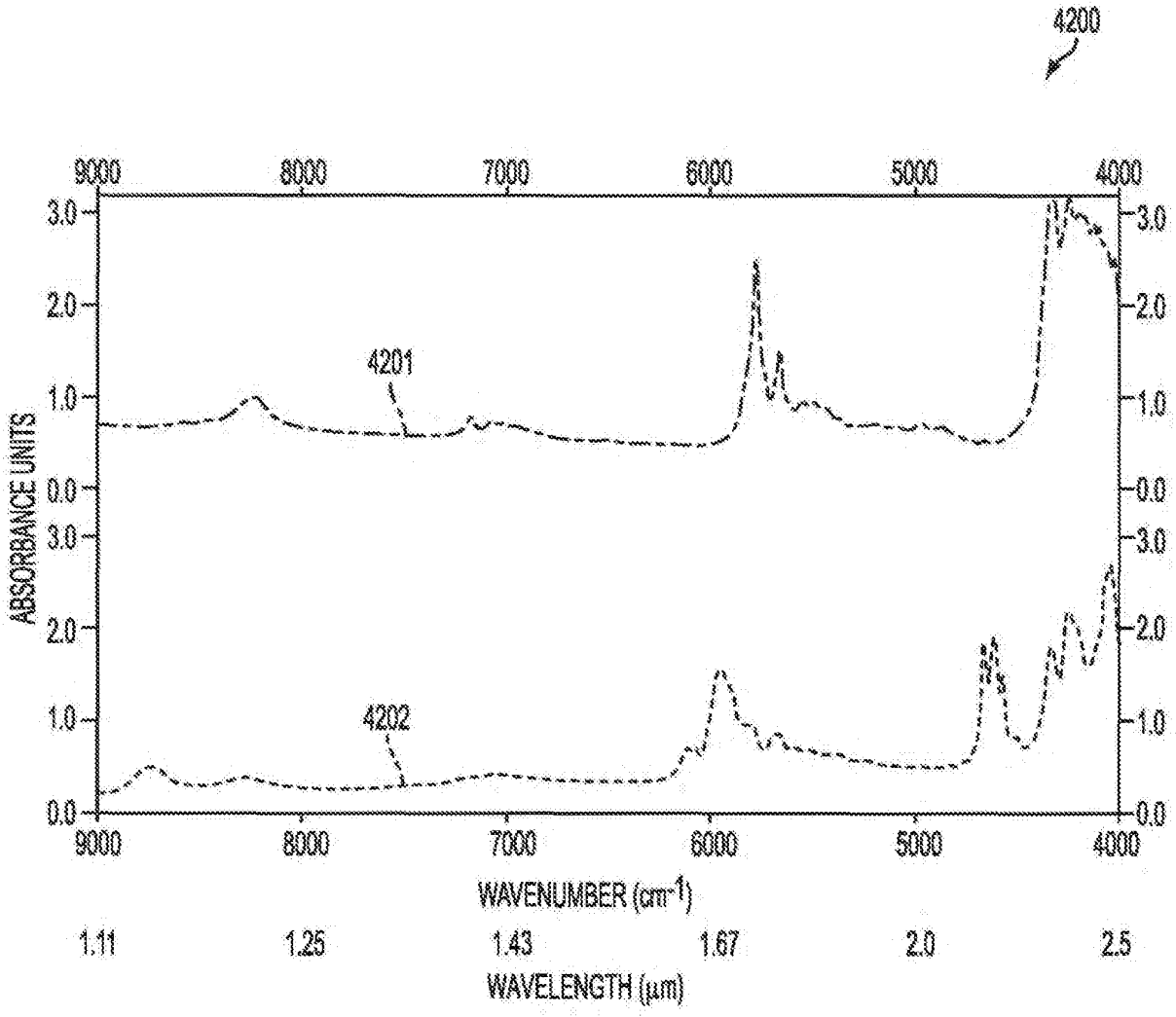

4200
9000
8000
7000
6000
5000
4000
3.0
2.0
1.0
0.0
4201
4202
ABSORBANCE UNITS
WAVENUMBER (cm-1)
1.11
1.25
1.43
1.67
2.0
2.5
WAVELENGTH (μm)

FIG. 42

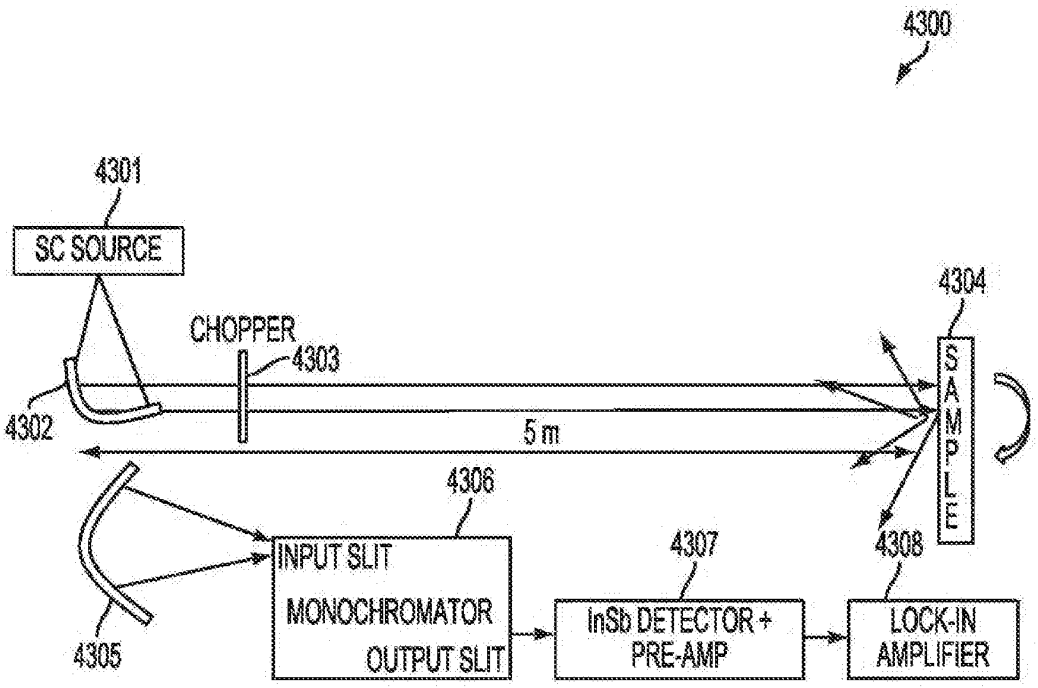

4300
4301
SC SOURCE
CHOPPER
4303
4302
5 m
4304
SAMPLE
4306
INPUT SLIT
MONOCHROMATOR
OUTPUT SLIT
4307
InSb DETECTOR +
PRE-AMP
4308
LOCK-IN
AMPLIFIER
4305

FIG. 43

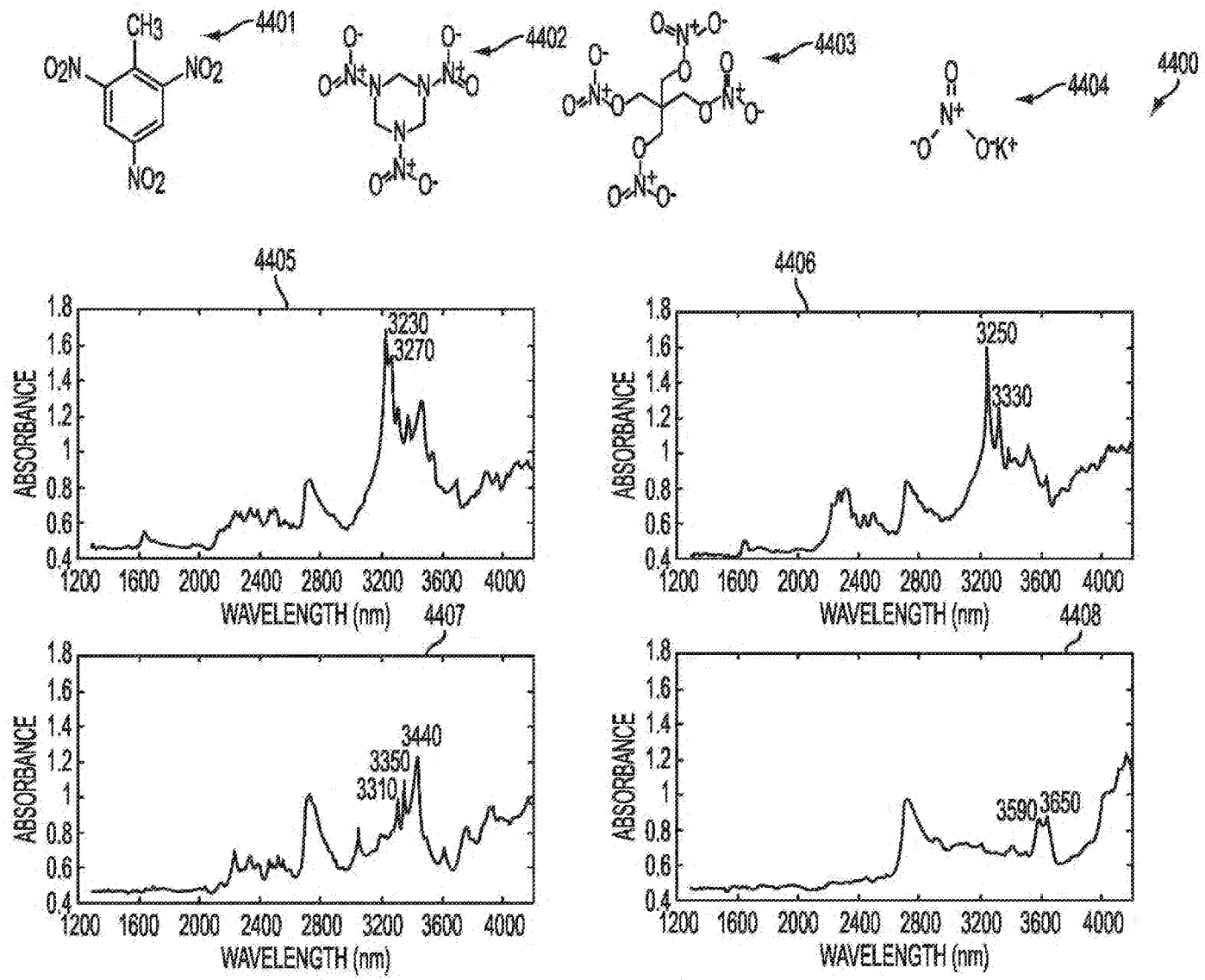

4400
4401
4402
4403
4404
4405
4406
4407
4408
ABSORBANCE
WAVELENGTH (nm)
3230
3270
3250
3330
3440
3350
3310
3590
3650

FIG. 44

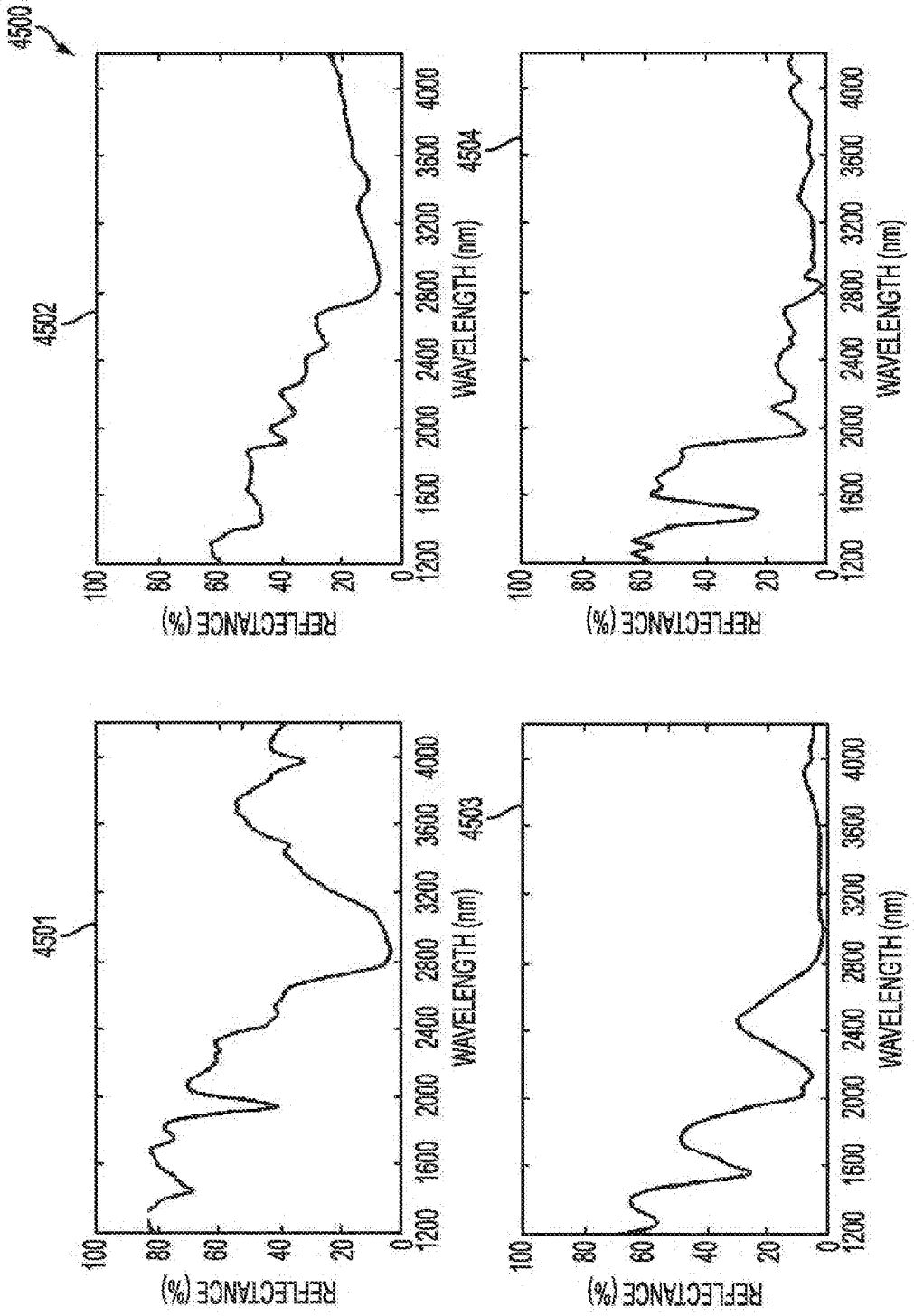

4500
4501
4502
4503
4504
REFLECTANCE (%)
WAVELENGTH (nm)
100
80
60
40
20
0
1200
1600
2000
2400
2800
3200
3600
4000

FIG. 45A

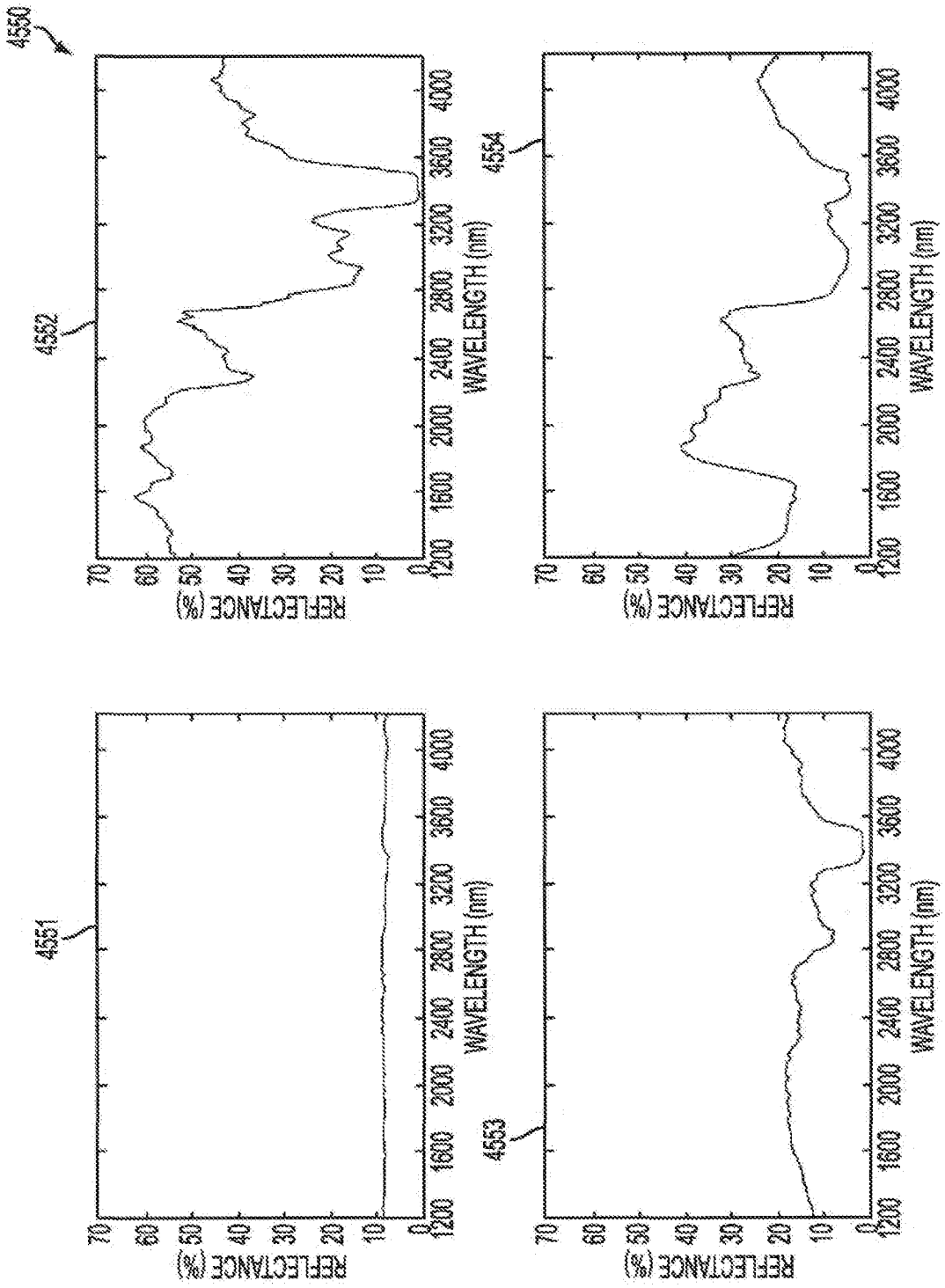

4550
4551
4552
4553
4554
REFLECTANCE (%)
WAVELENGTH (nm)
70
60
50
40
30
20
10
0
1200
1600
2000
2400
2800
3200
3600
4000

FIG. 45B

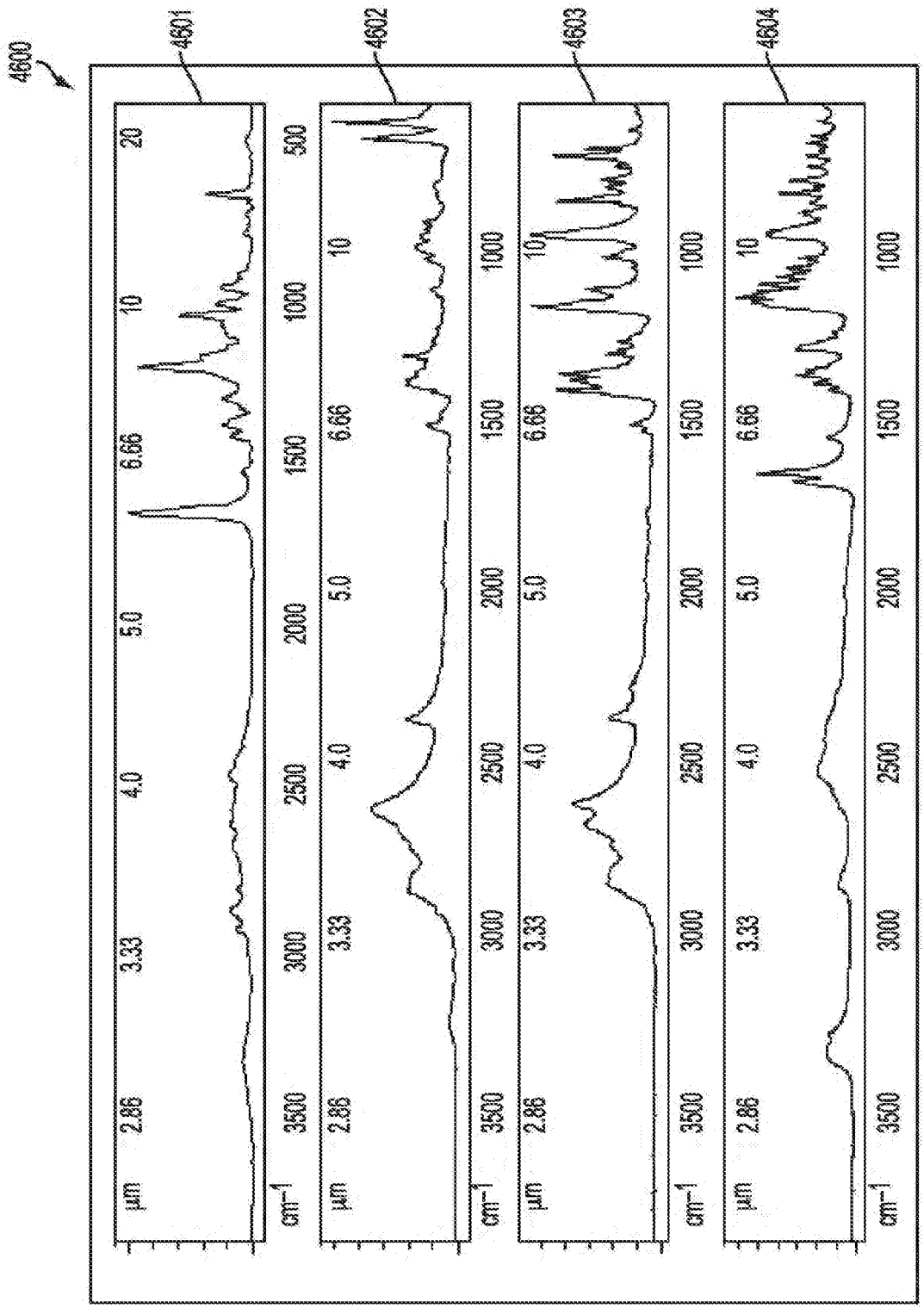

4600
4601
4602
4603
4604
μm
2.86
3.33
4.0
5.0
6.66
10
20
cm⁻¹
3500
3000
2500
2000
1500
1000
500

FIG. 46

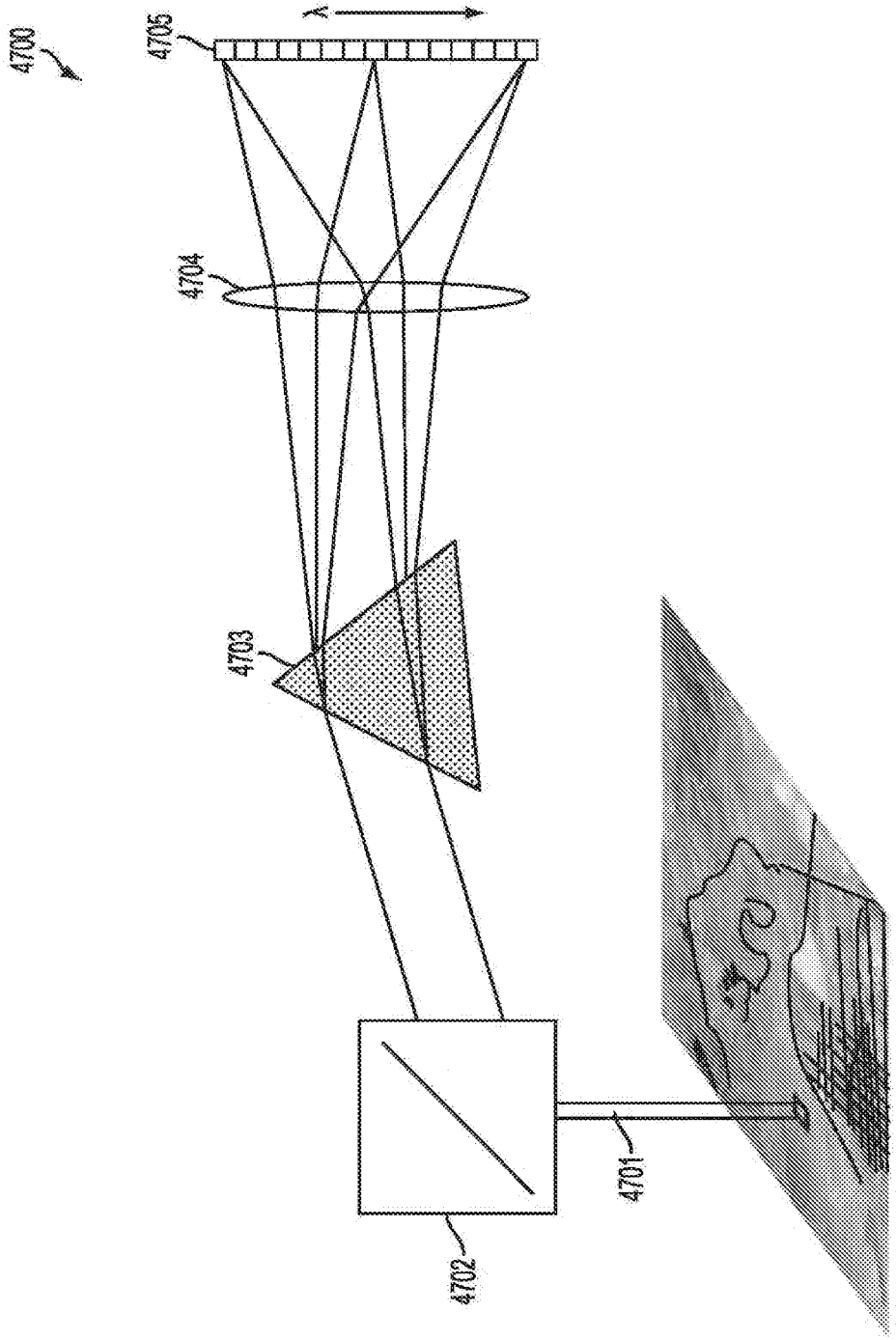


FIG. 47A

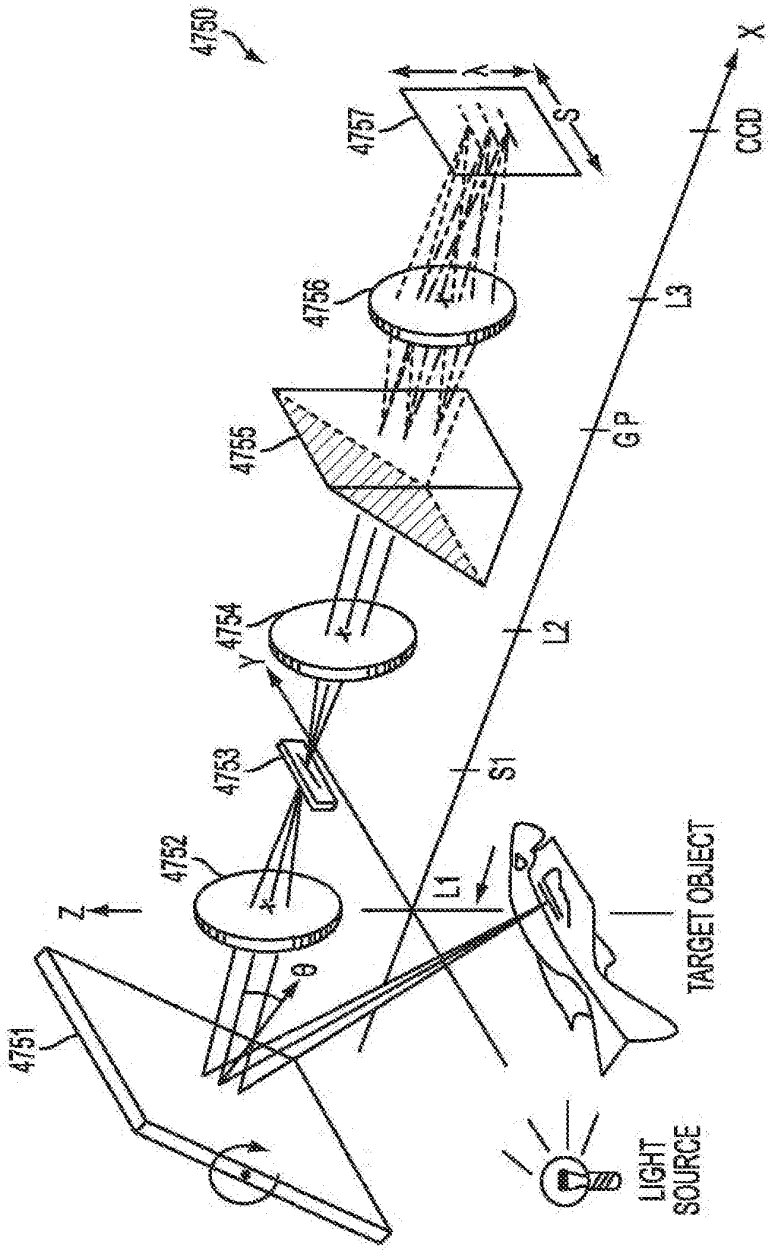

4750
4751
Z
4752
θ
4753
Y
4754
4755
4756
4757
λ
S
X
CCD
L3
GP
L2
S1
L1
TARGET OBJECT
LIGHT SOURCE

FIG. 47B

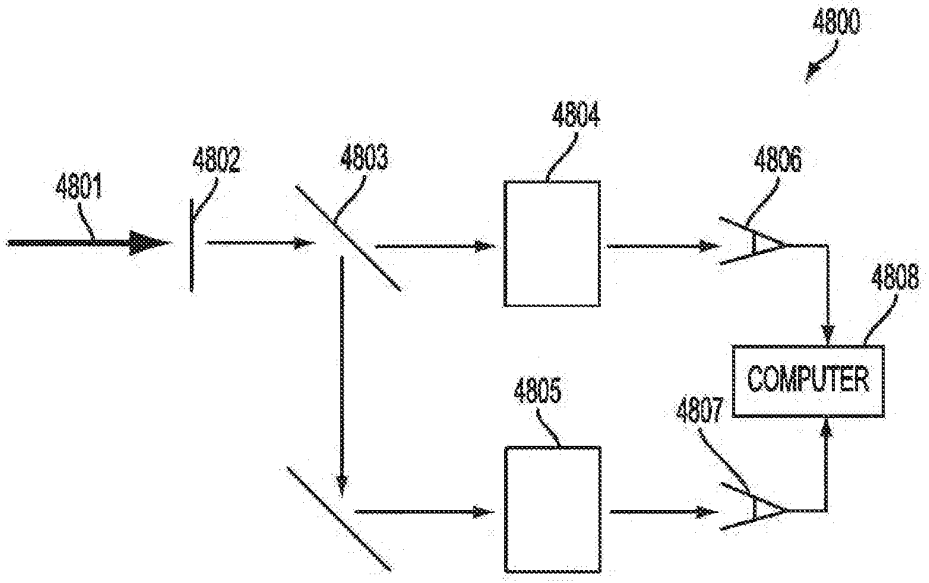


FIG. 48

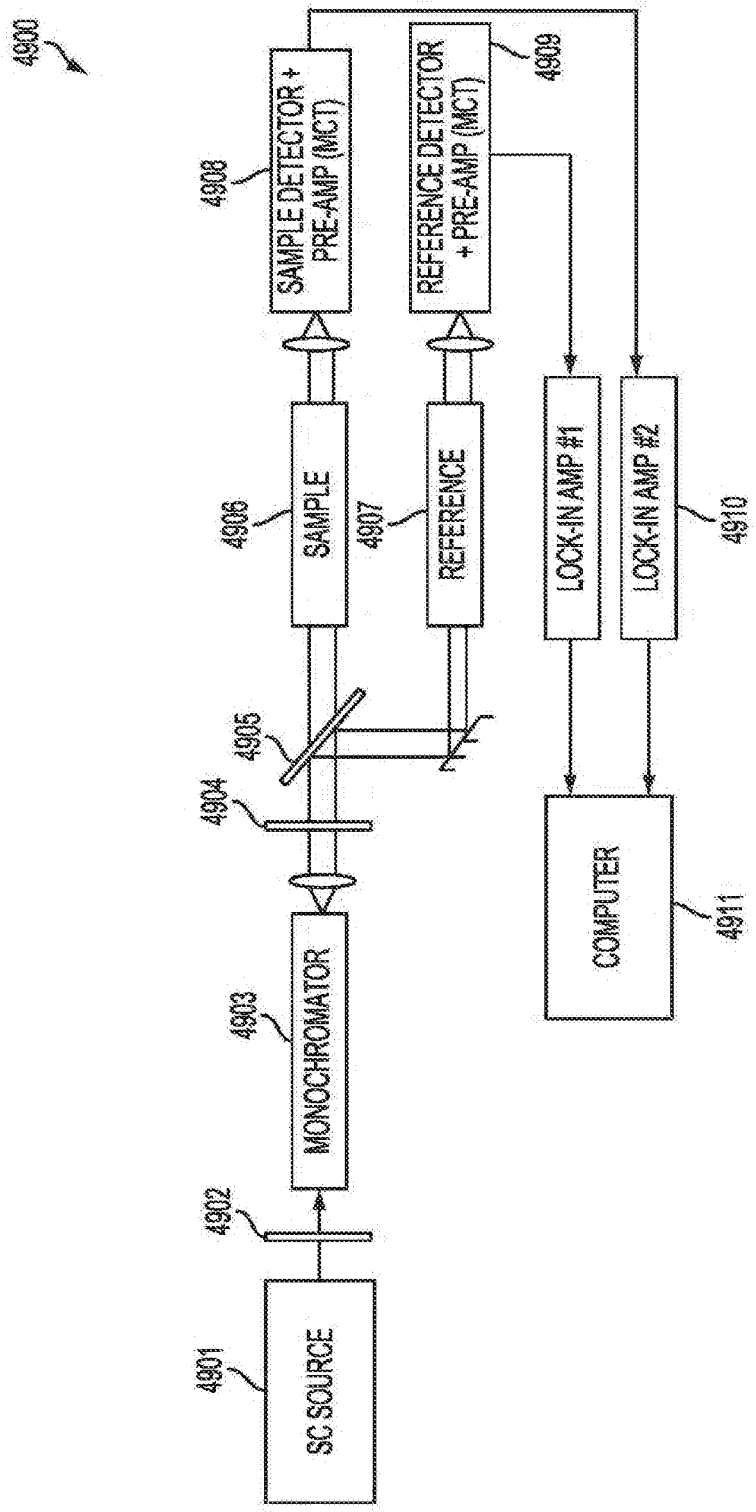

4900
SC SOURCE
4901
4902
MONOCHROMATOR
4903
4904
4905
SAMPLE
4906
REFERENCE
4907
SAMPLE DETECTOR + PRE-AMP (MCT)
4908
REFERENCE DETECTOR + PRE-AMP (MCT)
4909
LOCK-IN AMP #1
LOCK-IN AMP #2
4910
COMPUTER
4911

FIG. 49

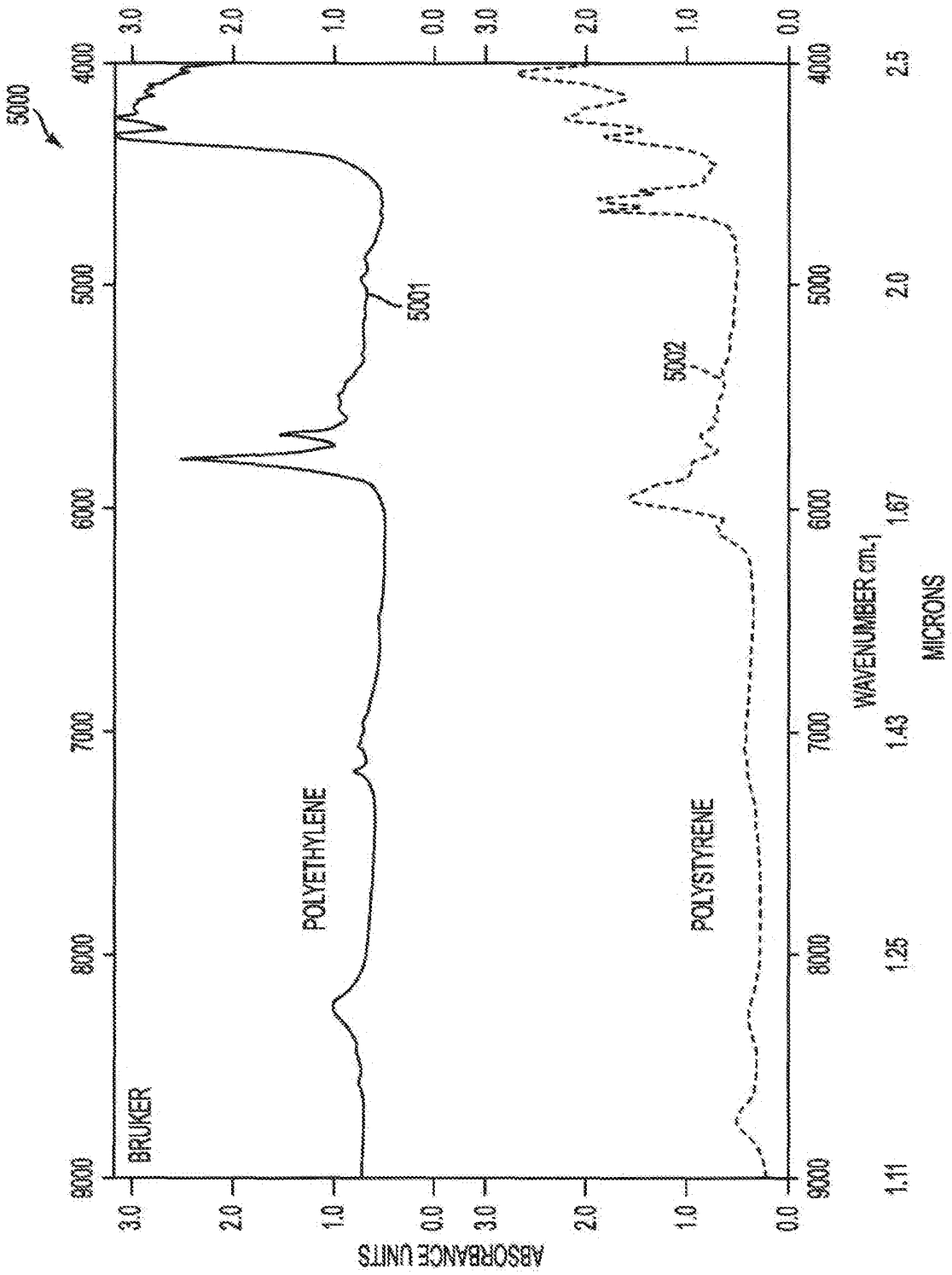

5000
BRUKER
POLYETHYLENE
5001
POLYSTYRENE
5002
ABSORBANCE UNITS
3.0
2.0
1.0
0.0
9000
8000
7000
6000
5000
4000
WAVENUMBER cm.-1
MICRONS
1.11
1.25
1.43
1.67
2.0
2.5

FIG. 50

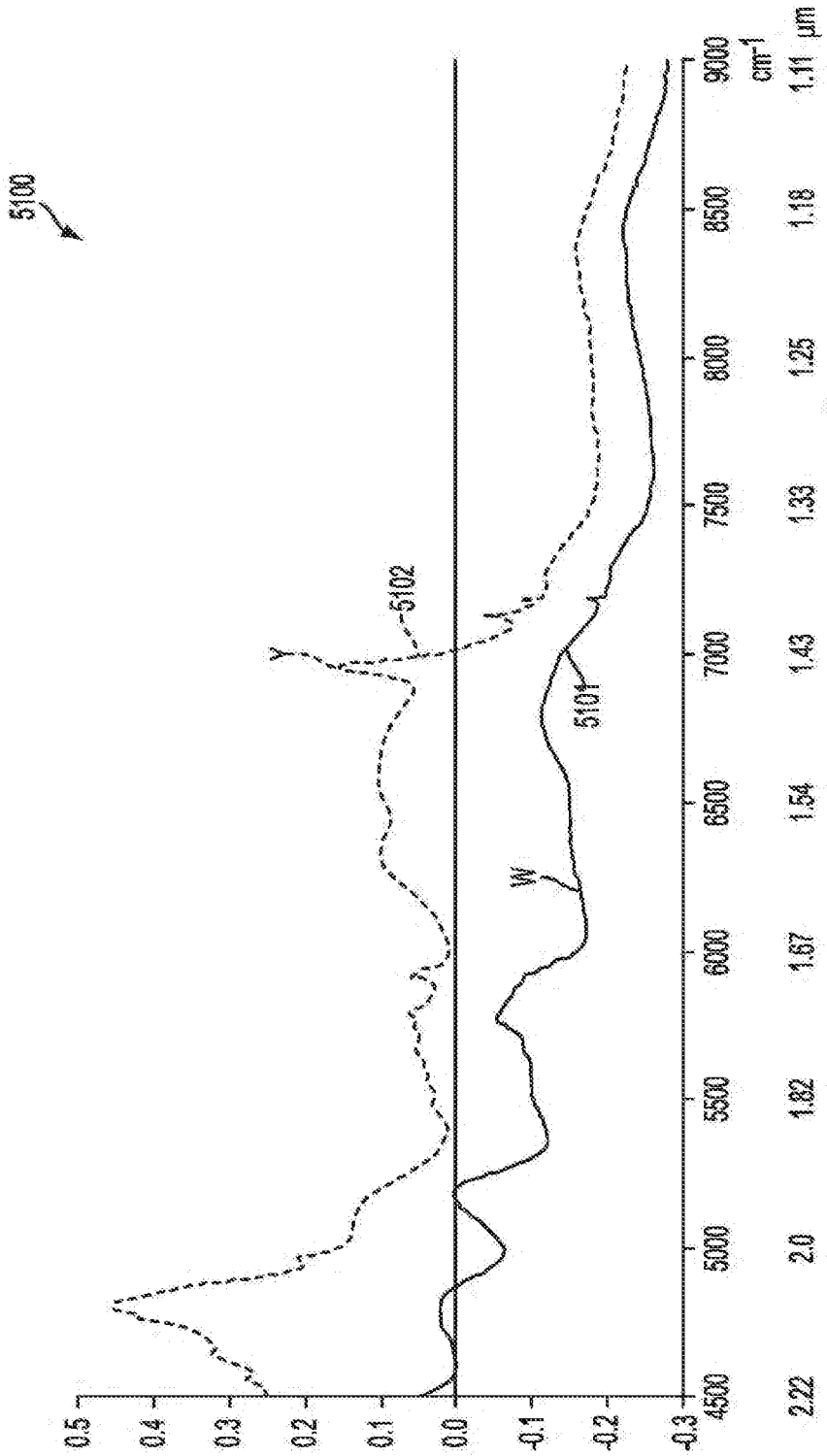

5100
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
4500
5000
5500
6000
6500
7000
7500
8000
8500
9000
cm-1
2.22
2.0
1.82
1.67
1.54
1.43
1.33
1.25
1.18
1.11 µm
Y
5102
W
5101

FIG. 51

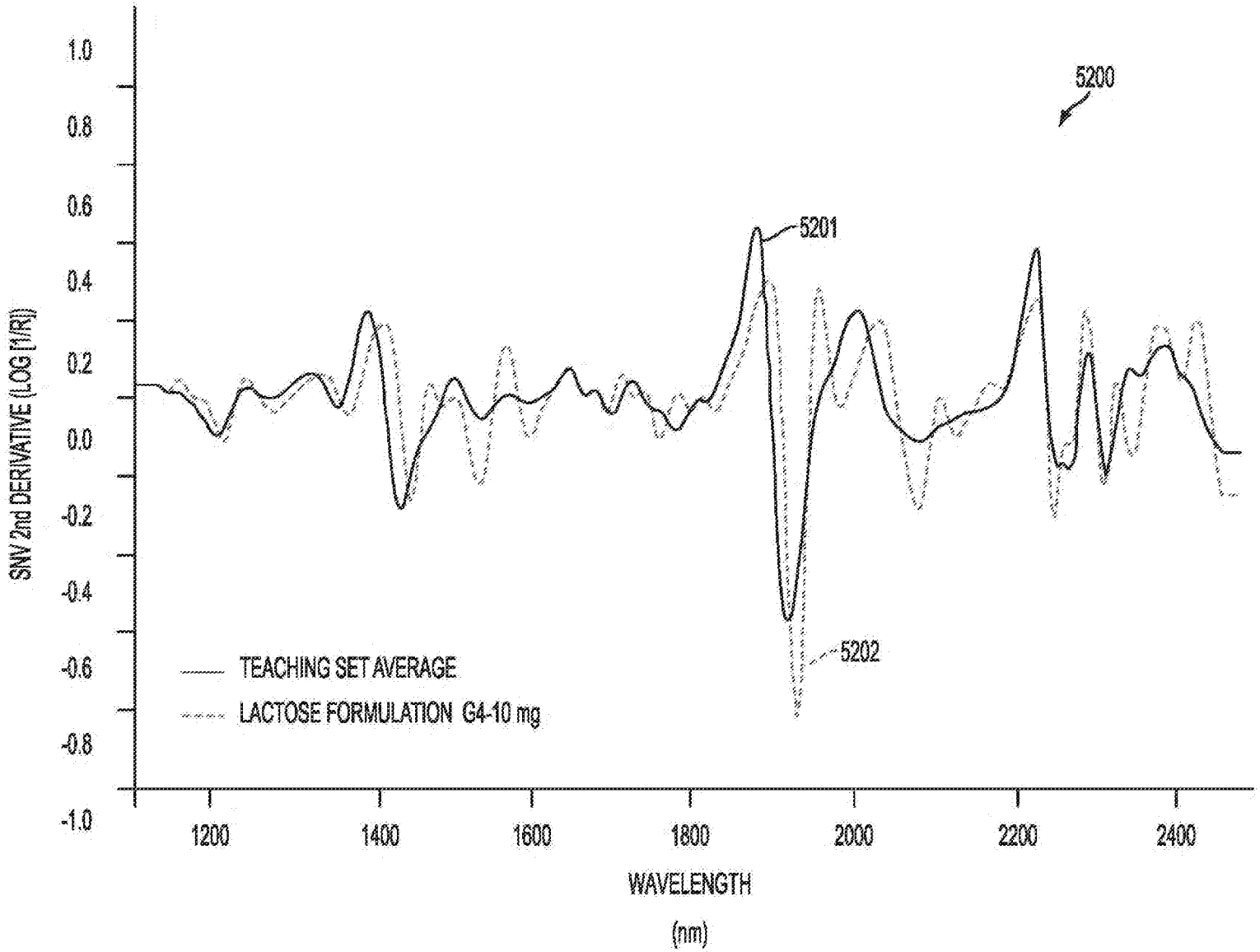

5200
5201
5202
SNV 2nd DERIVATIVE (LOG [1/R])
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
1200
1400
1600
1800
2000
2200
2400
WAVELENGTH
(nm)
TEACHING SET AVERAGE
LACTOSE FORMULATION G4-10 mg

FIG. 52

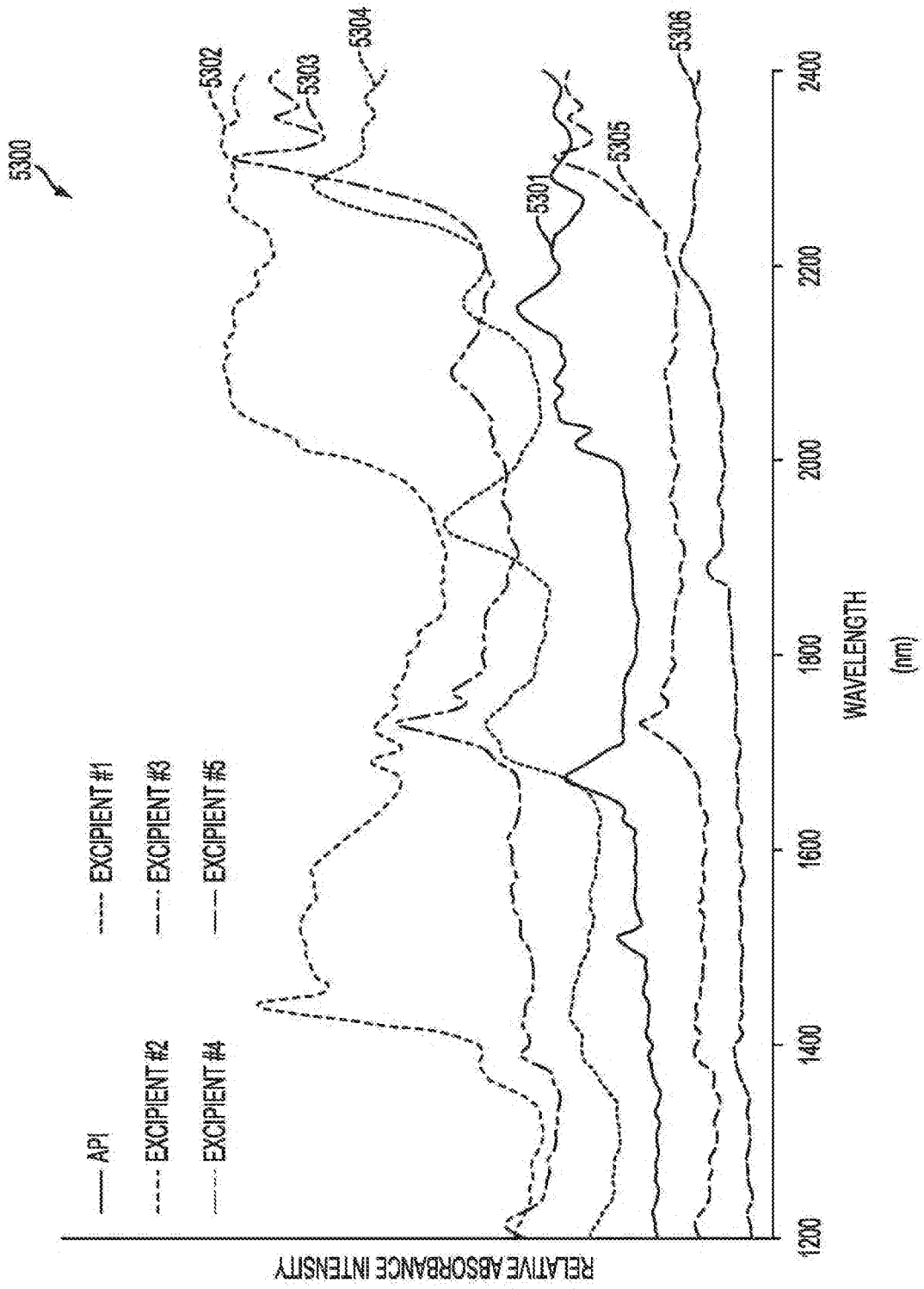

5300
API
EXCIPIENT #1
EXCIPIENT #2
EXCIPIENT #3
EXCIPIENT #4
EXCIPIENT #5
5301
5302
5303
5304
5305
5306
RELATIVE ABSORBANCE INTENSITY
1200
1400
1600
1800
2000
2200
2400
WAVELENGTH
(nm)

FIG. 53

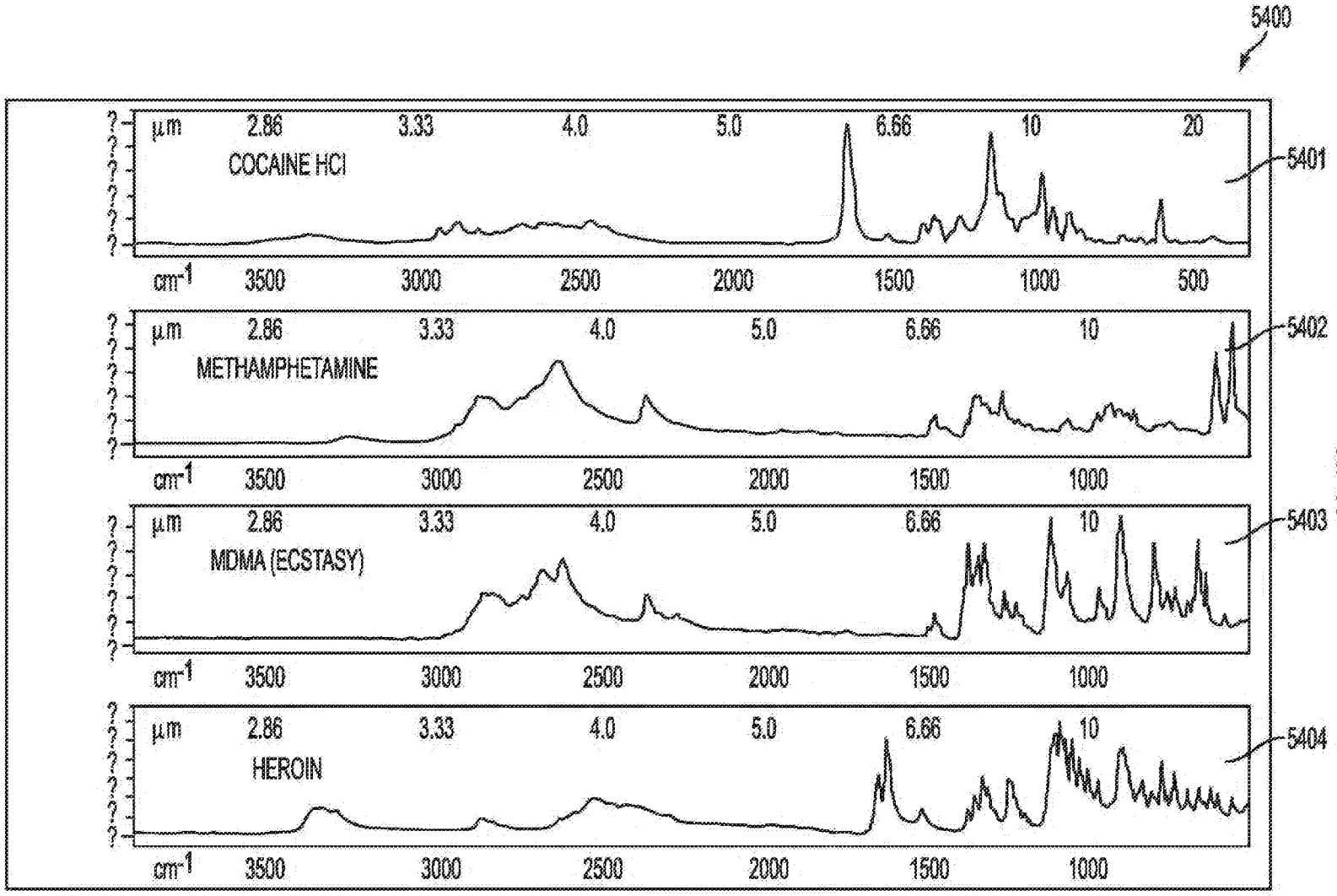

5400
5401
5402
5403
5404
COCAINE HCl
METHAMPHETAMINE
MDMA (ECSTASY)
HEROIN
µm
2.86
3.33
4.0
5.0
6.66
10
20
cm-1
3500
3000
2500
2000
1500
1000
500

FIG. 54

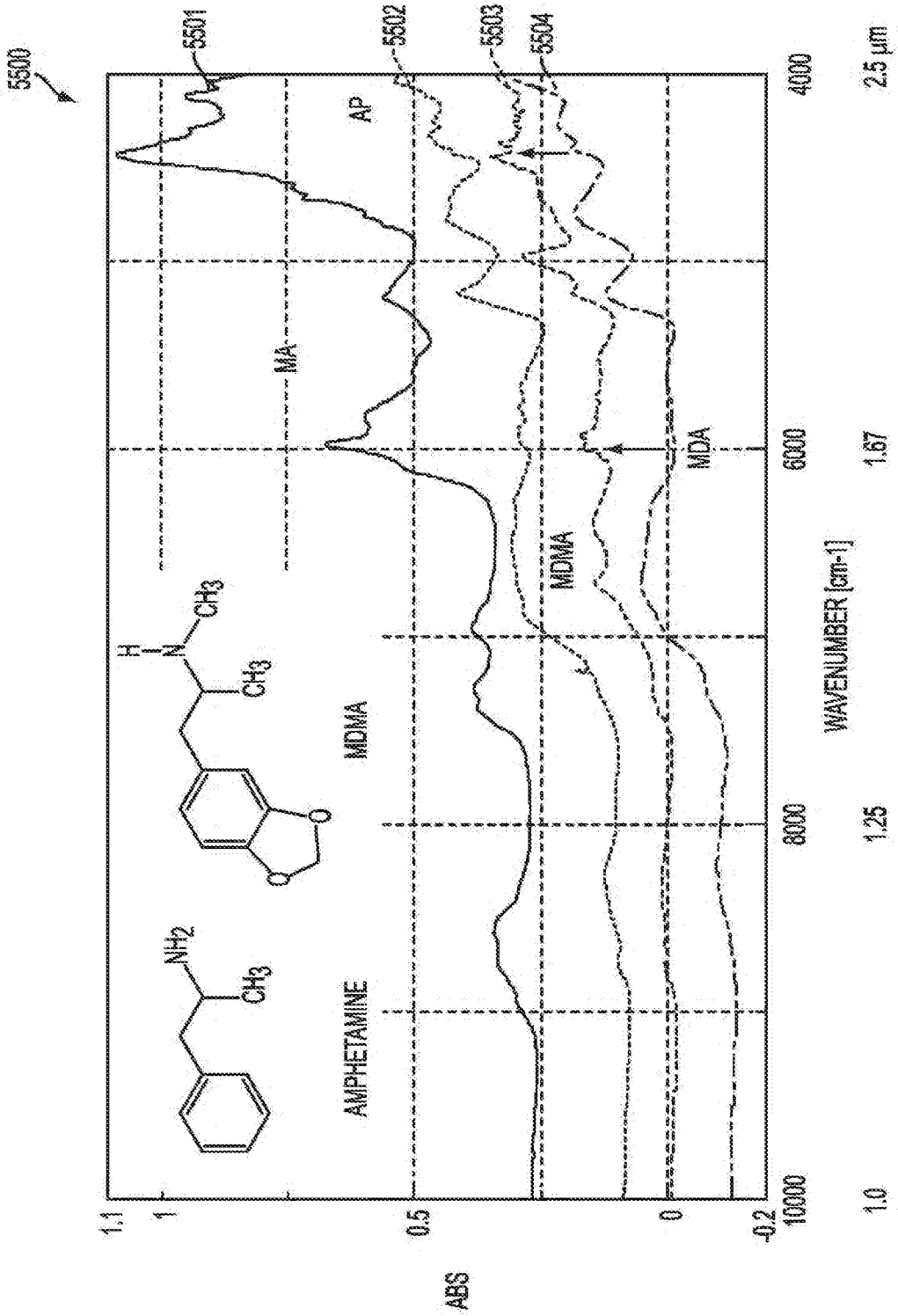

5500
5501
5502
5503
5504
AP
MA
MDA
MDMA
MDMA
AMPHETAMINE
NH2
CH3
H
N
CH3
CH3
O
O
1.1
1
0.5
0
-0.2
ABS
10000
8000
6000
4000
WAVENUMBER [cm-1]
1.0
1.25
1.67
2.5 µm

FIG. 55

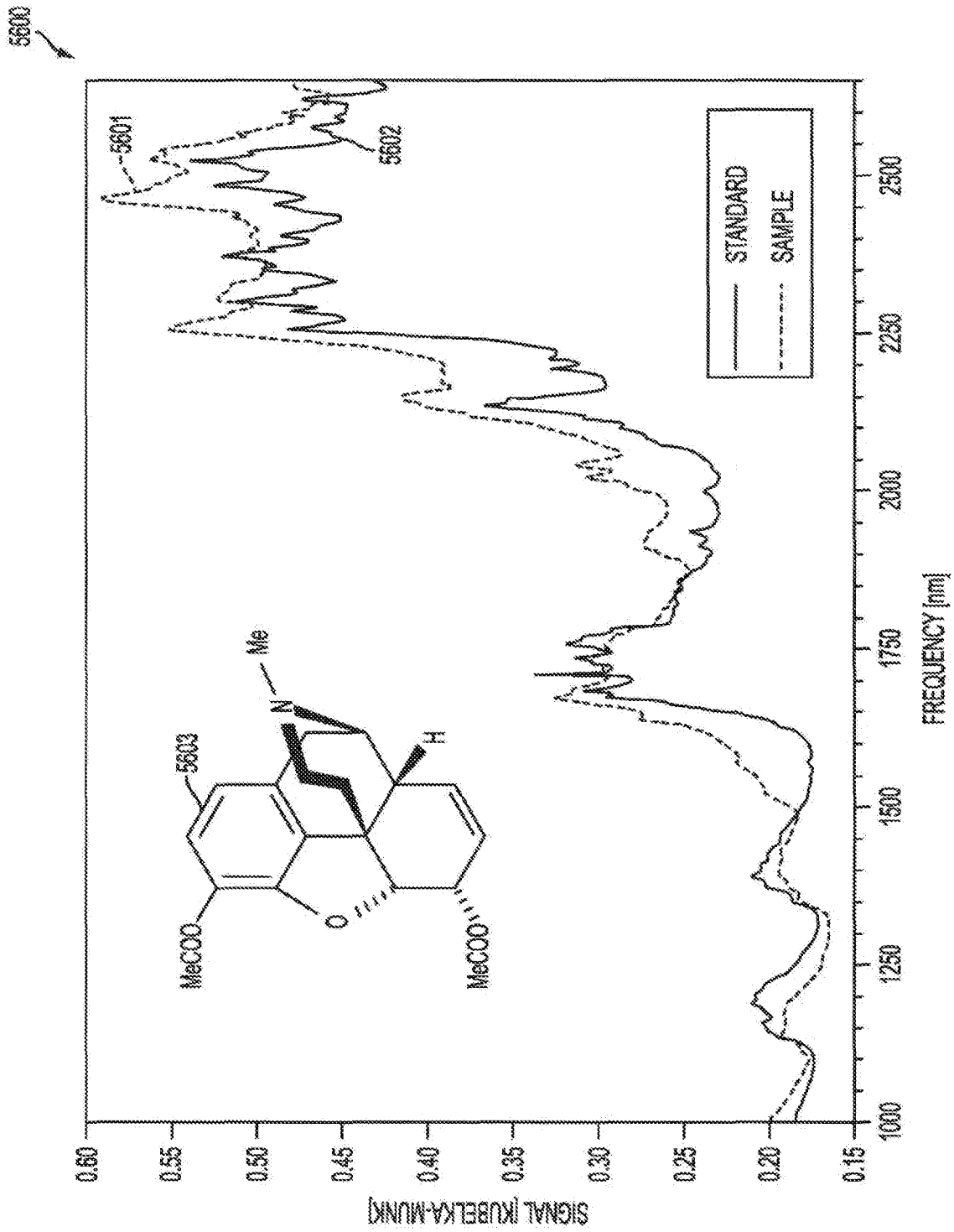

5600
5601
5602
5603
STANDARD
SAMPLE
Me
N
H
O
MeCOO
MeCOO
SIGNAL [KUBELKA-MUNK]
FREQUENCY [nm]
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
1000
1250
1500
1750
2000
2250
2500

FIG. 56

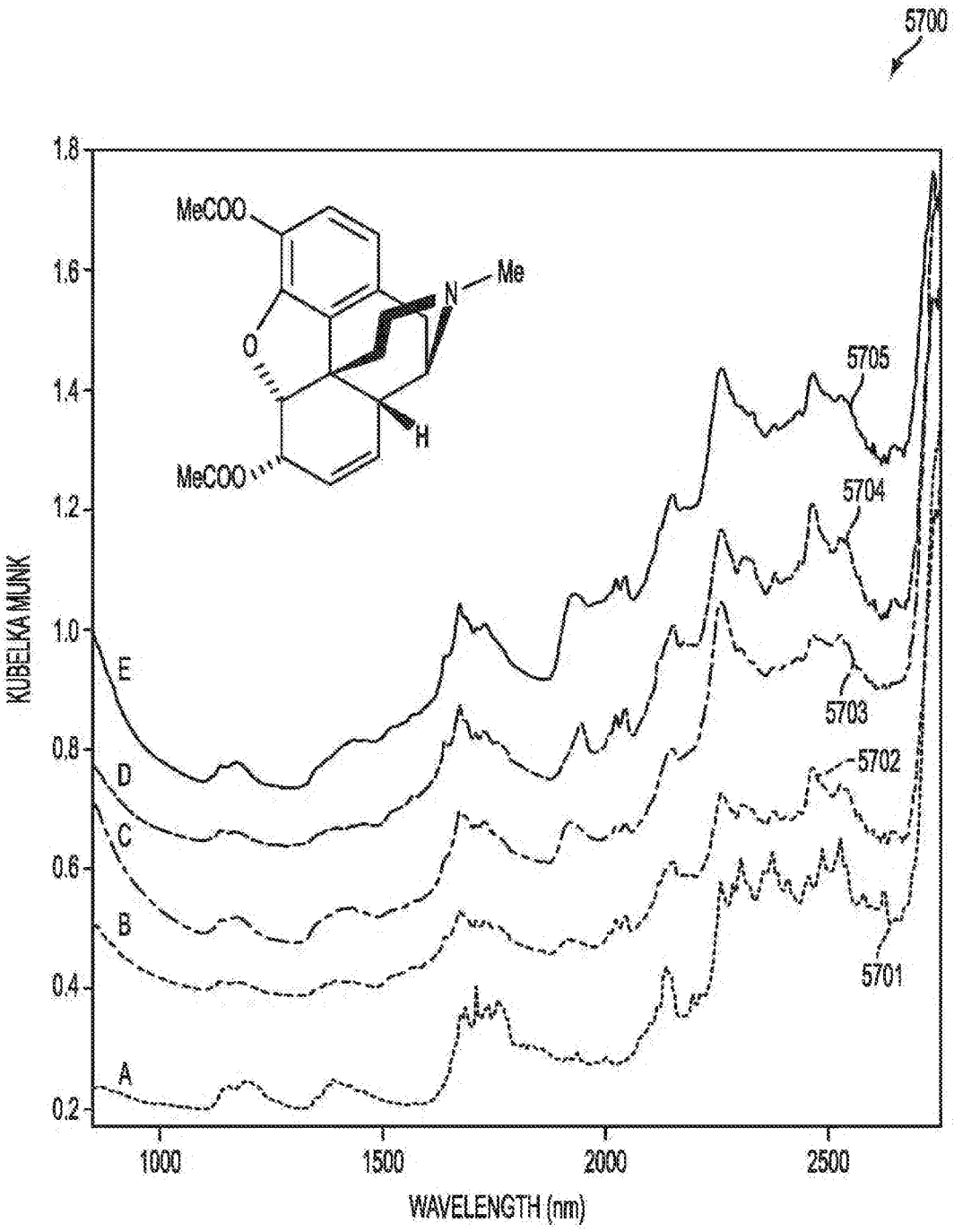

5700
MeCOO
N
Me
O
H
MeCOO
5705
5704
5703
5702
5701
E
D
C
B
A
KUBELKA MUNK
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
1000
1500
2000
2500
WAVELENGTH (nm)

FIG. 57

5800

TENTATIVE FREQUENCIES OF HEROIN BANDS (nm)	ACTUALLY MEASURED PEAK FREQUENCIES (nm)	FORMS OF MODES OF VIBRATION ASSIGNMENT
1160	1157	C—O STRETCH FOURTH OVERTONE
1195	1190	C—H SECOND OVERTONE
	1200	C—H SECOND OVERTONE
1360	1357	C—H COMBINATION
1395	1391	C—H COMBINATION
1420	1425	O—H FIRST OVERTONE
1570	1570	N—H STRETCH FIRST OVERTONE
1685	1684	C—H STRETCH FIRST OVERTONE
1705	1709	C—H STRETCH FIRST OVERTONE
1725	1727	C—H STRETCH FIRST OVERTONE
1765	1767	C—H STRETCH FIRST OVERTONE
1780	1780	C—H STRETCH FIRST OVERTONE
1920	1914	C—O STRETCH SECOND OVERTONE
1950	1936	C—O STRETCH SECOND OVERTONE
1990	2000	N—H STRETCH/N—H BEND COMBINATION
2070	2074	N—H DEFORMATION OVERTONE
2090	2100	C—H COMBINATION
2140	2135	C—H STRETCH/C—O STRETCH COMBINATION OR SYM C—H DEFORMATION
	2144	C—H STRETCH/C—O STRETCH COMBINATION OR SYM C—H DEFORMATION

TO FIG. 58B

FIG. 58A

FROM FIG. 58A

2170	2172	ASYMMETRIC C—H STRETCH/C—H DEFORMATION COMBINATION
2180	2178	N—H BEND SECOND OVERTONE OR C—H STRETCH/C—O STRETCH COMBINATION, OR C—O STRETCH C—N STRETCH; N—H IN-PLANE BEND.
2200	2194	CH STRETCH/C—O STRETCH COMBINATION
2280	2284	C—H STRETCH/CH_2 DEFORMATION
2300	2300	C—H BEND SECOND OVERTONE
2325	2320	CH STRETCH/CH_2 DEFORMATION COMBINATION
2352	2352	CH_2 BEND SECOND OVERTONE
2380	2384	C—H STRETCH/C—C STRETCH COMBINATION
2470	2454	C—H COMBINATION OR SYM C—N—C STRETCH OVERTONE
2488	2485	C—H STRETCH/C—C STRETCH COMBINATION
2530	2524	ASYMMETRIC C—N—C STRETCH FIRST OVERTONE
2530	2537	ASYMMETRIC C—N—C STRETCH FIRST OVERTONE

FIG. 58B

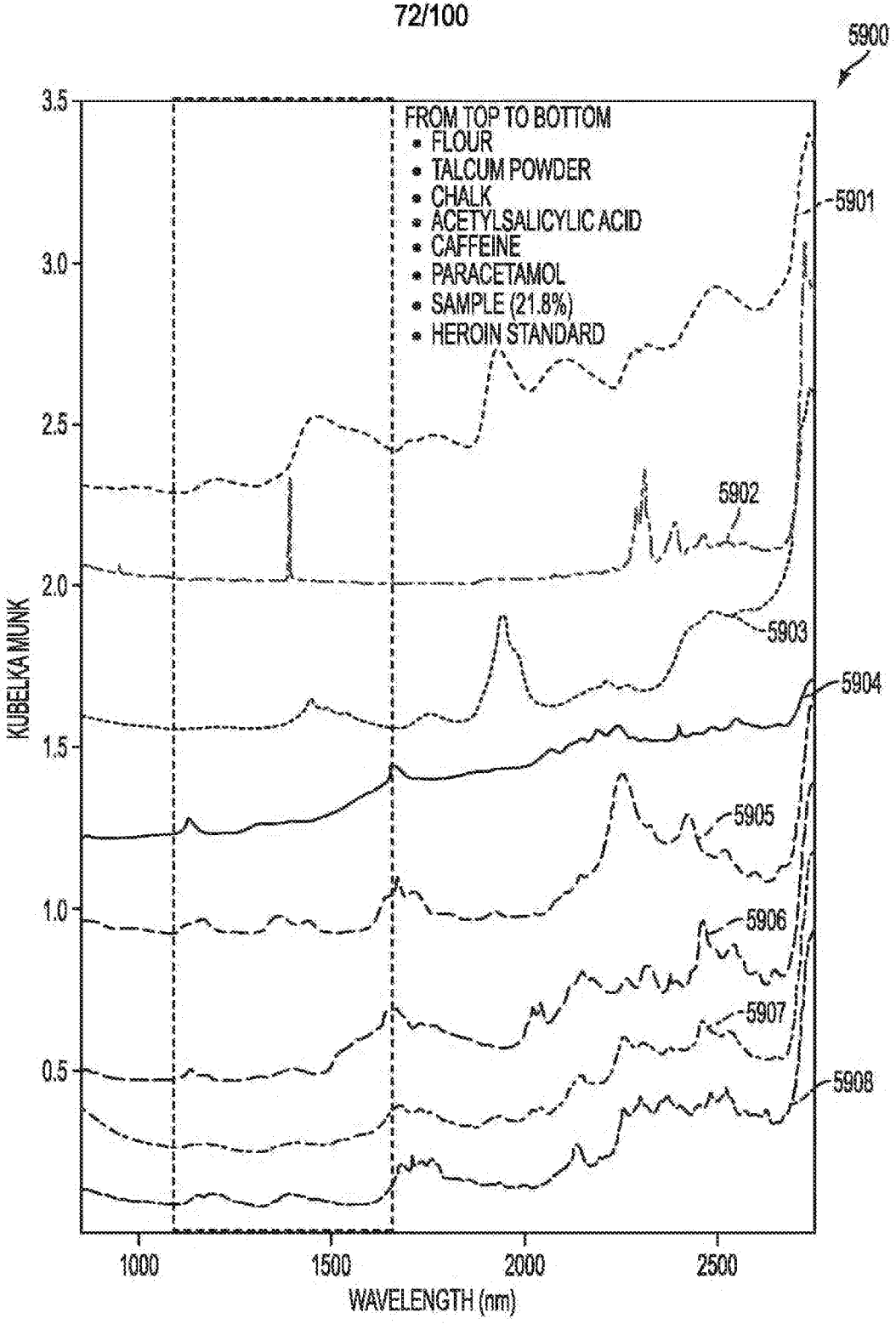

5900
FROM TOP TO BOTTOM
• FLOUR
• TALCUM POWDER
• CHALK
• ACETYLSALICYLIC ACID
• CAFFEINE
• PARACETAMOL
• SAMPLE (21.8%)
• HEROIN STANDARD
5901
5902
5903
5904
5905
5906
5907
5908
KUBELKA MUNK
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1000
1500
2000
2500
WAVELENGTH (nm)

FIG. 59

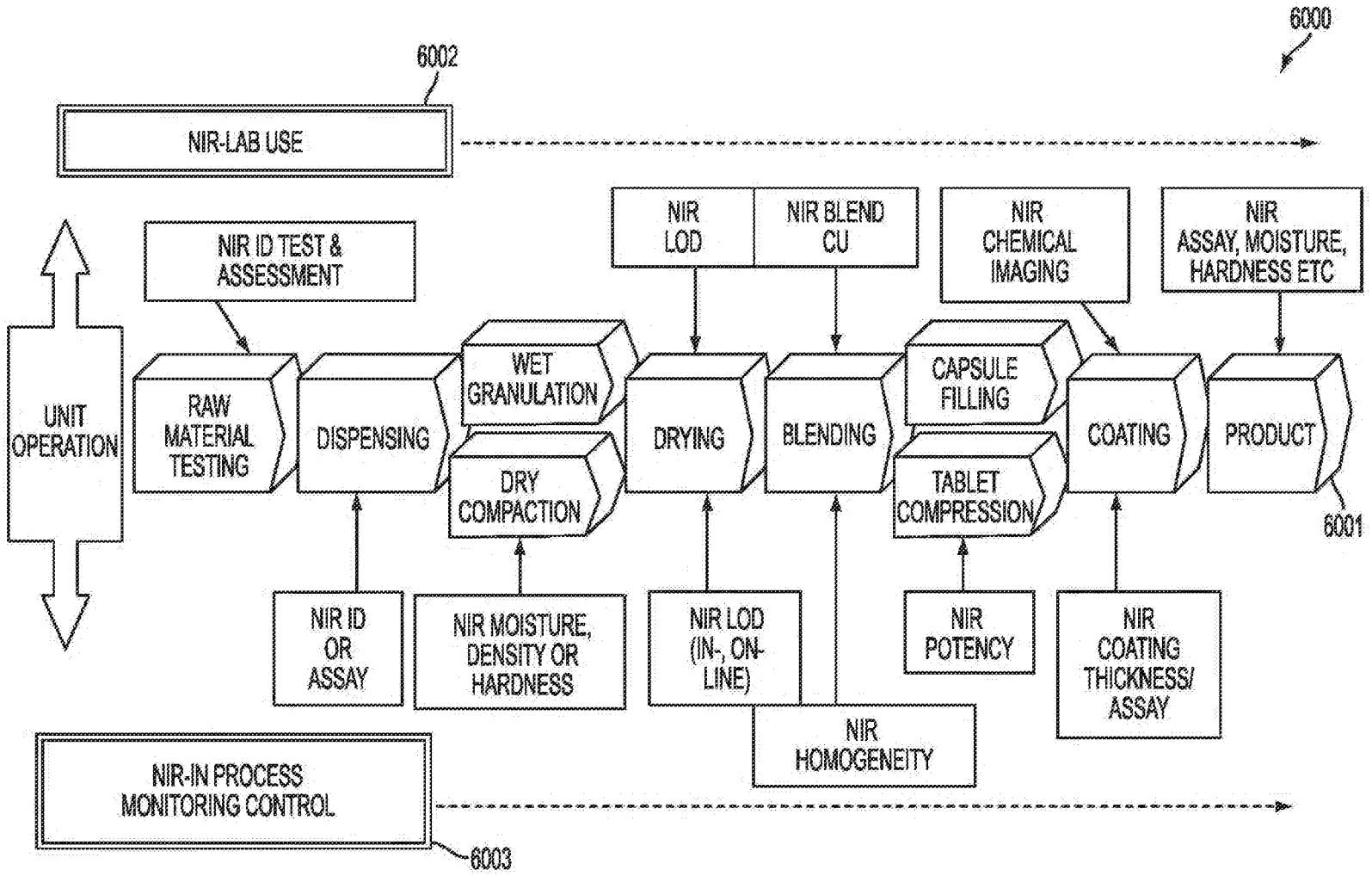

6000
6002
NIR-LAB USE
UNIT OPERATION
NIR ID TEST & ASSESSMENT
RAW MATERIAL TESTING
DISPENSING
WET GRANULATION
DRY COMPACTION
DRYING
NIR LOD
NIR BLEND CU
BLENDING
CAPSULE FILLING
TABLET COMPRESSION
NIR CHEMICAL IMAGING
COATING
NIR ASSAY, MOISTURE, HARDNESS ETC
PRODUCT
6001
NIR ID OR ASSAY
NIR MOISTURE, DENSITY OR HARDNESS
NIR LOD (IN-, ON-LINE)
NIR HOMOGENEITY
NIR POTENCY
NIR COATING THICKNESS/ ASSAY
NIR-IN PROCESS MONITORING CONTROL
6003

FIG. 60

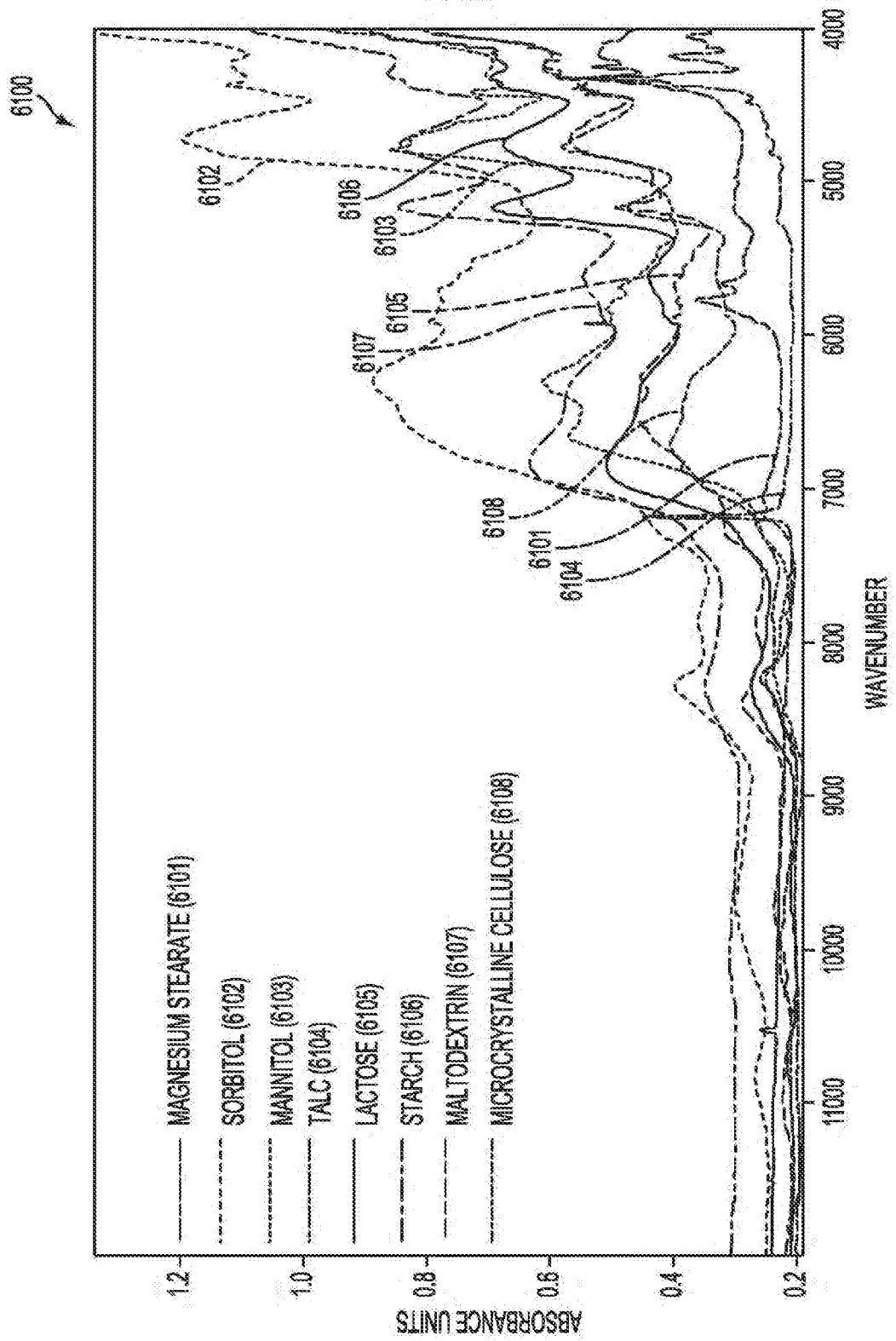

6100
6102
6106
6103
6105
6107
6108
6101
6104
MAGNESIUM STEARATE (6101)
SORBITOL (6102)
MANNITOL (6103)
TALC (6104)
LACTOSE (6105)
STARCH (6106)
MALTODEXTRIN (6107)
MICROCRYSTALLINE CELLULOSE (6108)
ABSORBANCE UNITS
1.2
1.0
0.8
0.6
0.4
0.2
11000
10000
9000
8000
7000
6000
5000
4000
WAVENUMBER
cm-1

FIG. 61

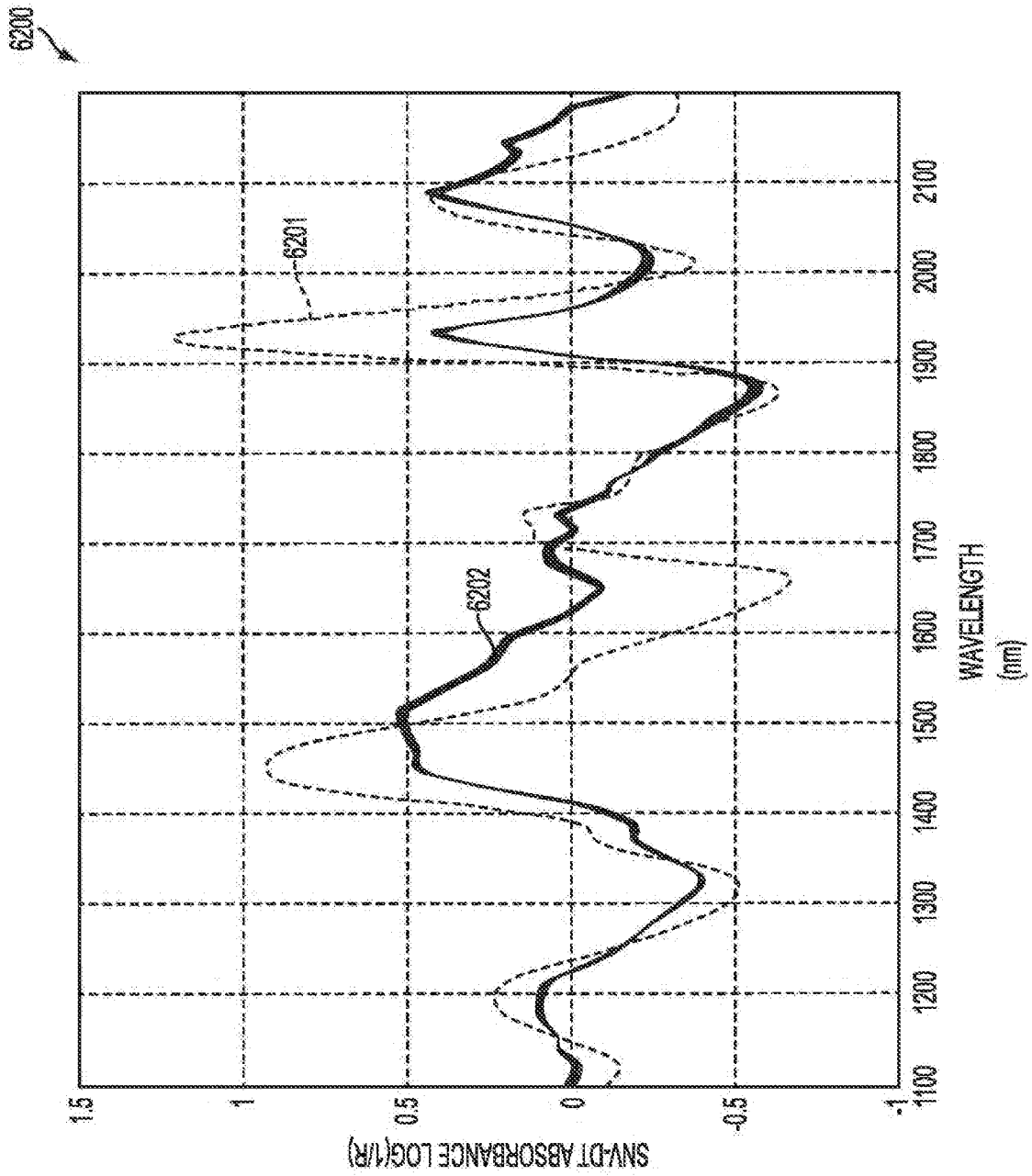

6200
6201
6202
SNV-DT ABSORBANCE LOG(1/R)
1.5
1
0.5
0
-0.5
-1
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
WAVELENGTH
(nm)

FIG. 62

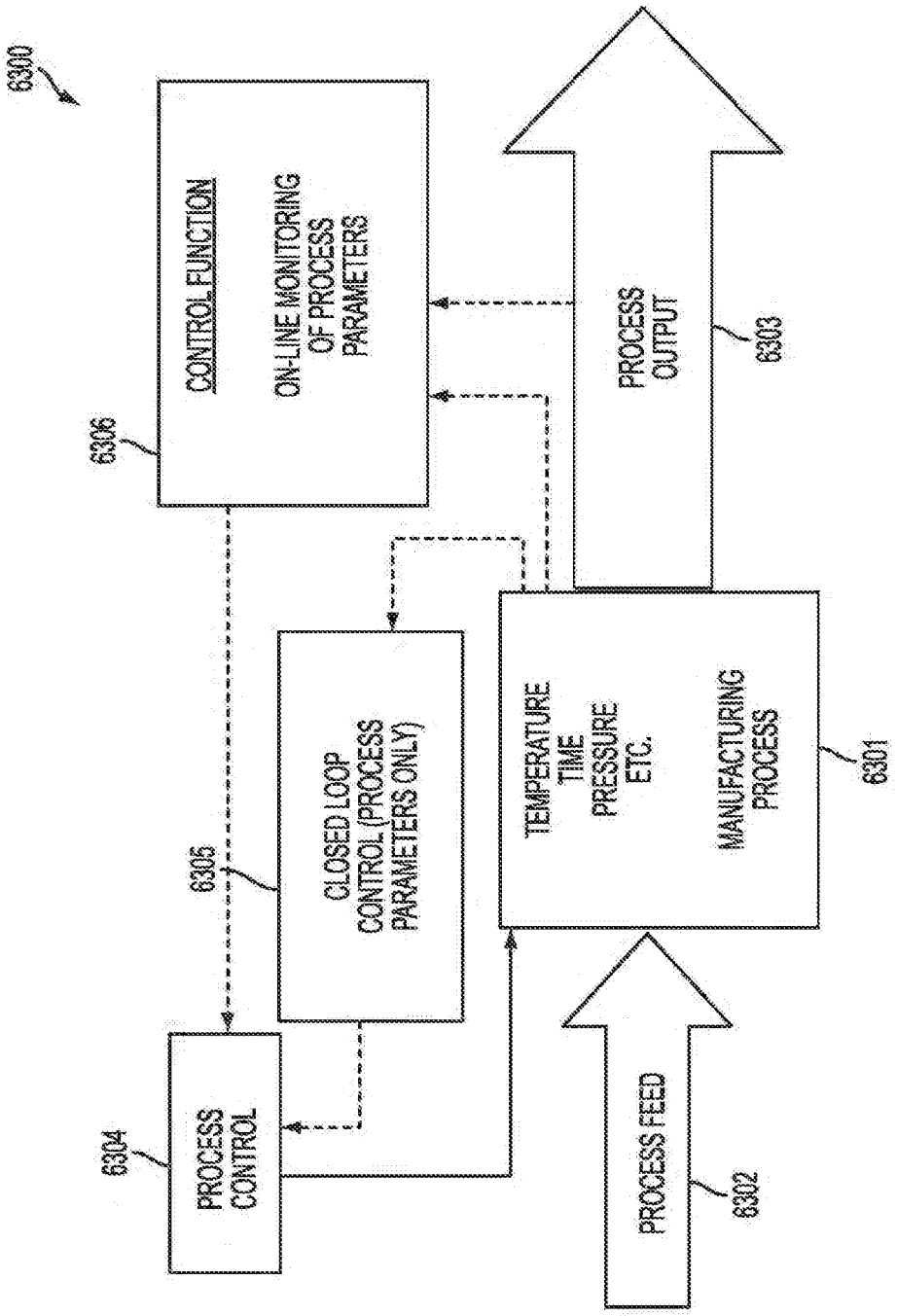

6300
CONTROL FUNCTION
ON-LINE MONITORING OF PROCESS PARAMETERS
6306
PROCESS OUTPUT
6303
CLOSED LOOP CONTROL (PROCESS PARAMETERS ONLY)
6305
TEMPERATURE
TIME
PRESSURE
ETC.
MANUFACTURING PROCESS
6301
PROCESS CONTROL
6304
PROCESS FEED
6302

FIG. 63

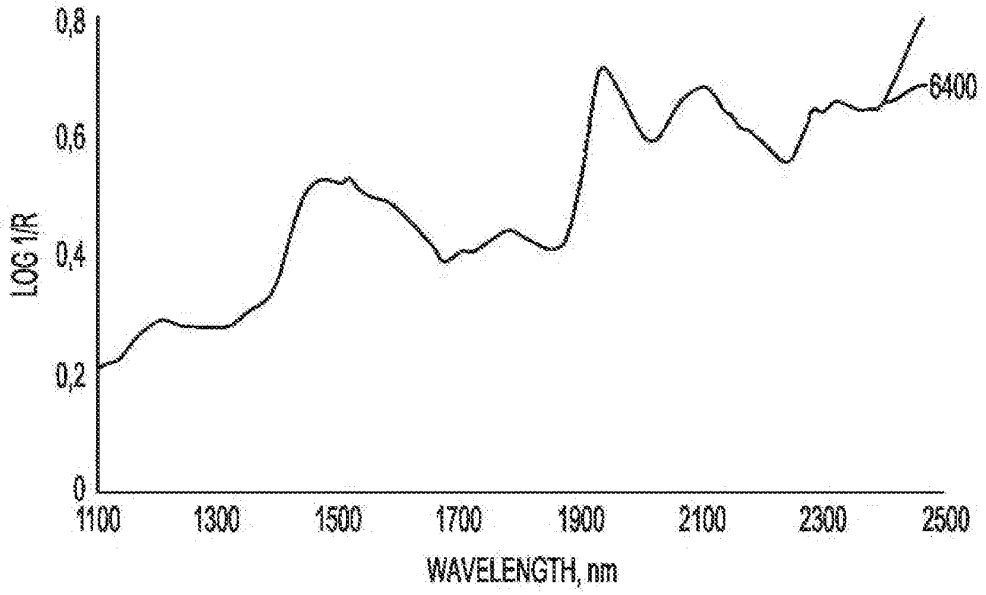


FIG. 64A

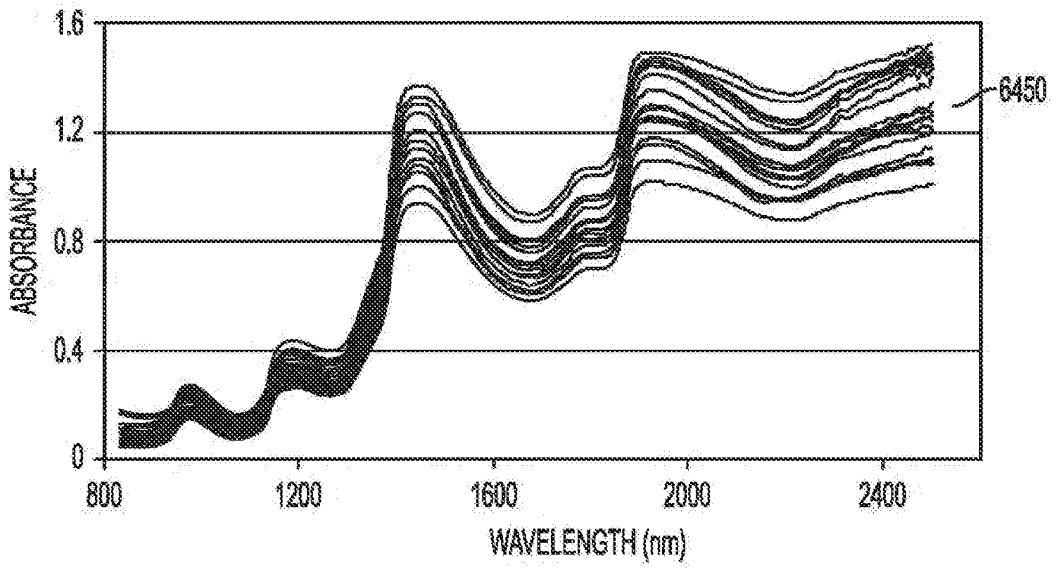


FIG. 64B

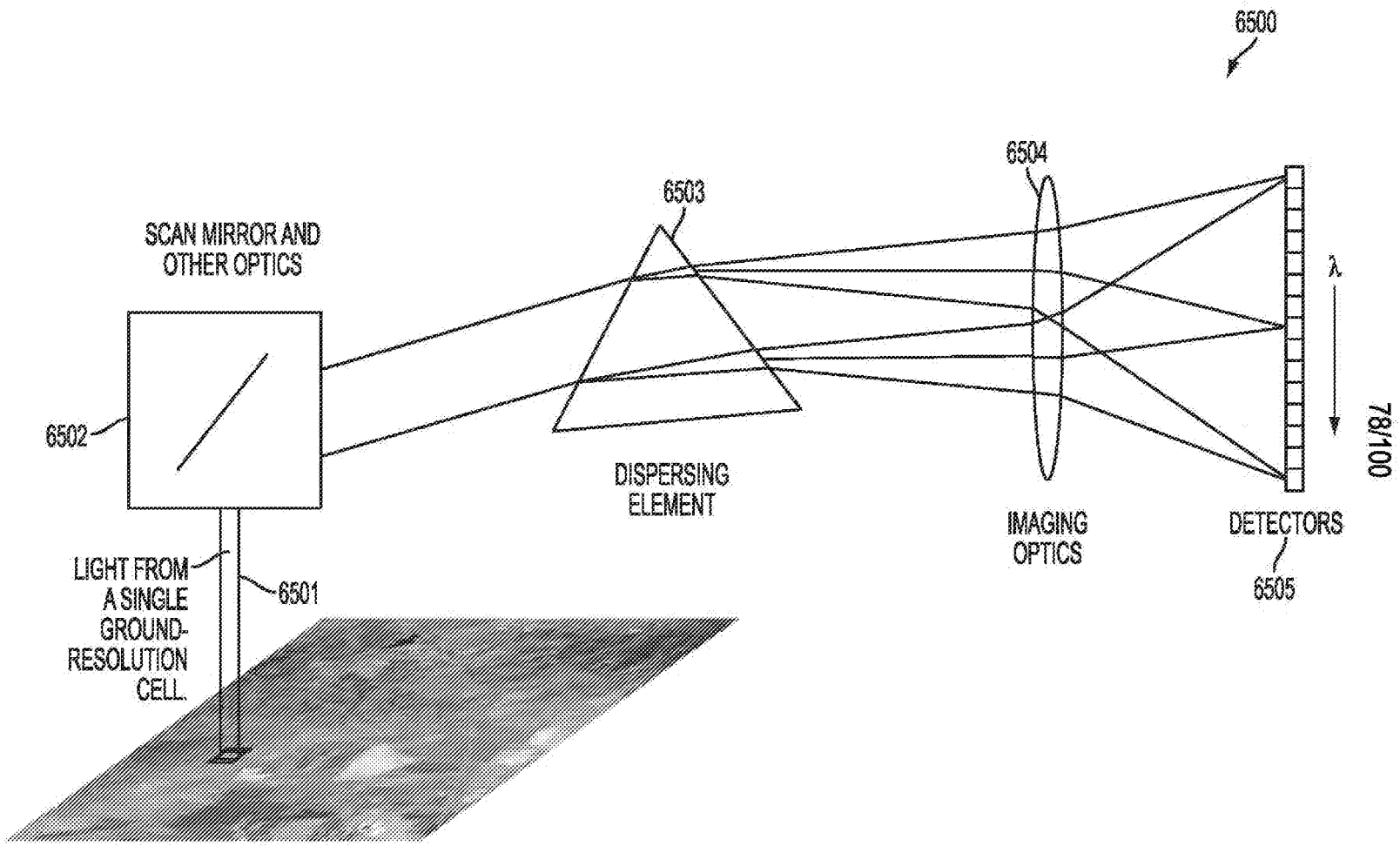

6500
SCAN MIRROR AND
OTHER OPTICS
6502
LIGHT FROM
A SINGLE
GROUND-
RESOLUTION
CELL
6501
6503
DISPERSING
ELEMENT
6504
IMAGING
OPTICS
λ
DETECTORS
6505

FIG. 65A

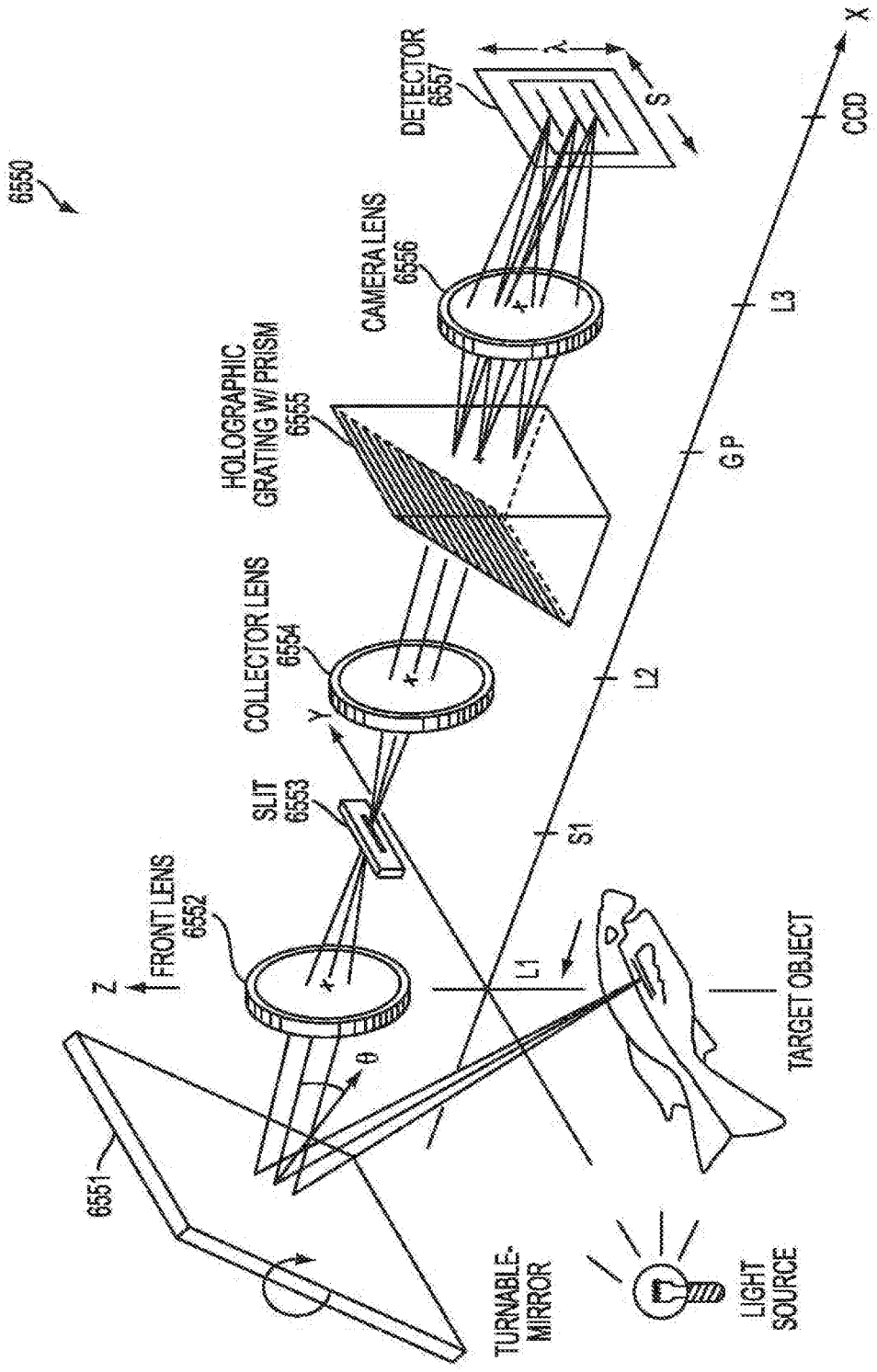

6550
6551
TURNABLE-MIRROR
LIGHT SOURCE
Z
FRONT LENS 6552
θ
SLIT 6553
Y
COLLECTOR LENS 6554
HOLOGRAPHIC GRATING W/ PRISM 6555
CAMERA LENS 6556
DETECTOR 6557
λ
S
X
L1
S1
L2
GP
L3
CCD
TARGET OBJECT

FIG. 65B

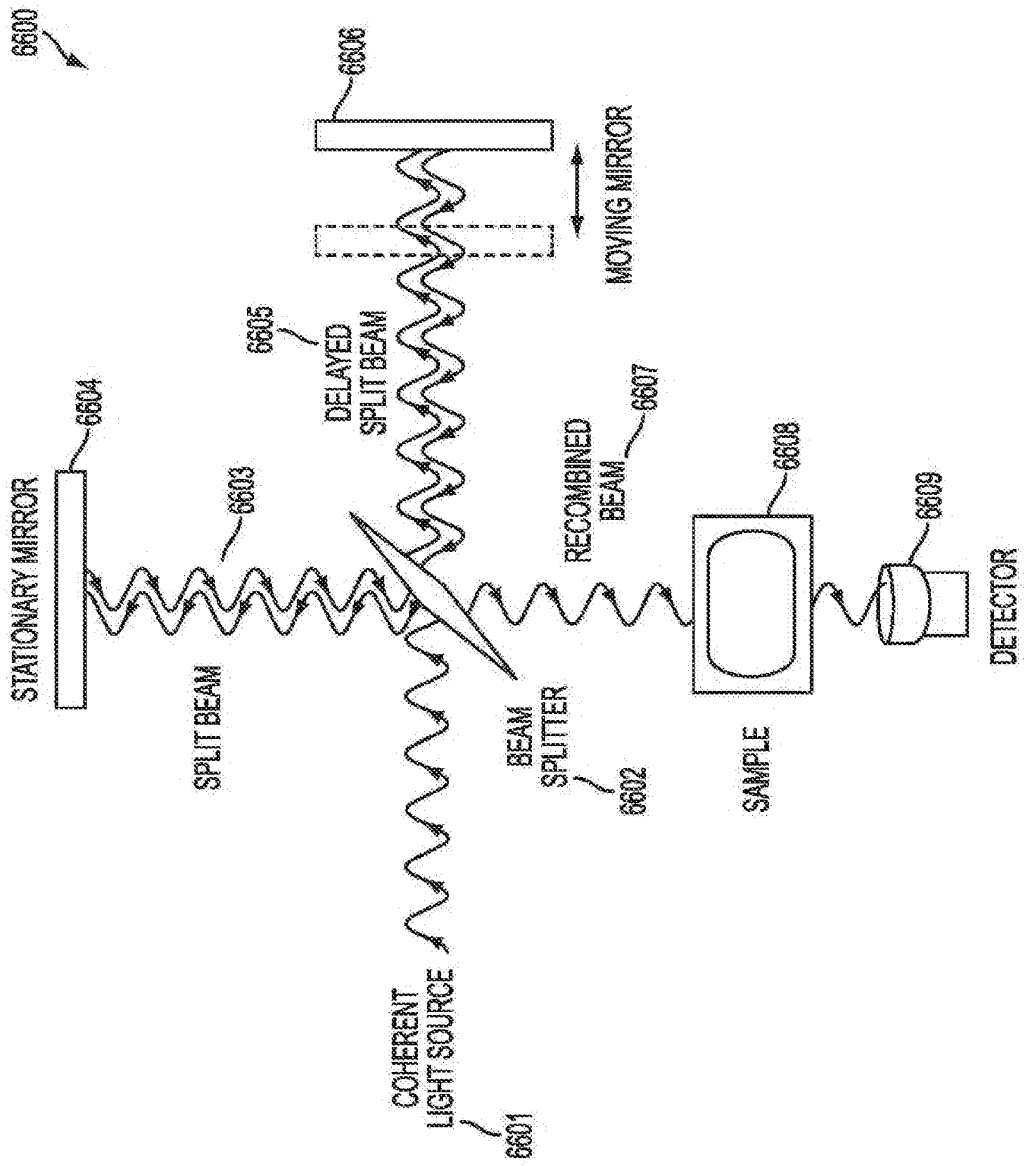

6600
STATIONARY MIRROR
6604
SPLIT BEAM
6603
DELAYED SPLIT BEAM
6605
6606
MOVING MIRROR
BEAM SPLITTER
6602
RECOMBINED BEAM
6607
SAMPLE
6608
DETECTOR
6609
COHERENT LIGHT SOURCE
6601

FIG. 66

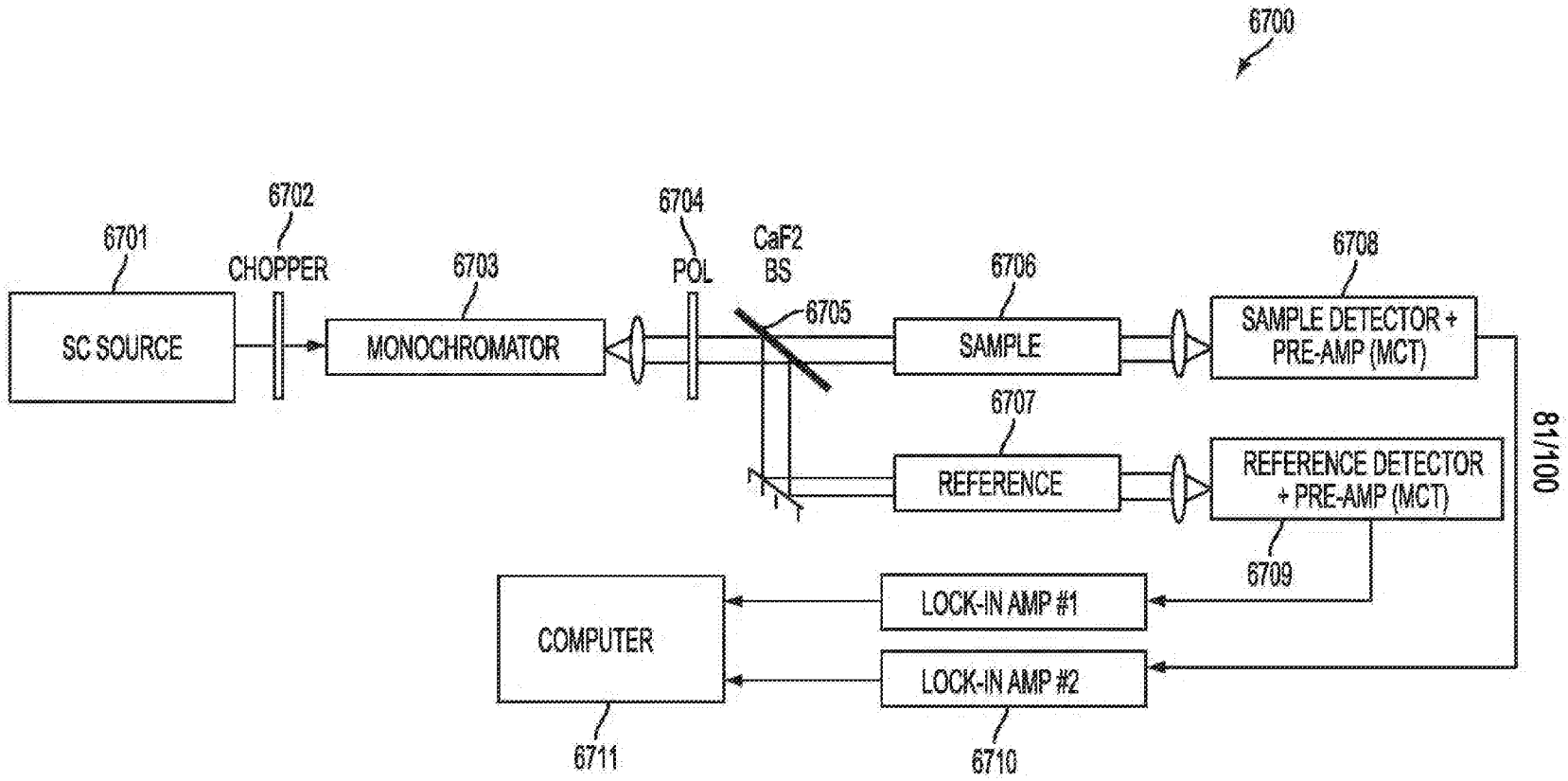

6700
6701
SC SOURCE
6702
CHOPPER
6703
MONOCHROMATOR
6704
POL
CaF2
BS
6705
6706
SAMPLE
6707
REFERENCE
6708
SAMPLE DETECTOR +
PRE-AMP (MCT)
REFERENCE DETECTOR
+ PRE-AMP (MCT)
6709
LOCK-IN AMP #1
LOCK-IN AMP #2
6710
COMPUTER
6711

FIG. 67

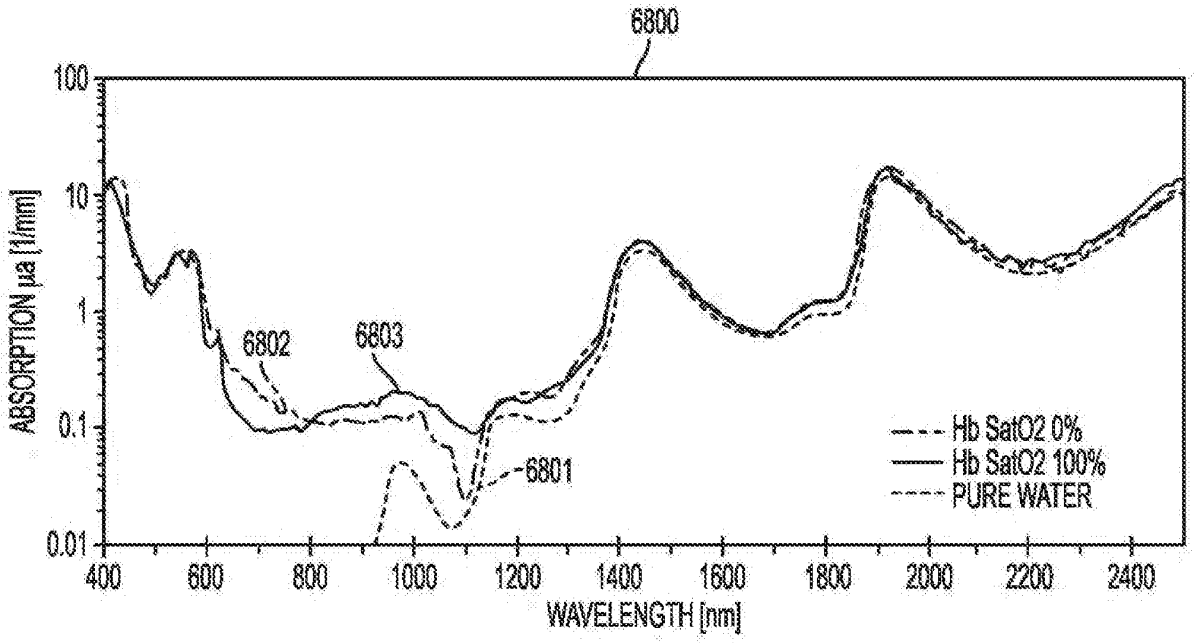

6800
100
10
1
0.1
0.01
ABSORPTION μa [1/mm]
6802
6803
6801
Hb SatO2 0%
Hb SatO2 100%
PURE WATER
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
WAVELENGTH [nm]

FIG. 68

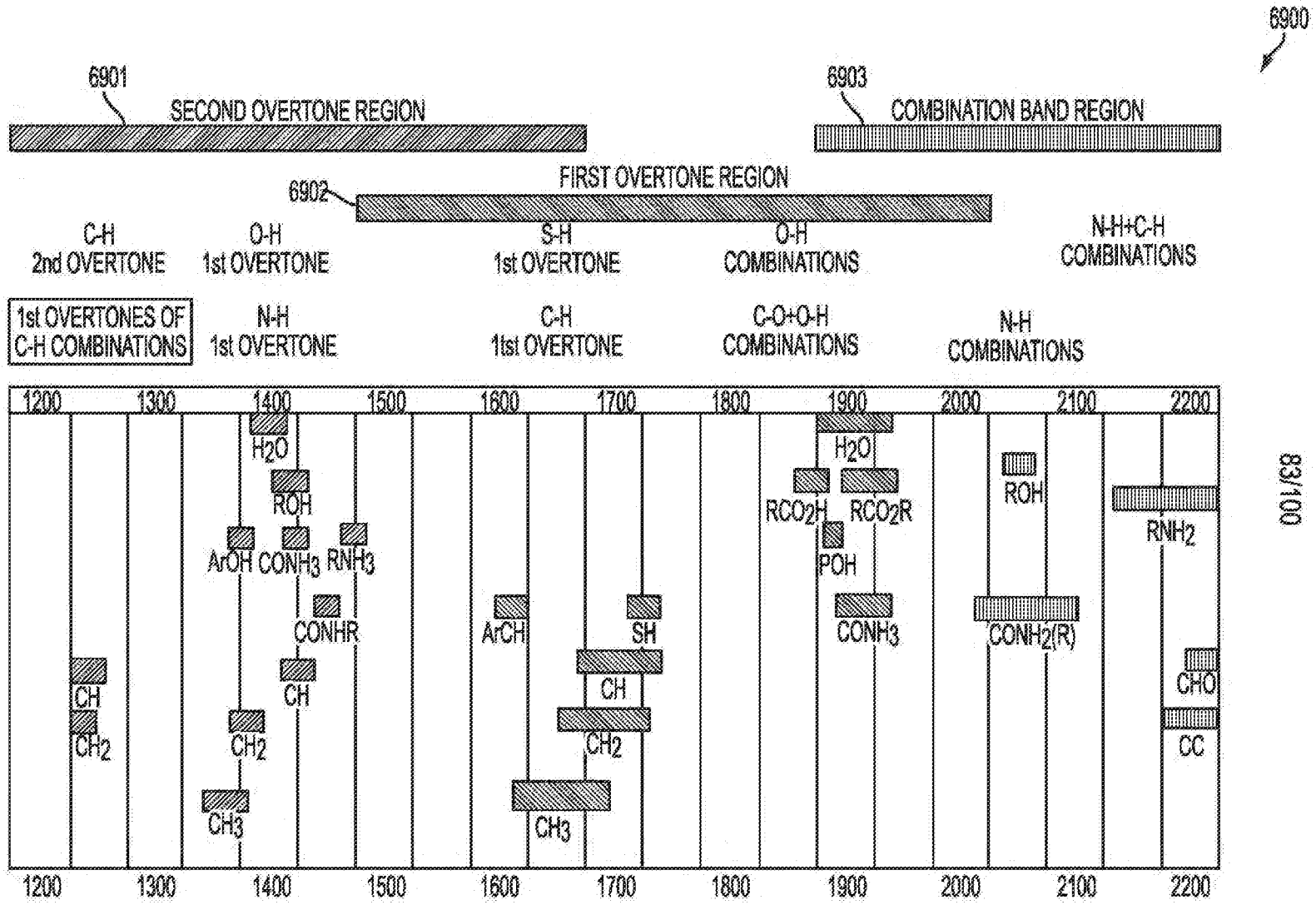

6900
6901
SECOND OVERTONE REGION
6903
COMBINATION BAND REGION
6902
FIRST OVERTONE REGION
C-H
2nd OVERTONE
O-H
1st OVERTONE
S-H
1st OVERTONE
O-H
COMBINATIONS
N-H+C-H
COMBINATIONS
1st OVERTONES OF
C-H COMBINATIONS
N-H
1st OVERTONE
C-H
1st OVERTONE
C-O+O-H
COMBINATIONS
N-H
COMBINATIONS
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
H2O
ROH
ArOH
CONH3
RNH3
CONHR
CH
CH2
CH3
ArCH
SH
RCO2H
RCO2R
POH
CONH2(R)
RNH2
CHO
CC

FIG. 69

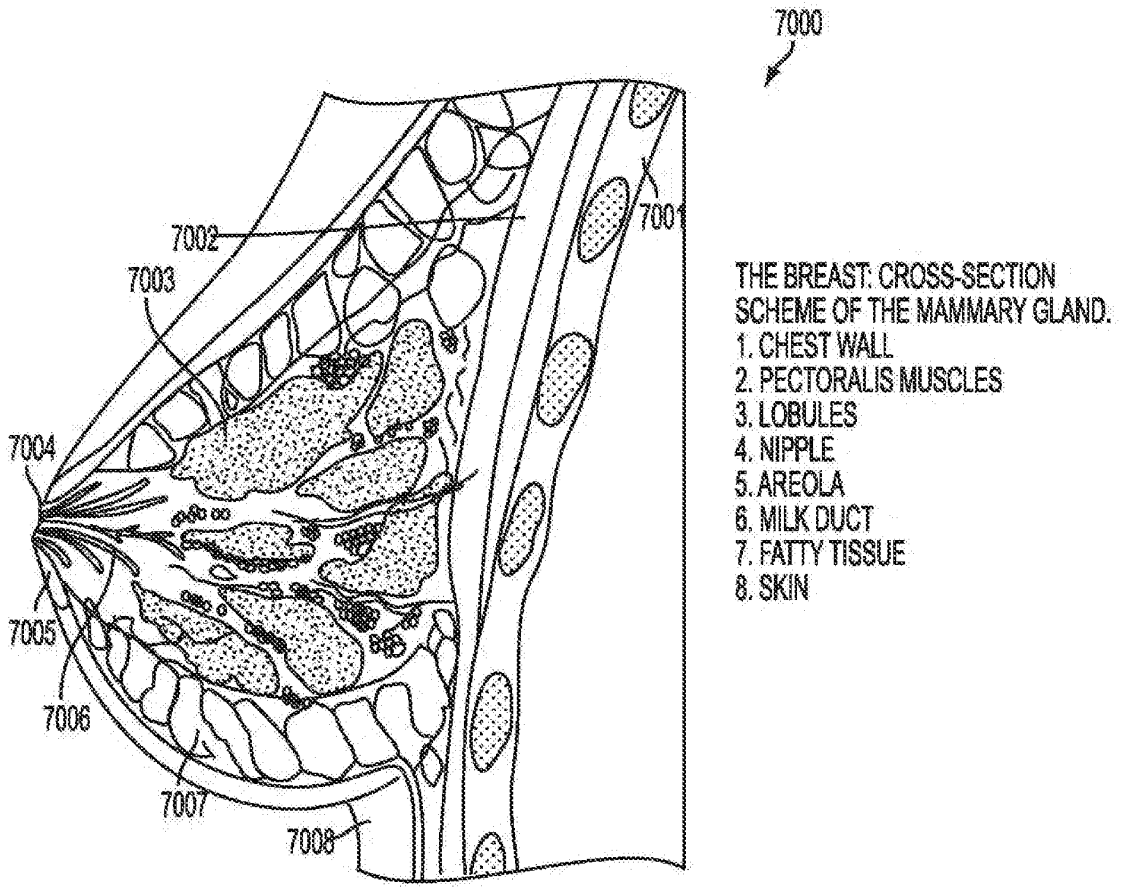

7000
7001
7002
7003
7004
7005
7006
7007
7008
THE BREAST: CROSS-SECTION
SCHEME OF THE MAMMARY GLAND.
1. CHEST WALL
2. PECTORALIS MUSCLES
3. LOBULES
4. NIPPLE
5. AREOLA
6. MILK DUCT
7. FATTY TISSUE
8. SKIN

FIG. 70

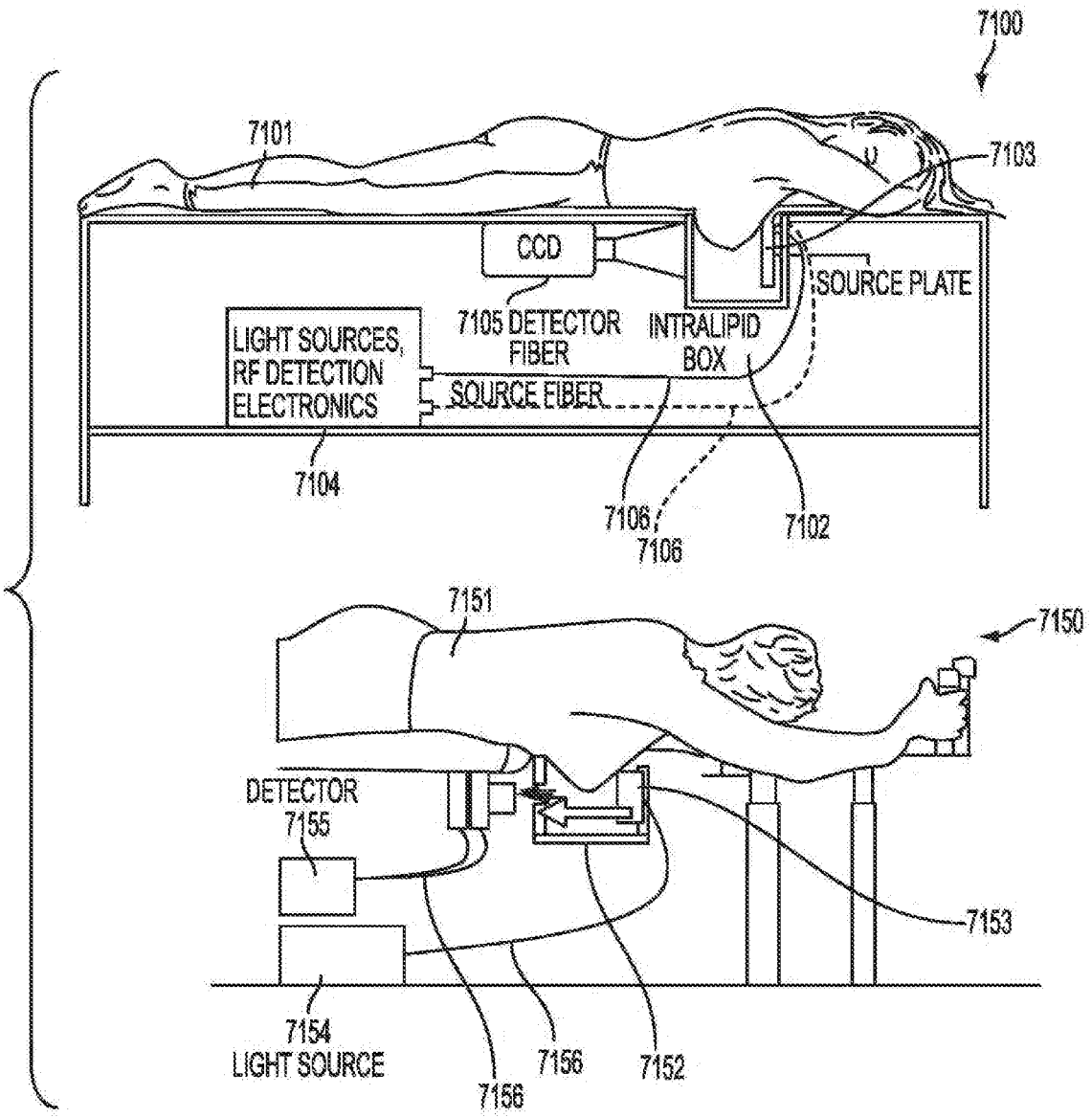

7100
7101
7103
CCD
SOURCE PLATE
7105 DETECTOR FIBER
INTRALIPID BOX
LIGHT SOURCES, RF DETECTION ELECTRONICS
SOURCE FIBER
7104
7106
7106
7102
7151
7150
DETECTOR 7155
7153
7154 LIGHT SOURCE
7156
7156
7152

FIG. 71

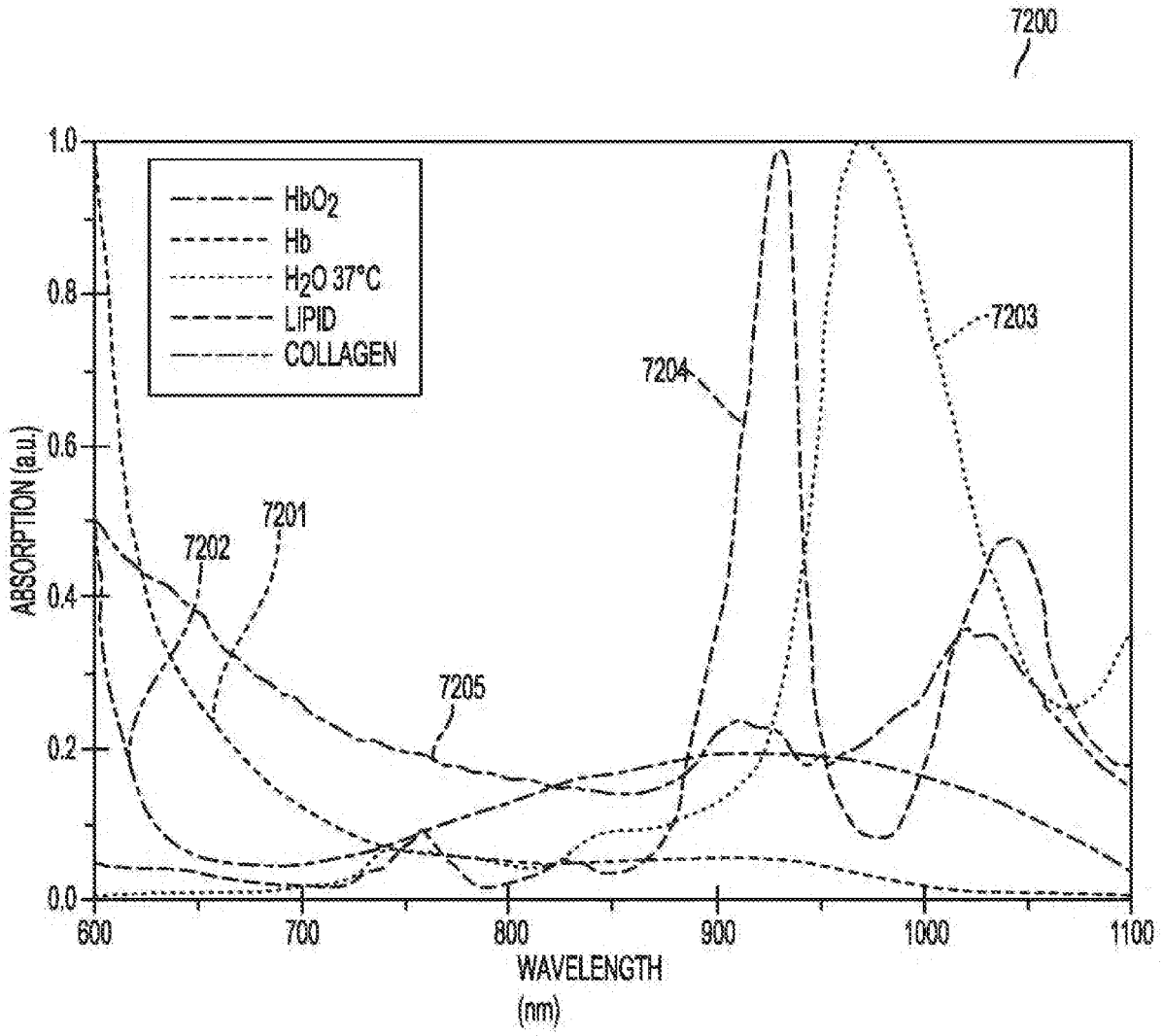

7200
1.0
0.8
0.6
0.4
0.2
0.0
ABSORPTION (a.u.)
HbO2
Hb
H2O 37°C
LIPID
COLLAGEN
7201
7202
7203
7204
7205
600
700
800
900
1000
1100
WAVELENGTH
(nm)

FIG. 72

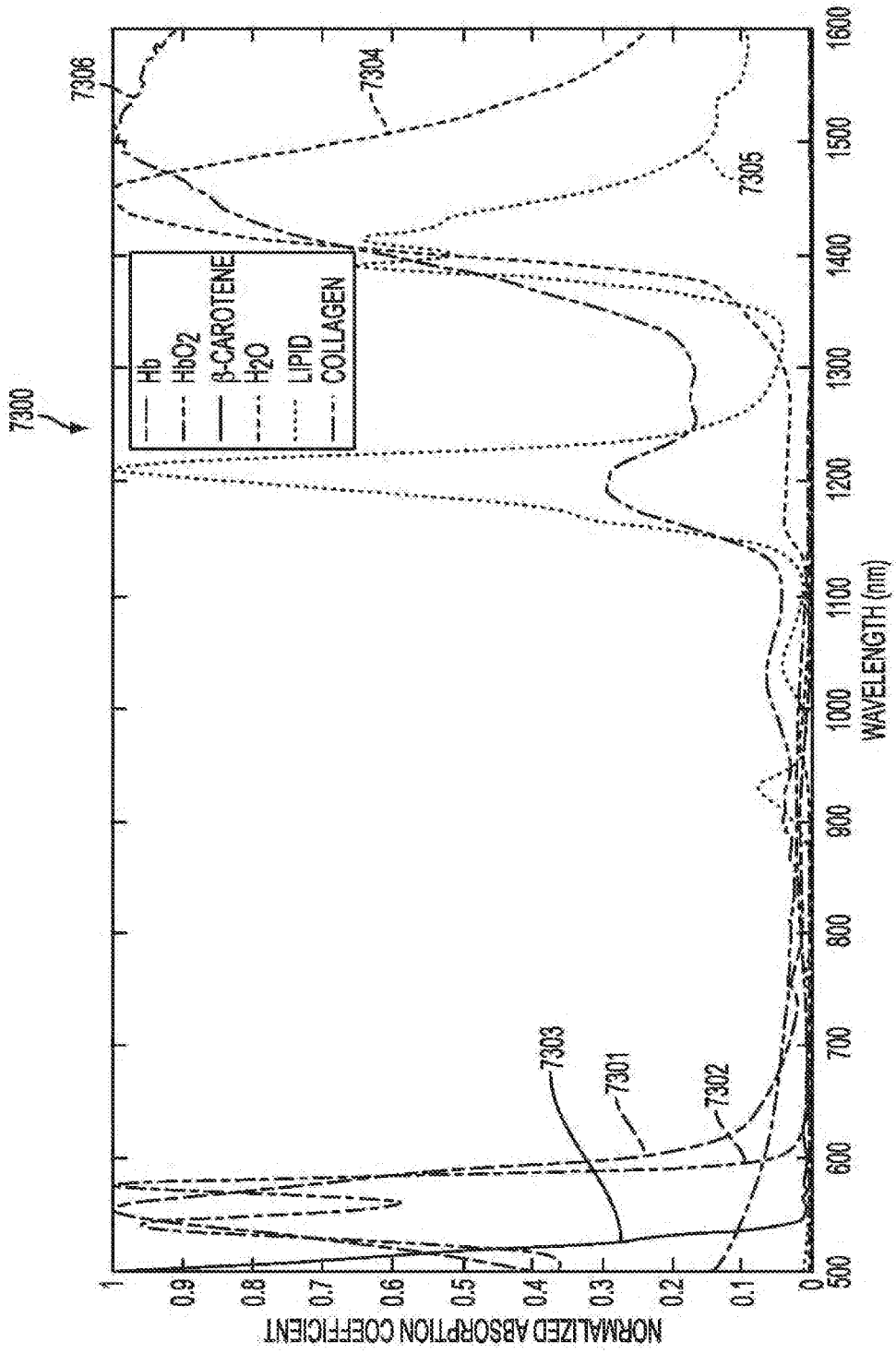

7300
7306
7304
7305
7303
7301
7302
Hb
HbO2
β-CAROTENE
H2O
LIPID
COLLAGEN
NORMALIZED ABSORPTION COEFFICIENT
WAVELENGTH (nm)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600

FIG. 73

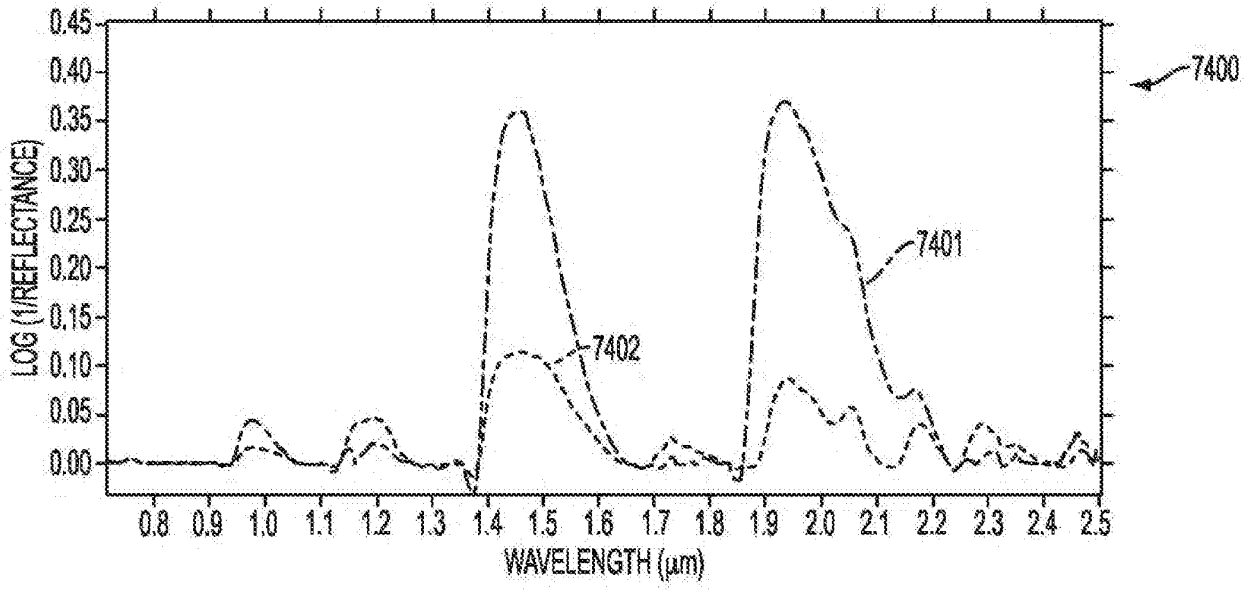


FIG. 74A

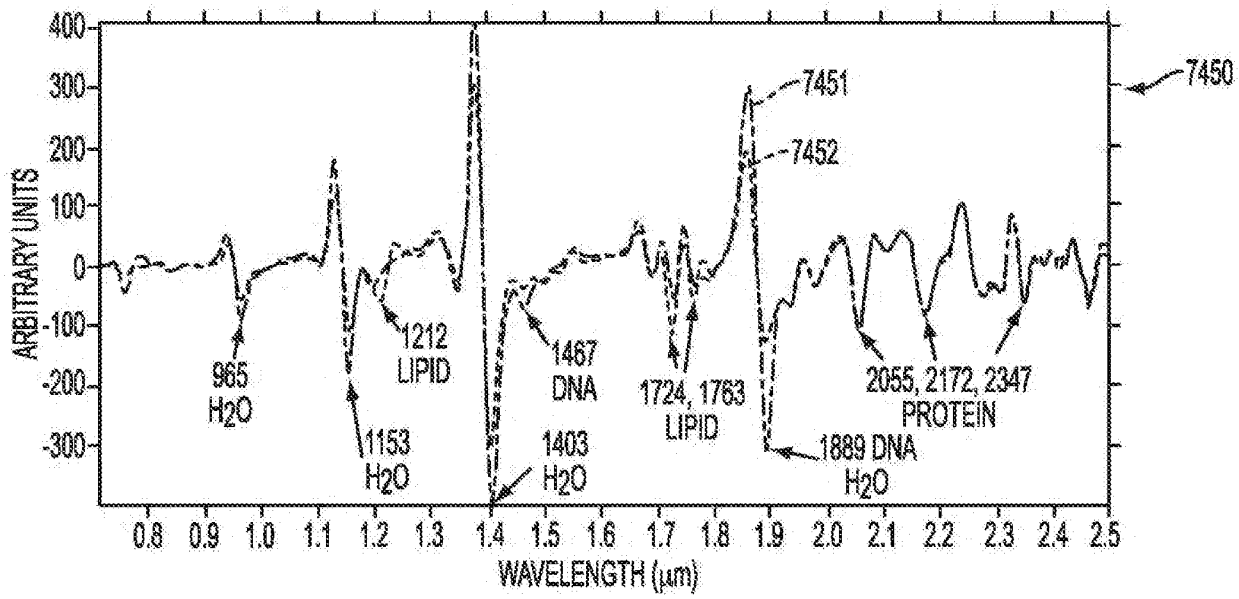


FIG. 74B

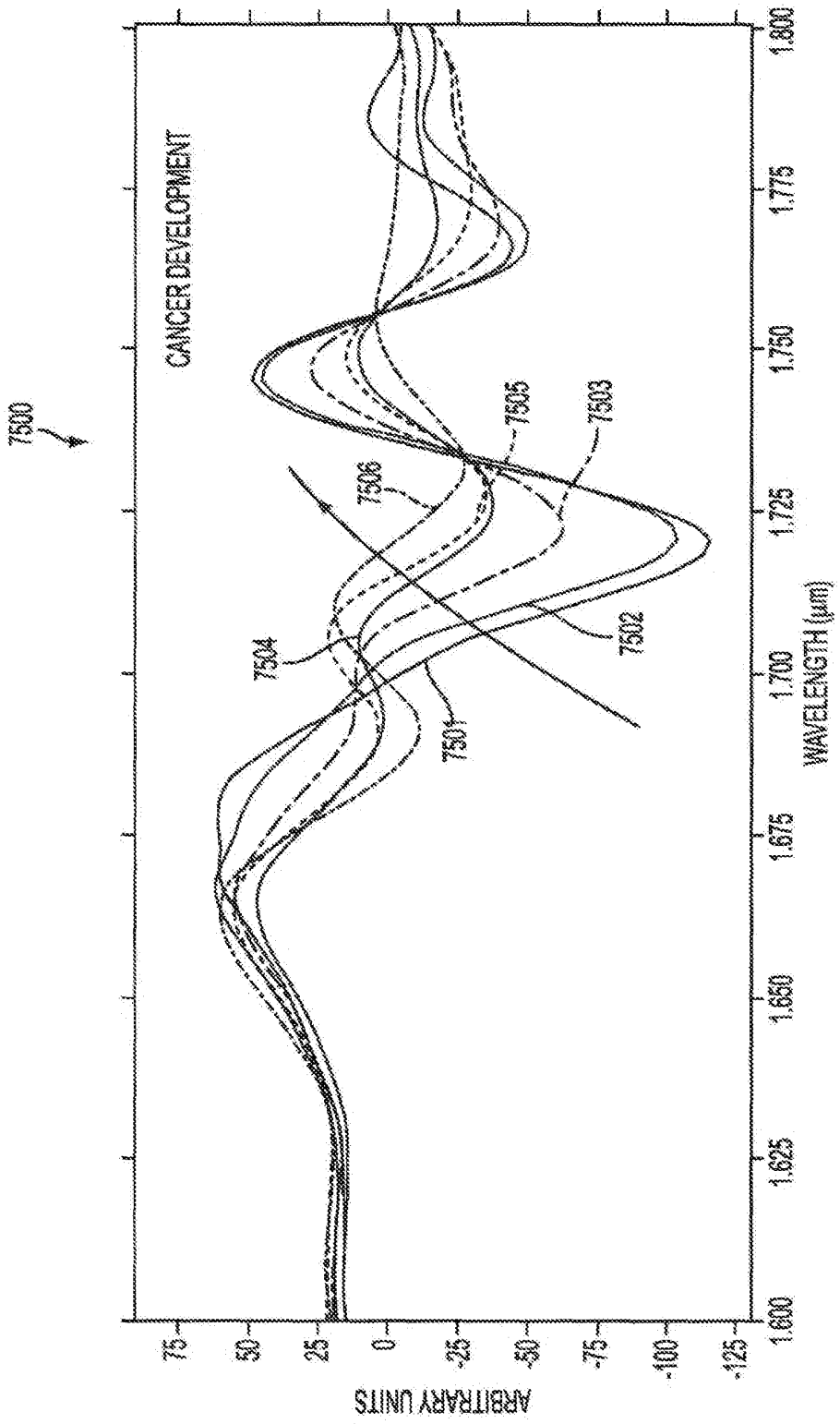

7500
CANCER DEVELOPMENT
7501
7502
7503
7504
7505
7506
ARBITRARY UNITS
75
50
25
0
-25
-50
-75
-100
-125
1.600
1.625
1.650
1.675
1.700
1.725
1.750
1.775
1.800
WAVELENGTH (μm)

FIG. 75

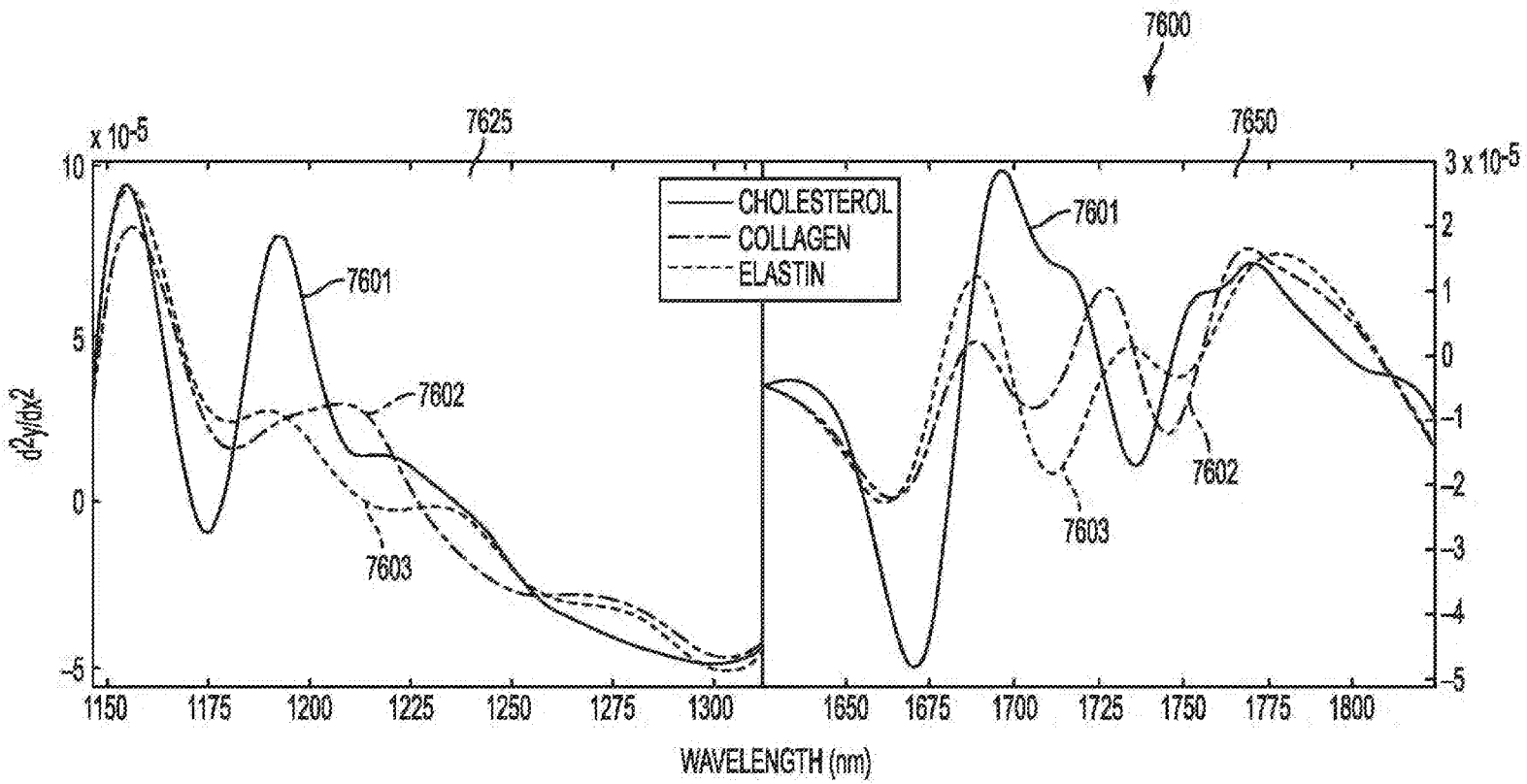

7600
7625
7650
x 10-5
3 x 10-5
10
5
0
-5
2
1
0
-1
-2
-3
-4
-5
d2y/dx2
CHOLESTEROL
COLLAGEN
ELASTIN
7601
7602
7603
1150
1175
1200
1225
1250
1275
1300
1650
1675
1700
1725
1750
1775
1800
WAVELENGTH (nm)

FIG. 76

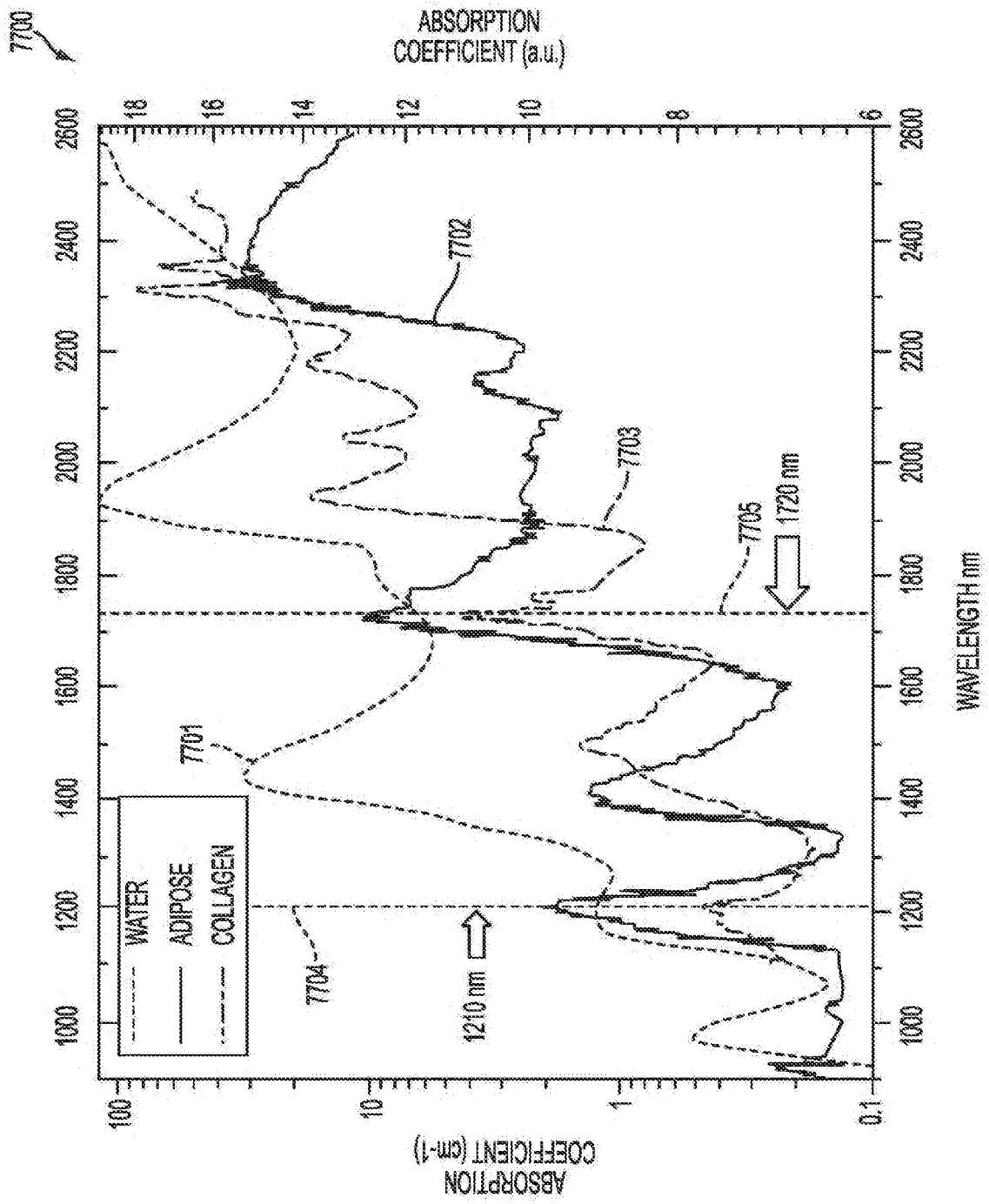

7700
ABSORPTION COEFFICIENT (a.u.)
18
16
14
12
10
8
6
2600
2400
2200
2000
1800
1600
1400
1200
1000
7702
7703
7705
1720 nm
7701
7704
1210 nm
WATER
ADIPOSE
COLLAGEN
100
10
1
0.1
ABSORPTION COEFFICIENT (cm-1)
WAVELENGTH nm

FIG. 77

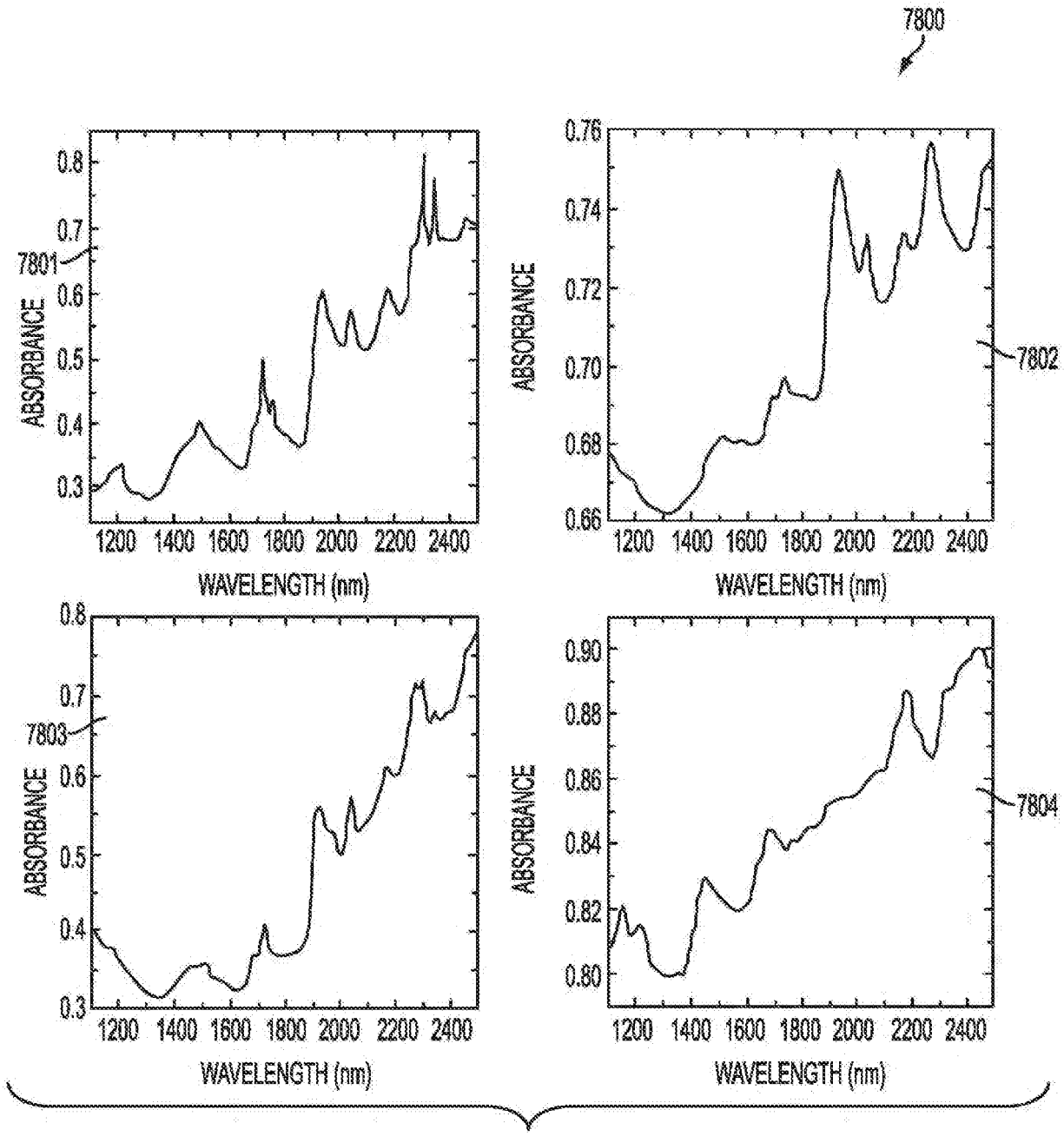

7800
7801
7802
7803
7804
ABSORBANCE
WAVELENGTH (nm)
0.3
0.4
0.5
0.6
0.7
0.8
0.66
0.68
0.70
0.72
0.74
0.76
0.80
0.82
0.84
0.86
0.88
0.90
1200
1400
1600
1800
2000
2200
2400

FIG. 78

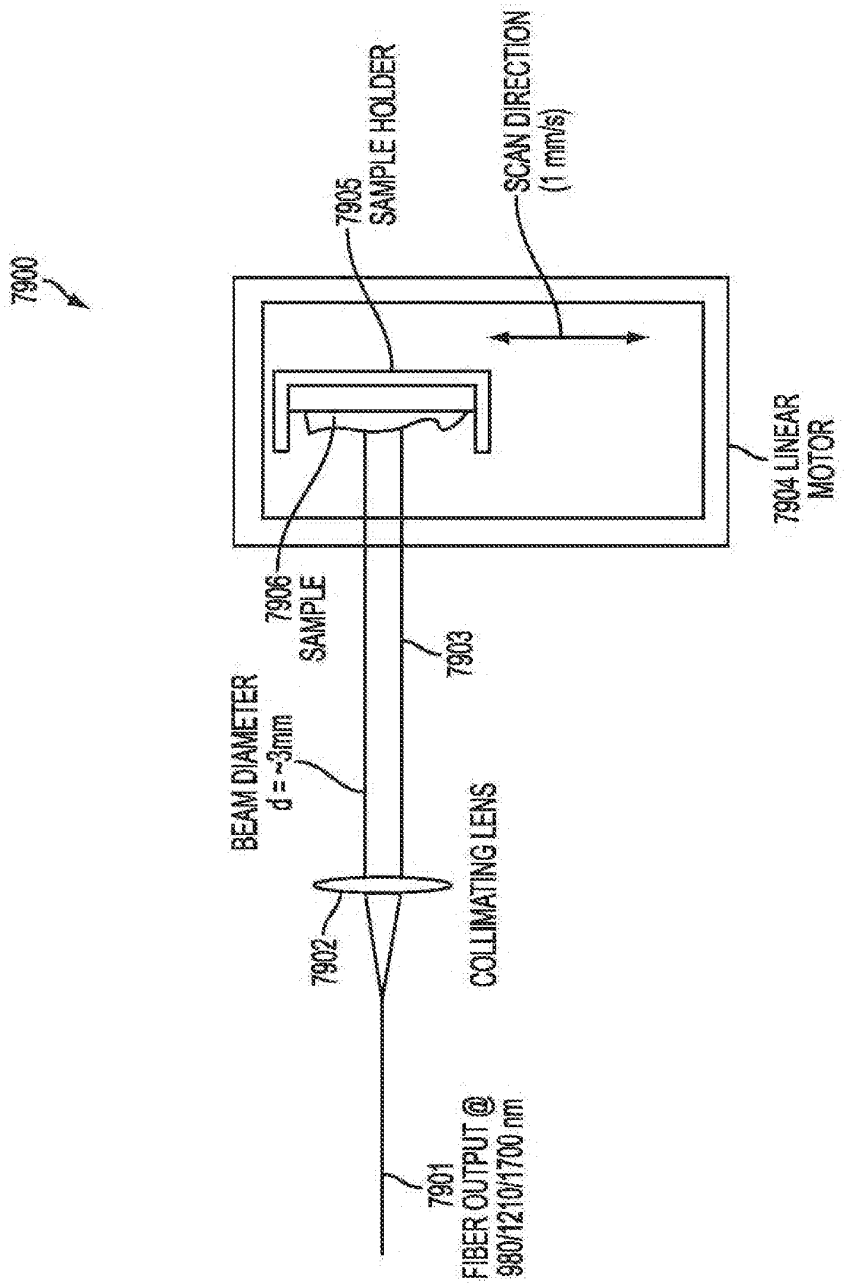

7900
7905
SAMPLE HOLDER
SCAN DIRECTION
(1 mm/s)
7904 LINEAR
MOTOR
7906
SAMPLE
7903
BEAM DIAMETER
d = ~3mm
7902
COLLIMATING LENS
7901
FIBER OUTPUT @
980/1210/1700 nm

FIG. 79

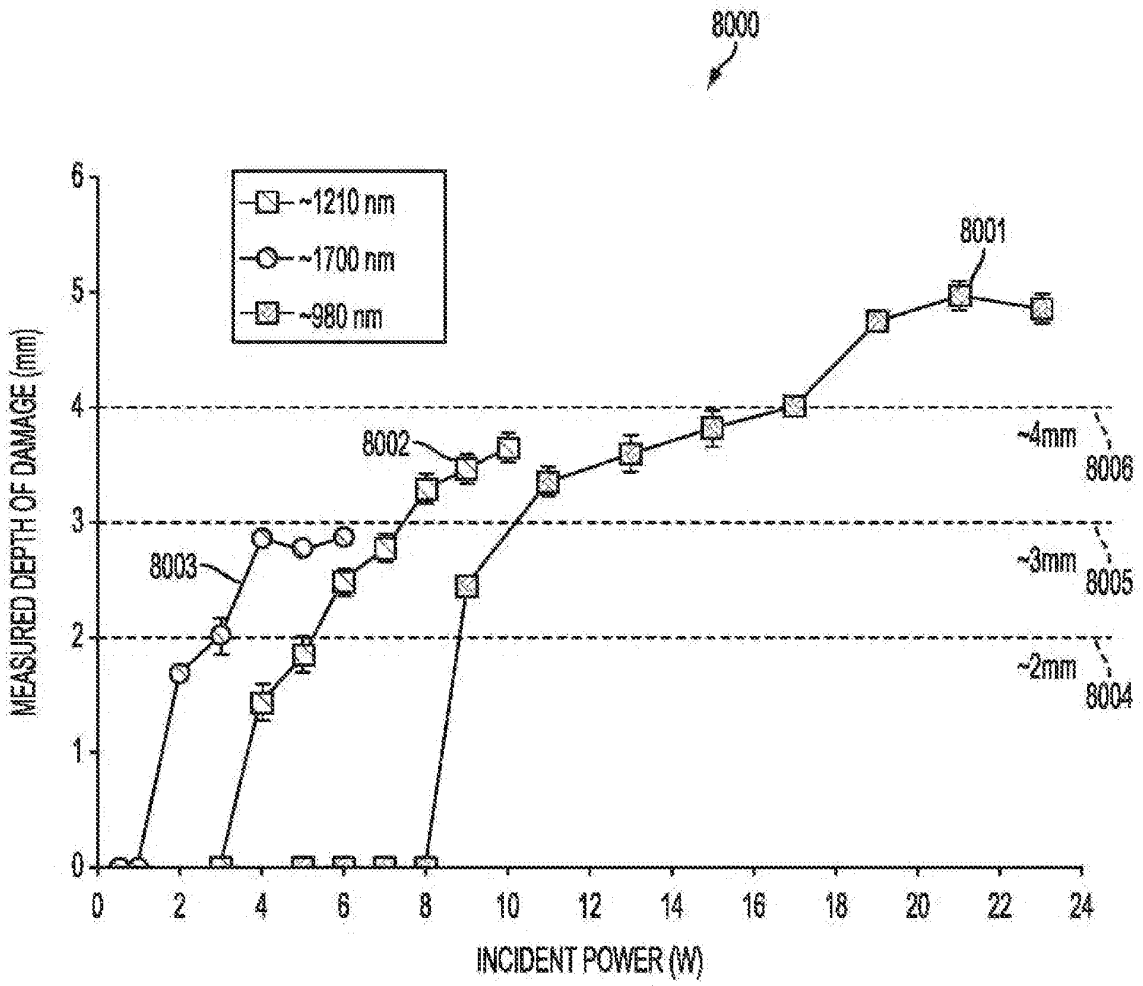

8000
~1210 nm
~1700 nm
~980 nm
8001
8002
8003
~4mm
8006
~3mm
8005
~2mm
8004
MEASURED DEPTH OF DAMAGE (mm)
INCIDENT POWER (W)
0
1
2
3
4
5
6
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 80

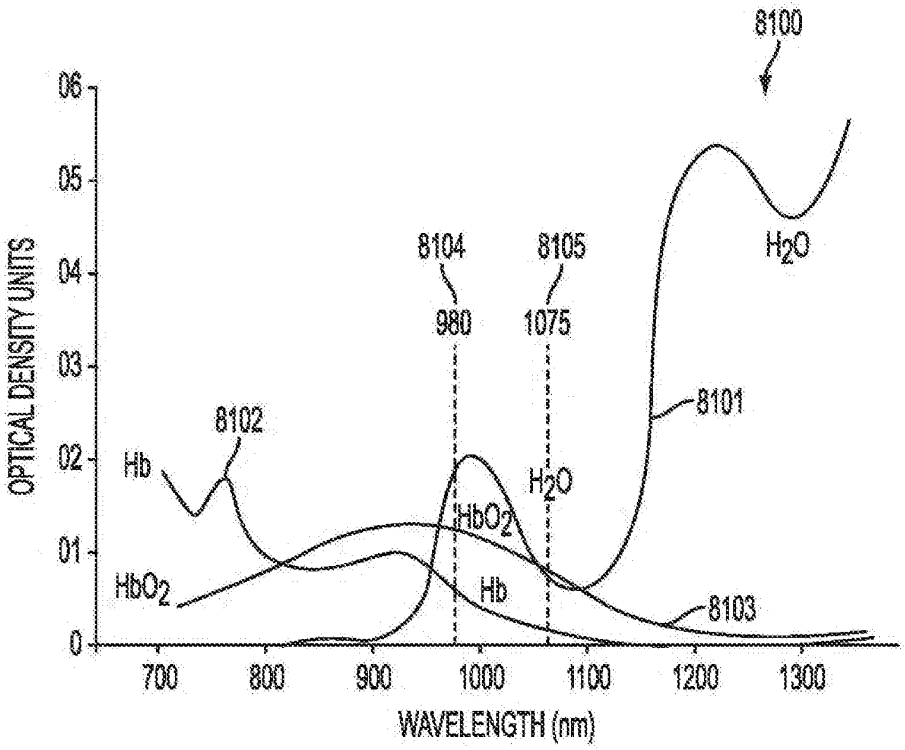

8100
06
05
04
03
02
01
0
OPTICAL DENSITY UNITS
8104
980
8105
1075
H_2O
8101
8102
Hb
HbO_2
H_2O
HbO_2
Hb
8103
700
800
900
1000
1100
1200
1300
WAVELENGTH (nm)

FIG. 81

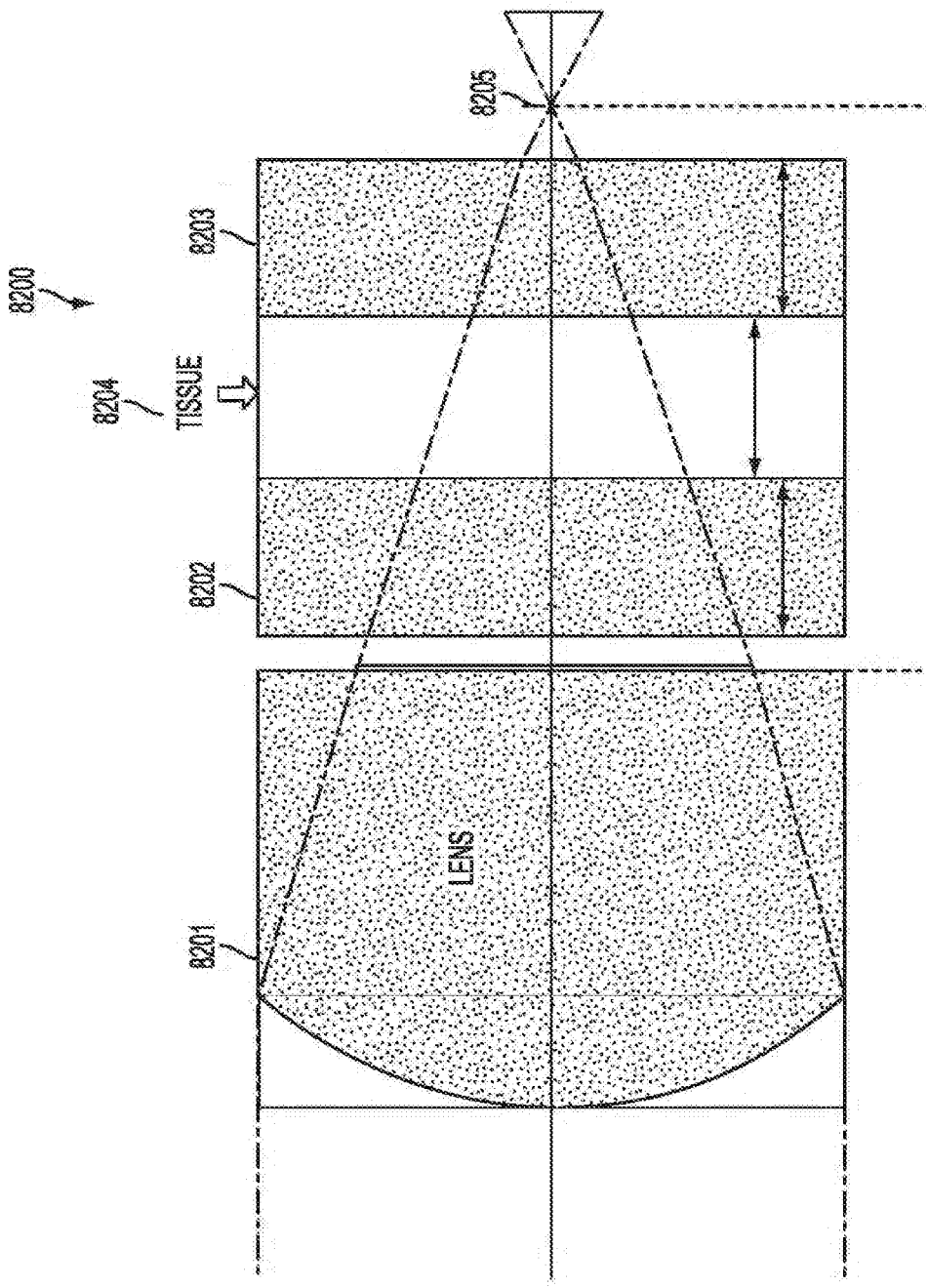


FIG. 82

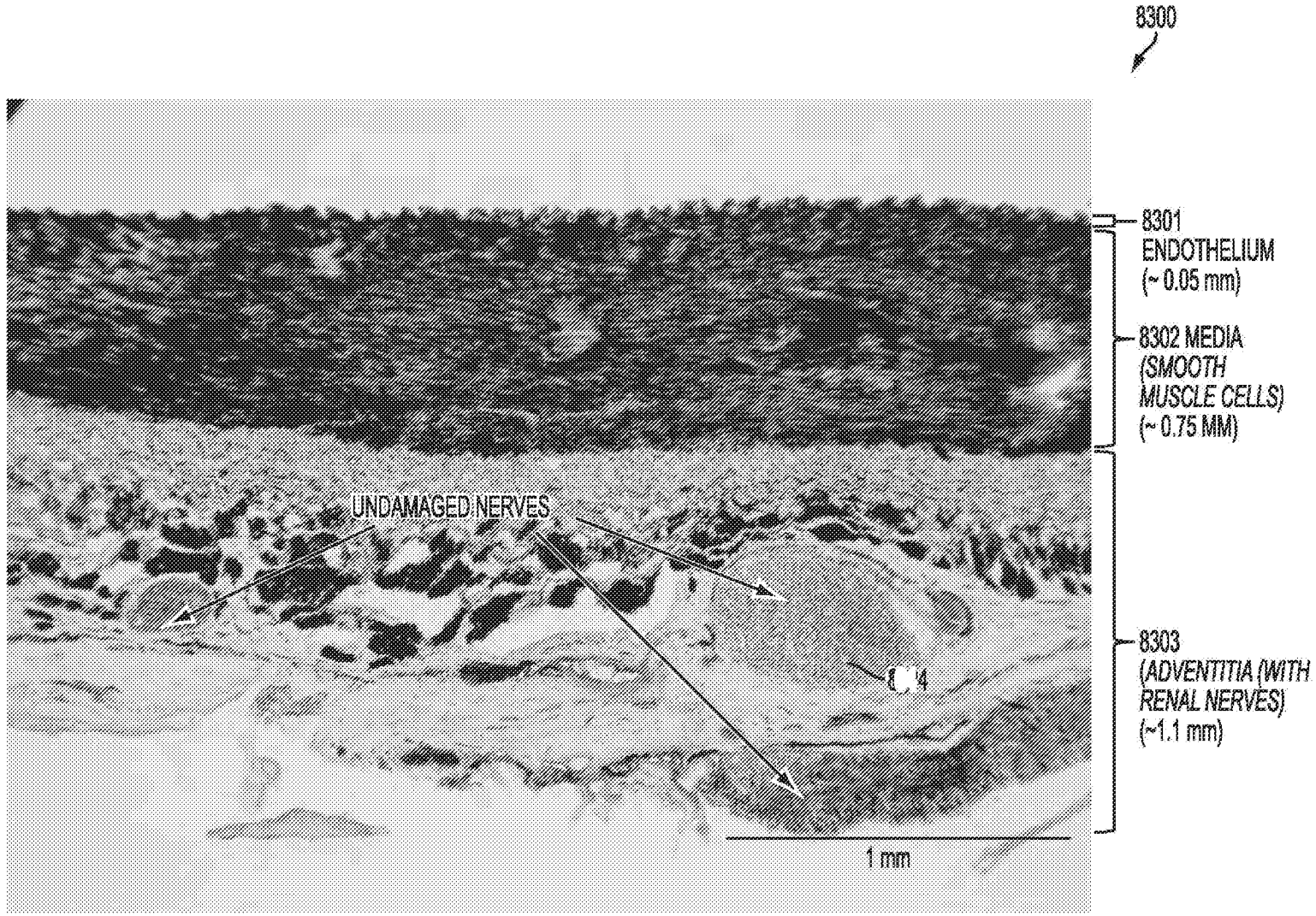

8300
8301
ENDOTHELIUM
(~ 0.05 mm)
8302 MEDIA
(SMOOTH
MUSCLE CELLS)
(~ 0.75 MM)
8303
(ADVENTITIA (WITH
RENAL NERVES)
(~1.1 mm)
UNDAMAGED NERVES
1 mm

FIG. 83A

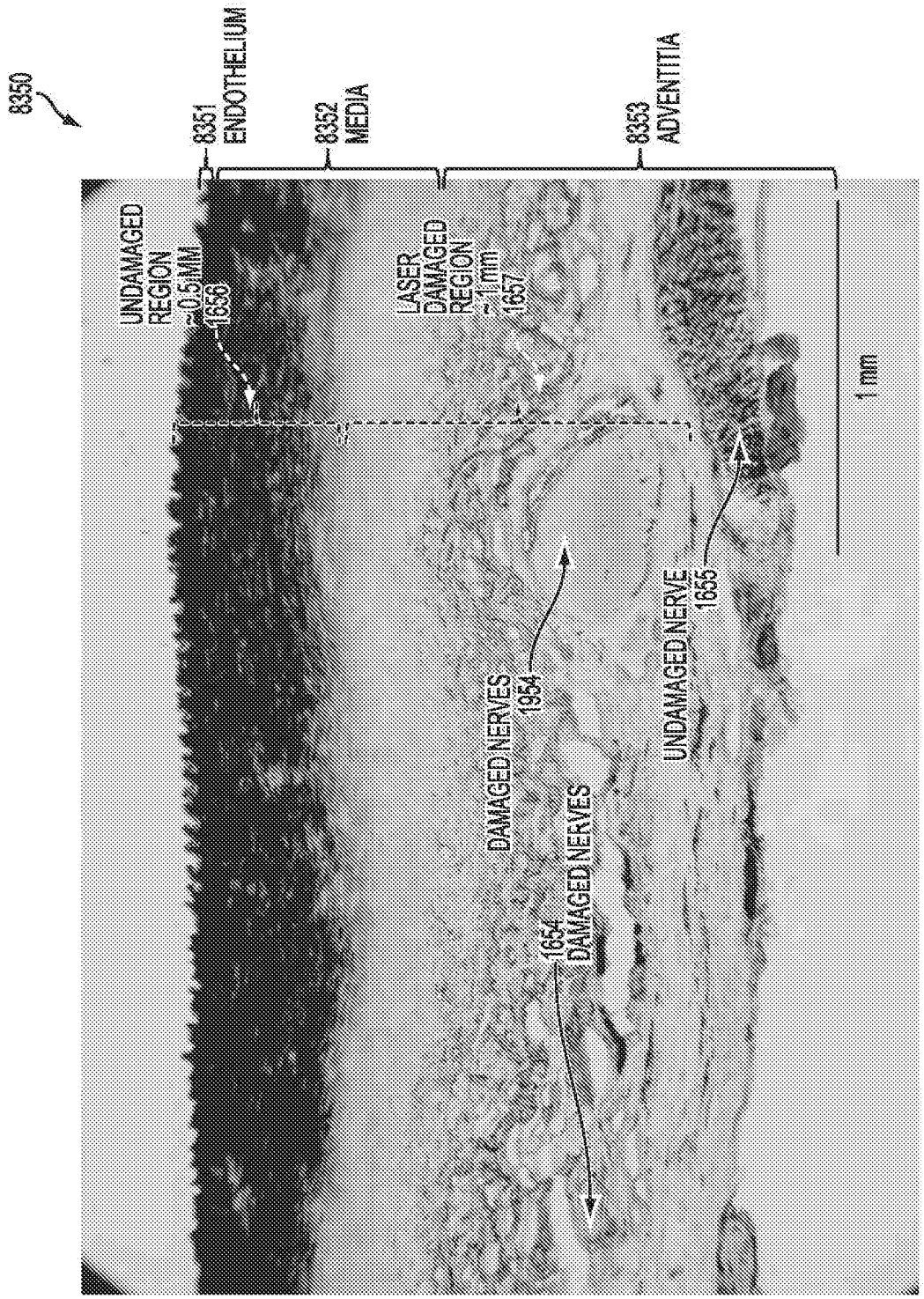

8350
8351
ENDOTHELIUM
8352
MEDIA
8353
ADVENTITIA
UNDAMAGED
REGION
≈0.5MM
1656
LASER
DAMAGED
REGION
~1mm
1657
1 mm
DAMAGED NERVES
1654
1654
DAMAGED NERVES
UNDAMAGED NERVE
1655

FIG. 83B

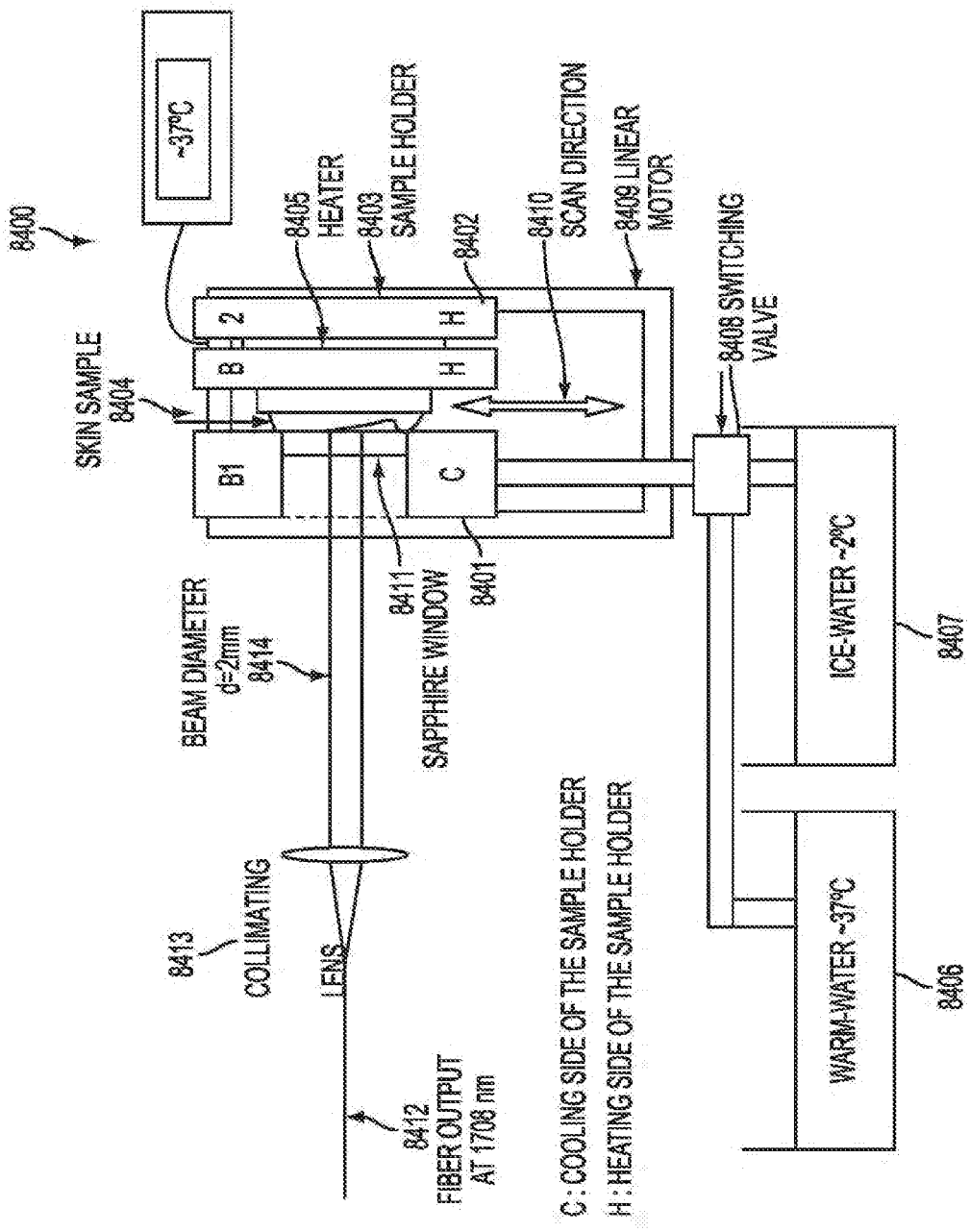

8400
~37°C
8405
HEATER
8403
SAMPLE HOLDER
8402
8410
SCAN DIRECTION
8409 LINEAR
MOTOR
8408 SWITCHING
VALVE
SKIN SAMPLE
8404
B1
B
2
H
H
C
8401
8411
SAPPHIRE WINDOW
BEAM DIAMETER
d=2mm
8414
8413
COLLIMATING
LENS
8412
FIBER OUTPUT
AT 1708 nm
C : COOLING SIDE OF THE SAMPLE HOLDER
H : HEATING SIDE OF THE SAMPLE HOLDER
ICE-WATER ~2°C
8407
WARM-WATER ~37°C
8406

FIG. 84

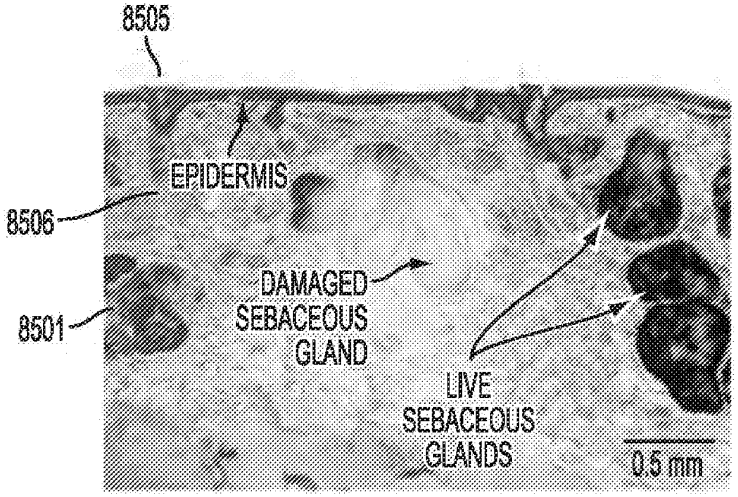


FIG. 85A

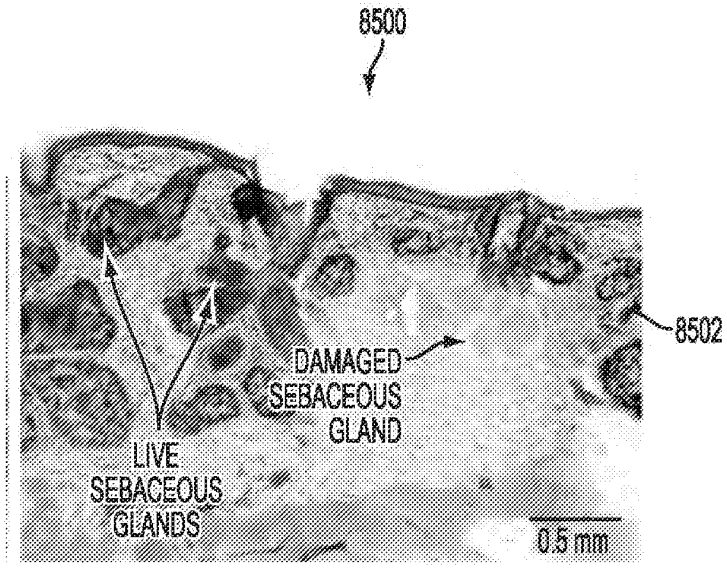


FIG. 85B

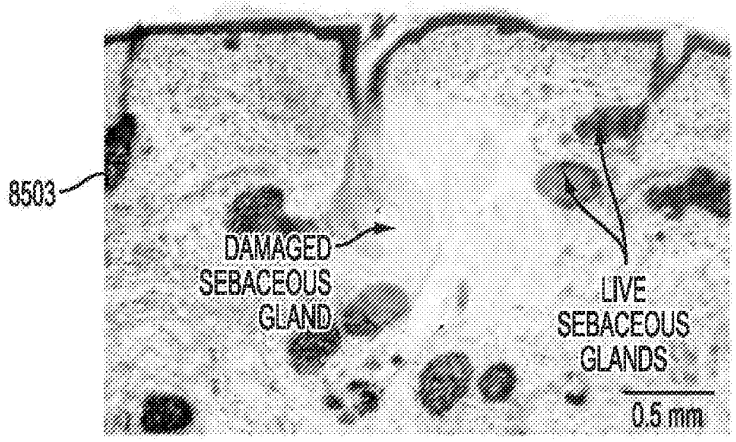


FIG. 85C

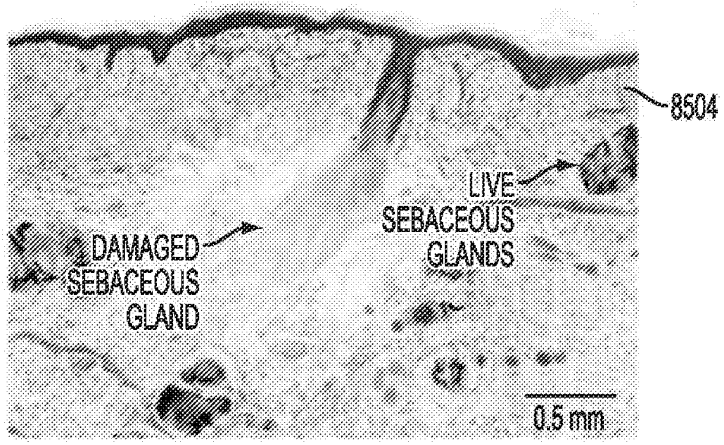


FIG. 85D

Attorney Docket Number	OMNI0101PUSA9

ASSIGNMENT AND DECLARATION (37 C.F.R. 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. 1.76)

Title of Invention	SHORT-WAVE INFRARED SENSOR FOR IDENTIFYING BASED ON WATER CONTENT

As a below named inventor, I hereby declare that:

This declaration is directed to:

[X] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____. (I hereby authorize the insertion of the application filing date and number when they become known.)

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I am aware of the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged, I do hereby assign, sell and set over to OMNI MEDSCI, INC., a corporation organized and existing under the laws of the state of Michigan, and having a place of business at 1718 Newport Creek Drive, Ann Arbor, MI 48103, hereinafter referred to as the ASSIGNEE, its successors, assigns or other legal representatives, my entire right, title and interest, domestic and foreign, in and to the inventions and discoveries in the above-identified application including the right of said ASSIGNEE, its successors, assigns or other legal representatives to make applications and to receive Letters Patent for said inventions and discoveries in any and all foreign countries in its or their own name or names, or in my name, at its or their election, and I hereby assign, sell and set over to said ASSIGNEE, its successors, assigns or other legal representatives, all rights of priority, including any provisional applications, in and to said inventions and discoveries in all countries, including all applications claiming benefit of the filing date hereof, continuations, continuations-in-part, divisionals, reexaminations and reissue applications.

And I hereby agree for myself, my heirs, successors, assigns or other legal representatives to execute any and all papers, including applications for Letters Patent of any and all kinds and in any and all countries and to perform any and all acts which said ASSIGNEE, its successors, assigns or other legal representatives may deem necessary to secure thereto the rights herein assigned, sold and set over.

And I hereby represent and warrant that I have not granted any rights inconsistent with the rights granted herein.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years or both.

LEGAL NAME OF INVENTOR

Inventor: MOHAMMED N. ISLAM Date: 10/21/2020

Signature: _____

Page 1 (Supplemental Sheet with Additional Joint Inventors is attached if necessary)

Note: An Application Data Sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. 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 contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mohammed	N.	ISLAM	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Ann Arbor	State/Province	MI	Country of Residence	US

Mailing Address of Inventor:

Address 1	1718 Newport Creek Drive		
Address 2			
City	Ann Arbor	**State/Province**	MI
Postal Code	48103	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	109543		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO		
Attorney Docket Number	OMNI0101PUSA10	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	100	**Suggested Figure for Publication (if any)**	11

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	109543		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18103408	2023-01-30

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18103408	Continuation of	17514778	2021-10-29	11564577	2023-01-31
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17514778	Continuation of	17078771	2020-10-23	11160455	2021-11-02
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17078771	Continuation of	16/722188	2019-12-20	10820807	2020-11-03
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/722188	Continuation of	16/506885	2019-07-09	10517484	2019-12-31
Prior Application Status	Abandoned				Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16/506885	Continuation of	16/272069	2019-02-11		
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/272069	Continuation of	16/029611	2018-07-08	10201283	2019-02-12
Prior Application Status	Abandoned				Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16/029611	Continuation of	15/888052	2018-02-04		
Prior Application Status	Abandoned				Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
15/888052	Continuation of	15/212549	2016-07-18		
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/212549	Continuation of	14/650897	2015-06-10	9494567	2016-11-15
Prior Application Status	Expired				Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/650897	a 371 of international	PCT/US2013/075700	2013-12-17		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2013/075700	Claims benefit of provisional	61/747472	2012-12-31

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/506885	Continuation of	16/004359	2018-06-09	11109761	2021-09-07

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/004359	Continuation of	14/109007	2013-12-17	9993159	2018-06-12

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/109007	Claims benefit of provisional	61/747553	2012-12-31

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/506885	Continuation of	16/188194	2018-11-12

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/188194	Continuation of	16/004154	2018-06-08	10126283	2018-11-13

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/004154	Continuation of	15/855201	2017-12-27

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/855201	Continuation of	15/711907	2017-09-21

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/711907	Division of	15/357225	2016-11-21

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/357225	Continuation of	14/650981	2015-06-10	9500634	2016-11-22

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/650981	a 371 of international	PCT/US2013/07576	2013-12-17

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2013/075767	Claims benefit of provisional	61/747485	2012-12-31

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/506885	Continuation of	16/241628	2017-01-07	10441176	2019-10-15

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/241628	Continuation of	16/015737	2018-06-22

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/015737	Continuation of	15/594053	2017-05-12

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/594053	Continuation of	14/875709	2015-10-06	9651533	2017-05-16

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/875709	Continuation of	14/108986	2013-12-17

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/108986	Claims benefit of provisional	61/747487	2012-12-31

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/506885	Continuation of	16/284514	2019-02-25
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/284514	Continuation of	16/016649	2018-06-24
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/016649	Continuation of	15/860065	2018-01-02
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/860065	Continuation of	15/686198	2017-08-25
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/686198	Continuation of	15/357136	2016-11-21
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/357136	Continuation of	14/651367	2015-06-11	9500635	2016-11-22

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/651367	a 371 of international	PCT/US2013/075736	2013-12-17
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2013/075736	Claims benefit of provisional	61/747477	2012-12-31
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2013/075736	Claims benefit of provisional	61/754698	2013-01-21

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☒ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

- (●) Assignee
- ( ) Legal Representative under 35 U.S.C. 117
- ( ) Joint Inventor
- ( ) Person to whom the inventor is obligated to assign.
- ( ) Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. [X]

Organization Name	OMNI MEDSCI, INC.		
Mailing Address Information For Applicant:			
Address 1	1718 Newport Creek Drive		
Address 2			
City	Ann Arbor	**State/Province**	MI
Country[i]	US	Postal Code	48103
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Kevin J. Heinl/			Date (YYYY-MM-DD)	2024-02-09
First Name	Kevin J.	Last Name	Heinl	Registration Number	29,805

Additional Signature may be generated within this form by selecting the Add button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	OMNI0101PUSA10
	Application Number	
Title of Invention	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

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 the Freedom of Information Act requires disclosure of these records.

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 CooperationTreaty.

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 inspections 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.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B or equivalent) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	
Filing Date	
First Named Inventor	MOHAMMED N. ISLAM
Title	WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO
Art Unit	
Examiner Name	
Attorney Docket Number	OMNI0101PUSA10

SIGNATURE of Applicant or Patent Practitioner

Signature	/Kevin J. Heinl/	Date (Optional)	2024-02-09
Name	Kevin J. Heinl	Registration Number	29,805
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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/AIA/82B(07-12)
Approved for use through 11/30/2014. OMB 0651-0035
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.

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in the attached transmittal letter.

[x] I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent): 109543

OR

[ ] I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

Name	Registration Number	Name	Registration Number

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

[x] The address associated with the above-mentioned Customer Number.
OR
[ ] The address associated with Customer Number:
OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant:

[ ] Inventor or Joint Inventor
[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor
[x] Assignee or Person to Whom the Inventor is Under an Obligation to Assign
[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (*e.g.*, a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)

SIGNATURE of Applicant for Patent

Signature		Date	October 10, 2012
Name	Mohammed N. Islam	Telephone	734-647-6941
Title and Company	President - OMNI MEDSCI, INC		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below *.

[ ] *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/438,144	02/09/2024		1000	OMNI0101PUSA10	20	3

CONFIRMATION NO. 6361

FILING RECEIPT

109543
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

Date Mailed: 02/26/2024

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Mohammed N. ISLAM, Ann Arbor, MI;

Applicant(s)

OMNI MEDSCI, INC., Ann Arbor, MI;

Power of Attorney: The patent practitioners associated with Customer Number 109543

Domestic Priority data as claimed by applicant

This application is a CON of 18/103,408 01/30/2023 PAT 11,896,346
which is a CON of 17/514,778 10/29/2021 PAT 11,564,577
which is a CON of 17/078,771 10/23/2020 PAT 11,160,455
which is a CON of 16/722,188 12/20/2019 PAT 10,820,807
which is a CON of 16/506,885 07/09/2019 PAT 10,517,484
which is a CON of 16/272,069 02/11/2019 ABN
which is a CON of 16/029,611 07/08/2018 PAT 10,201,283
which is a CON of 15/888,052 02/04/2018 PAT 10,136,819
which is a CON of 15/212,549 07/18/2016 PAT 9,885,698
which is a CON of 14/650,897 06/10/2015 PAT 9,494,567
which is a 371 of PCT/US2013/075700 12/17/2013
which claims benefit of 61/747,472 12/31/2012
and said 16/506,885 07/09/2019 is a CON of 16/004,359 06/09/2018 PAT 11,109,761
which is a CON of 14/109,007 12/17/2013 PAT 9,993,159
which claims benefit of 61/747,553 12/31/2012
and said 16/506,885 07/09/2019 is a CON of 16/188,194 11/12/2018 PAT 10,386,230

which is a CON of 16/004,154 06/08/2018 PAT 10,126,283
which is a CON of 15/855,201 12/27/2017 PAT 9,995,722
which is a CON of 15/711,907 09/21/2017 PAT 9,897,584
which is a DIV of 15/357,225 11/21/2016 PAT 9,797,876
which is a CON of 14/650,981 06/10/2015 PAT 9,500,634
and said 16/506,885 07/09/2019 is a CON of 16/241,628 01/07/2019 PAT 10,441,176
which is a CON of 16/015,737 06/22/2018 PAT 10,172,523
which is a CON of 15/594,053 05/12/2017 PAT 10,188,299
which is a CON of 14/875,709 10/06/2015 PAT 9,651,533
which is a CON of 14/108,986 12/17/2013 PAT 9,164,032
which claims benefit of 61/747,487 12/31/2012
and said 16/506,885 07/09/2019 is a CON of 16/284,514 02/25/2019 ABN
which is a CON of 16/016,649 06/24/2018 PAT 10,213,113
which is a CON of 15/860,065 01/02/2018 PAT 10,098,546
which is a CON of 15/686,198 08/25/2017 PAT 9,861,286
which is a CON of 15/357,136 11/21/2016 PAT 9,757,040
which is a CON of 14/651,367 06/11/2015 PAT 9,500,635
which is a 371 of PCT/US2013/075736 12/17/2013
which claims benefit of 61/747,477 12/31/2012
and claims benefit of 61/754,698 01/21/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 02/23/2024

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/438,144**

Projected Publication Date: 06/06/2024

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: Yes

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
18/438,144

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	* 0	x =	0	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x =	0			
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).			336			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1000		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
AMENDMENT A	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
AMENDMENT A	Application Size Fee (37 CFR 1.16(s))									
AMENDMENT A	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
AMENDMENT B	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
AMENDMENT B	Application Size Fee (37 CFR 1.16(s))									
AMENDMENT B	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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".
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Under Secretary of Commerce for Intellectual Property and
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Derrick Brent
Deputy Under Secretary of Commerce for Intellectual Property and
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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
18/438,144	02/09/2024	ISLAM, Mohammed N.	OMNI0101PUSA10

		EXAMINER	
Brooks, Kushman P.C./Cheetah Omni MedSci 150 W 2nd St., Suite 400N Royal Oak, MI 48067		--	
		ART UNIT	PAPER
		--	20240427-nsQz9G

DATE MAILED: 27 April 2024

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

PTO-90C (Rev.04-03)

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Inquiries regarding this matter may be directed to Mark Polutta, Senior Legal Advisor, at (571) 272-7709 or Andrew Stclair, Legal Advisor, at (571) 270-0238, both of the Office of Patent Legal Administration or via email addressed to Patent.Practice@uspto.gov.

Henry "Jamie" Holcombe
Chief Information Officer
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Dated: April 27th, 2024

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/438,144	02/09/2024	Mohammed N. ISLAM	OMNI0101PUSA10

CONFIRMATION NO. 6361

109543
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

PUBLICATION NOTICE

OC000000073590547

Date Mailed: 06/06/2024

Title:WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Publication No.US-2024-0180428-A1
Publication Date:06/06/2024

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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 viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html.

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APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
18438144	**02/09/2024**	**Mohammed ISLAM**	**OMNI0101PUSA10**

Title of Invention

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

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OMNI MEDSCI, INC.	100%
Total	**100%**

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Application #	Filing Date

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Patent #
11896346
9494567
9993159
10441176
11564577
9500635
9164032
9500634

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Signature	Name	Registration #
/Kevin J. Heinl/	Kevin Heinl	29805

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* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

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APPROVAL LETTER

APPLICATION #	FILING DATE	APPLICANT/PATENT UNDER REEXAMINATION
18/438,144	**02/09/2024**	**Mohammed ISLAM**

Title of Invention

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Electronic terminal disclaimer filed on 08/20/2024

Approved

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/438,144	**08/20/2024 05:18:46 PM Z ET**	**OMNI0101PUSA10**

Title of Invention

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6361	FILED BY	Sharon Kaiser
PATENT CENTER #	66856256	FILING DATE	02/09/2024
CUSTOMER #	109543	FIRST NAMED INVENTOR	Mohammed N. ISLAM
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kevin Heinl

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	47 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic-Approved	18 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	D488F00B46C9719357C83C4380E85B4E3B12C04290760071B3BC3E42650402A1AC7C58C34D62AAE7255B5EFB0FAEAF99FF20CD83A0339ED317176A1965D75407

grantLetter.pdf

9390E60C7DA65849B7AF6389919A31741CE18E92C3C45CF9E
3D1B555432B7E2F30D3BCF671CE973D8F0B7A9F6639EE76B1
E1B310C6D0EE2492899FFBC1871ED5

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/438,144	**08/20/2024 05:18:46 PM Z ET**	**OMNI0101PUSA10**

Title of Invention

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6361	FILED BY	Sharon Kaiser
PATENT CENTER #	66856256	AUTHORIZED BY	Kevin Heinl
CUSTOMER #	109543	FILING DATE	02/09/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Mohammed N. ISLAM

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DA / 023978	**E20248JH19476140**	**Kevin Heinl**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
023978	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
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Examiner-Initiated Interview Summary	**Application No.** 18/438,144	**Applicant(s)** ISLAM, Mohammed N.		
	Examiner MD M RAHMAN	**Art Unit** 2877	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
MD M RAHMAN	Primary Examiner	Telephonic
Kevin Heinl	Attorney	

Date of Interview: 19 August 2024

Issues Discussed:

Proposed Amendment(s)

Examiner initiated an interview notifying the applicant's representative that the application would be in condition for allowance considering applicant agrees to file the terminal disclaimer.

/MD M RAHMAN/ Primary Examiner, Art Unit 2877	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

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Notice of References Cited	Application/Control No. 18/438,144	Applicant(s)/Patent Under Reexamination ISLAM, Mohammed N.	
	Examiner MD M RAHMAN	Art Unit 2877	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-9915726-B2	2018-03-13	Bailey; Howard	G01S7/4814	1/1
*	B	US-9430093-B2	2016-08-30	Harrison; Chris	G06F3/0421	1/1
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC 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 YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	08/23/2024								
1	1	=								
2	2	=								
3	3	=								
4	4	=								
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16	16	=								
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18	18	=								
19	19	=								
20	20	=								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

CPC - Searched*		
Symbol	**Date**	**Examiner**
(A61B5/0088 or A61B5/0013 or A61B5/0022 or A61B5/0075 or A61B5/0086 or A61B5/14532 or A61B5/14546 or A61B5/1455 or A61B5/4547 or A61B5/6801 or A61B5/7203 or A61B5/7257 or A61B5/7405 or A61B5/742 or A61C19/04 or G01J3/02 or G01J3/0218 or G01J3/108 or G01J3/14 or G01J3/28 or G01J3/2823 or G01J3/42 or G01J3/453 or G01N21/35 or G01N21/3504 or G01N21/3563 or G01N21/359 or G01N21/39 or G01N21/88 or G01N33/02 or G01N33/025 or G01N33/15 or G01N33/442 or G01N33/49 or G16H40/67 or G16Z99/00 or A61B5/0024 or A61B2562/0233 or A61B2562/0238 or A61B2562/146 or A61B2576/02 or A61C1/0046 or G01J3/1838 or G01J2003/104 or G01J2003/1208 or G01J2003/2826 or G01M3/38 or G01N21/85 or G01N21/9508 or G01N2021/3513 or G01N2021/3595 or G01N2021/399 or G01N2201/061 or G01N2201/06113 or G01N2201/062 or G01N2201/08 or G01N2201/12 or G01N2201/129 or H01S3/0092 or H01S3/06758 or H01S3/302 or Y02A90/10 or A61B5/682 or G01N21/474 or G16H40/63 or G16H50/20 or G01N2201/0221 or G01N2021/1789 or G01N2201/0626 or G01N2201/0627).cpc.	08/23/2024	MR

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
356	300	08/23/2024	MR

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/MD M RAHMAN/ Primary Examiner, Art Unit 2877	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

Search Notes		
Search Notes	**Date**	**Examiner**
INVENTOR SEARCH, US PG PUB AND PAT	08/23/2024	MR

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	(A61B5/0088 or A61B5/0013 or A61B5/0022 or A61B5/0075 or A61B5/0086 or A61B5/14532 or A61B5/14546 or A61B5/1455 or A61B5/4547 or A61B5/6801 or A61B5/7203 or A61B5/7257 or A61B5/7405 or A61B5/742 or A61C19/04 or G01J3/02 or G01J3/0218 or G01J3/108 or G01J3/14 or G01J3/28 or G01J3/2823 or G01J3/42 or G01J3/453 or G01N21/35 or G01N21/3504 or G01N21/3563 or G01N21/359 or G01N21/39 or G01N21/88 or G01N33/02 or G01N33/025 or G01N33/15 or G01N33/442 or G01N33/49 or G16H40/67 or G16Z99/00 or A61B5/0024 or A61B2562/0233 or A61B2562/0238 or A61B2562/146 or A61B2576/02 or A61C1/0046 or G01J3/1838 or G01J2003/104 or G01J2003/1208 or G01J2003/2826 or G01M3/38 or G01N21/85 or G01N21/9508 or G01N2021/3513 or G01N2021/3595 or G01N2021/399 or G01N2201/061 or G01N2201/06113 or G01N2201/062 or G01N2201/08 or G01N2201/12 or G01N2201/129 or H01S3/0092 or H01S3/06758 or H01S3/302 or Y02A90/10 or A61B5/682 or G01N21/474 or G16H40/63 or G16H50/20 or G01N2201/0221 or G01N2021/1789 or G01N2201/0626 or G01N2201/0627).cpc.	08/23/2024	MR

/MD M RAHMAN/ Primary Examiner, Art Unit 2877	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

CPC						
Symbol					**Type**	**Version**
A61B	/	5	/	0088	F	2013-01-01
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A61B	/	5	/	7257	I	2013-01-01
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G01N	/	21	/	35	I	2013-01-01
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G01N	/	21	/	359	I	2013-01-01
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A61B	/	5	/	14546	I	2013-01-01
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G01N	/	33	/	025	I	2013-01-01
A61B	/	5	/	1455	I	2013-01-01

Use images from artifact folder? (•) Yes ( ) No

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/MD M RAHMAN/ Primary Examiner, Art Unit 2877 (Primary Examiner)	23 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 21

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

CPC						
Symbol					**Type**	**Version**
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H01S	/	3	/	0092	A	2013-01-01
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A61B	/	2562	/	146	A	2013-01-01
A61B	/	2576	/	02	A	2013-01-01
A61B	/	2562	/	0238	A	2013-01-01
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G01N	/	2201	/	08	A	2013-01-01
G01N	/	2201	/	06113	A	2013-01-01
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A61C	/	1	/	0046	A	2013-01-01
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Use images from artifact folder? ◉ Yes ○ No

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/MD M RAHMAN/ Primary Examiner, Art Unit 2877 (Primary Examiner)	23 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 21

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	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**
/ /				

Use images from artifact folder? Yes No

NONE (Assistant Examiner) (Date)		**Total Claims Allowed:** 20	
/MD M RAHMAN/ Primary Examiner, Art Unit 2877 (Primary Examiner) (Date)	23 August 2024	O.G. Print Claim(s) 1	O.G. Print Figure 21

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

INTERNATIONAL CLASSIFICATION				
CLAIMED				
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G01J3/10	/	3	/	10
G01J3/28	/	3	/	28
G01J3/14	/	3	/	14
G01J3/453	/	3	/	453
G01J3/42	/	3	/	42
G01J3/02	/	3	/	02
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G01N21/359	/	21	/	359
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G01N33/49	/	33	/	49
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G01N21/39	/	21	/	39
G01N33/02	/	33	/	02
G01N33/44	/	33	/	44
G01N21/88	/	21	/	88
A61B5/1455	/	5	/	1455
G16Z99/00	/	99	/	00

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
356	300

Use images from artifact folder? (•) Yes ( ) No

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/MD M RAHMAN/ Primary Examiner, Art Unit 2877 (Primary Examiner)	23 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 21

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

Use images from artifact folder? Yes No

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/MD M RAHMAN/ Primary Examiner, Art Unit 2877 (Primary Examiner)	23 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 21

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	18/438,144	ISLAM, Mohammed N.
	Examiner	**Art Unit**
	MD M RAHMAN	2877

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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9	9	18	18												

Use images from artifact folder? ◉ Yes ○ No

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/MD M RAHMAN/ Primary Examiner, Art Unit 2877 (Primary Examiner)	23 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 21

Bibliographic Data

Application No: 18/438,144

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No | ☐ Met After Allowance

Verified and Acknowledged: /MD M RAHMAN/ (Examiner's Signature) | (Initials)

Title: WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
02/09/2024 **RULE**	250	2877	OMNI0101PUSA10

APPLICANTS

OMNI MEDSCI, INC., Ann Arbor, MI, UNITED STATES

INVENTORS

Mohammed N. ISLAM, Ann Arbor, MI, UNITED STATES

CONTINUING DATA

This application is a CON of 18103408 01/30/2023 PAT 11896346

18103408 is a CON of 17514778 10/29/2021 PAT 11564577

17514778 is a CON of 17078771 10/23/2020 PAT 11160455

17078771 is a CON of 16722188 12/20/2019 PAT 10820807

16722188 is a CON of 16506885 07/09/2019 PAT 10517484

16506885 is a CON of 16284514 02/25/2019ABN

16506885 is a CON of 16272069 02/11/2019ABN

16506885 is a CON of 16241628 01/07/2019 PAT 10441176

16506885 is a CON of 16188194 11/12/2018 PAT 10386230

16272069 is a CON of 16029611 07/08/2018 PAT 10201283

16284514 is a CON of 16016649 06/24/2018 PAT 10213113

16241628 is a CON of 16015737 06/22/2018 PAT 10172523

16506885 is a CON of 16004359 06/09/2018 PAT 11109761

16188194 is a CON of 16004154 06/08/2018 PAT 10126283

16029611 is a CON of 15888052 02/04/2018 PAT 10136819

16016649 is a CON of 15860065 01/02/2018 PAT 10098546

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15855201 is a CON of 15711907 09/21/2017 PAT 9897584

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16015737 is a CON of 15594053 05/12/2017 PAT 10188299

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14651367 is a 371 of PCT/US2013/075736 12/17/2013

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14108986 has PRO of 61747487 12/31/2012

14109007 has PRO of 61747553 12/31/2012

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

02/23/2024

**** SMALL ENTITY ****

STATE OR COUNTRY

UNITED STATES

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Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067
UNITED STATES

FILING FEE RECEIVED

$1,000

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
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L66	63	2 AND ((wrist ear) AND (light laser source beam) AND (detect$ sensor))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2024/08/23 11:05 AM

			IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L67	71	3 AND ((wrist ear) AND (light laser source beam) AND (detect$ sensor))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
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L70	10	4 AND (lens AND mirror AND reflect$)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L71	5628	5 AND (lens AND mirror AND reflect$)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2024/08/23 11:05 AM

			MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L72	87	2 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L73	92	3 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L74	10	4 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L75	14026	5 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L76	58	6 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO);	OR	ON	ON	2024/08/23 11:05 AM

			FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L77	4205	8 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L78	91	9 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L79	10	10 AND (obesity near3 epidemic, diabetes)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L80	82	3 AND (blood AND measur$ near3 glucose)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L81	10	4 AND (blood AND measur$ near3 glucose)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO;	OR	ON	ON	2024/08/23 11:05 AM

			DERWENT; IBM_TDB)				
L82	55	6 AND (blood AND measur$ near3 glucose)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L83	10	10 AND (blood AND measur$ near3 glucose)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L84	55	16 AND (blood AND measur$ near3 glucose)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L85	32436	1 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L86	115	2 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM

L87	128	3 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L88	10	4 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L89	3832	5 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L90	60	6 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L91	6481	8 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infrared ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L92	126	9 AND (infrared near3	(US-PGPUB; USPAT;	OR	ON	ON	2024/08/23

		spectroscopy, absorption near3 spectroscopy,near$infra red ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				11:05 AM
L93	58	16 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infra red ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L94	115	26 AND (infrared near3 spectroscopy, absorption near3 spectroscopy,near$infra red ADJ diffuse ADJ reflection, transmission near3 spectroscopy)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L95	10	10 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L96	87	12 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L97	10	14 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP,	OR	ON	ON	2024/08/23 11:05 AM

			AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L98	91	18 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L99	10	19 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L100	4719	25 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L101	10	28 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L102	58	33 AND (skin AND blood AND spectral)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	OR	ON	ON	2024/08/23 11:05 AM

			CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L103	926	15 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L104	31	18 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L105	10	19 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L106	29	22 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L107	33	26 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2024/08/23 11:05 AM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L108	10	28 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L109	679	29 AND (scatter AND wavelength AND absorb$ AND intensity)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L110	10	10 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L111	64	12 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L112	54	16 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA,	OR	ON	ON	2024/08/23 11:05 AM

			EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L113	64	18 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L114	214	25 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L115	10	28 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L116	75	29 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L117	56	30 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2024/08/23 11:05 AM

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L118	10	35 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM
L119	64	38 AND (hyper near3 spectral near3 imaging)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/23 11:05 AM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N40	188966	(A61B5/0088 OR A61B5/0013 OR A61B5/0022 OR A61B5/0075 OR A61B5/0086 OR A61B5/14532 OR A61B5/14546 OR A61B5/1455 OR A61B5/4547 OR A61B5/6801 OR A61B5/7203 OR A61B5/7257 OR A61B5/7405 OR A61B5/742 OR A61C19/04 OR G01J3/02 OR G01J3/0218 OR G01J3/108 OR G01J3/14 OR G01J3/28 OR G01J3/2823 OR G01J3/42 OR G01J3/453 OR G01N21/35 OR G01N21/3504 OR	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM

		G01N21/3563 OR G01N21/359 OR G01N21/39 OR G01N21/88 OR G01N33/02 OR G01N33/025 OR G01N33/15 OR G01N33/442 OR G01N33/49 OR G16H40/67 OR G16Z99/00 OR A61B5/0024 OR A61B2562/0233 OR A61B2562/0238 OR A61B2562/146 OR A61B2576/02 OR A61C1/0046 OR G01J3/1838 OR G01J2003/104 OR G01J2003/1208 OR G01J2003/2826 OR G01M3/38 OR G01N21/85 OR G01N21/9508 OR G01N2021/3513 OR G01N2021/3595 OR G01N2021/399 OR G01N2201/061 OR G01N2201/06113 OR G01N2201/062 OR G01N2201/08 OR G01N2201/12 OR G01N2201/129 OR H01S3/0092 OR H01S3/06758 OR H01S3/302 OR Y02A90/10 OR G01J2003/064 OR G01J2003/1213 OR G01J3/0208 OR G01J3/0224 OR G01J3/0245 OR G01J3/0264 OR G01J3/06 OR G01J3/1895 OR G01J3/32 OR G16H40/20 OR G16H70/40 OR G01N2021/1793 OR G01N2201/0214 OR G01N2201/0216 OR G01N2201/0221 OR G01N2201/0612 OR G01N2201/0691 OR G01N2333/00 OR H01S3/06754 OR H01S3/10023).cpc.					

N41	1533	1 AND ((wrist ear) AND (light laser source beam) AND (detect$ sensor)).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N42	2269	1 AND (lens AND mirror AND reflect$).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N43	11	2 AND (lens AND mirror AND reflect$).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N44	11	4 AND (lens AND mirror AND reflect$).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N45	28	2 AND (obesity near3 epidemic, diabetes).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N46	7	3 AND (obesity near3 epidemic, diabetes).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N47	1	4 AND (obesity near3 epidemic, diabetes).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N48	1	5 AND (obesity near3 epidemic, diabetes).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N49	28	6 AND (obesity near3 epidemic, diabetes).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N50	7	7 AND (obesity near3 epidemic, diabetes).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N51	2421	1 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N52	47	2 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N53	19	3 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N54	2	4 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N55	2	5 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N56	5	6 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N57	0	7 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N58	0	8 AND (blood AND measur$ near3 glucose).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM

N59	2	5 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N60	2	6 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N61	0	8 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N62	2	10 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N63	2	15 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N64	0	18 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N65	0	19 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N66	0	9 AND (skin AND blood AND spectral).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N67	0	5 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N68	0	6 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N69	0	8 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N70	0	10 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N71	0	13 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N72	0	16 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N73	0	18 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N74	0	19 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM

N75	0	25 AND (scatter AND wavelength AND absorb$ AND intensity).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N76	0	10 AND (hyper near3 spectral near3 imaging).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N77	0	14 AND (hyper near3 spectral near3 imaging).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM
N78	0	16 AND (hyper near3 spectral near3 imaging).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/23 11:07 AM

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

109543 7590 09/04/2024
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

EXAMINER
RAHMAN, MD M

ART UNIT	PAPER NUMBER
2877	

DATE MAILED: 09/04/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/438,144	02/09/2024	Mohammed N. ISLAM	OMNI0101PUSA10	6361

TITLE OF INVENTION: WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	12/04/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

109543 7590 09/04/2024
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

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 transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/438,144	02/09/2024	Mohammed N. ISLAM	OMNI0101PUSA10	6361

TITLE OF INVENTION: WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	12/04/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAHMAN, MD M	2877	250-341800

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/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/438,144	02/09/2024	Mohammed N. ISLAM	OMNI0101PUSA10	6361

109543 7590 09/04/2024
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

EXAMINER
RAHMAN, MD M

ART UNIT	PAPER NUMBER
2877	

DATE MAILED: 09/04/2024

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.

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 30 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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) 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));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/438,144	Applicant(s) ISLAM, Mohammed N.	
	Examiner MD M RAHMAN	Art Unit 2877	AIA (FITF) Status Yes

-- 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 2/9/24.
   ☐ 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 1-20 . 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 _____.

/MD M RAHMAN/
Primary Examiner, Art Unit 2877

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Terminal Disclaimer

The terminal disclaimer filed on 8/20/24 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of (US 11896346, US9494567, US9993159, US10441176, US9500635, US9164032, US9500634 and US11564577) has been reviewed and is accepted. The terminal disclaimer has been recorded.

Allowable Subject Matter

Claims 1-20 are allowed.

The following is an Examiner's statement of reasons for allowance: the closest prior art obtained from an Examiner's search (Harrison et al. (US 9430093 B2) does not teach nor suggest in detail the limitations:

As to claim 1, the prior arts alone or in combination fail to disclose the claimed limitations such as, "wherein the output signal is indicative of the one or more physiological parameters that change in response to the stretching of the hand or movement of the fingers or the thumb of the user; the wearable device configured to

increase the signal-to-noise ratio by increasing light intensity of at least one of the plurality of light emitting diodes from an initial light intensity; and the detection system further configured to: generate a first signal responsive to light received while the light emitting diodes are off, generate a second signal responsive to light received while at least one of the light emitting diodes is on, and increase the signal-to-noise ratio by comparing the first signal and the second signal; and wherein the wearable device is at least in part configured to identify an object" along with all other limitations of the claim.

As to claim 7, the prior arts alone or in combination fail to disclose the claimed limitations such as, "wherein the detection system is configured to be synchronized to the light source; wherein the detection system comprises a plurality of detectors that are spatially separated from each other, and wherein at least one analog to digital converter is coupled to at least one of the plurality of detectors; wherein the output signal is indicative of the one or more of the physiological parameters; the wearable device configured to increase the signal-to-noise ratio by increasing light intensity of at least one of the plurality of semiconductor diodes from an initial light intensity; and the detection system further configured to: generate a first signal responsive to light received while the semiconductor diodes are off, generate a second signal responsive to light received while at least one of the semiconductor diodes is on, and increase the signal-to-noise ratio by comparing the first signal and the second signal; and wherein the wearable device is at least in part configured to identify an object" along with all other limitations of the claim.

As to claim 16, the prior arts alone or in combination fail to disclose the claimed limitations such as, "measure time-of-flight of the at least a portion of the light from the

array of laser diodes reflected from the object relative to the at least a portion of the light generated by the array of laser diodes is configured to be directed to the object, and (iii) generate one or more images of the object based at least in part on an amplitude of the at least a portion of the light from the array of laser diodes reflected from the object; wherein the detection system is configured to synchronize to pulsing of the at least one of the laser diodes, and wherein the processor is configured to generate a time-of-flight measurement; and a camera system coupled to a lens system and the processor, the camera system configured to capture a second image including at least a part of the object; wherein the remote sensing system including the processor is configured to combine at least a portion of the second image and at least a portion of the time-of-flight measurement to create a combined portion; and wherein the remote sensing system including the processor is configured to communicate with a wearable device, a smart phone or a tablet that is further configured to process or display some of the combined portion" along with all other limitations of the claim.

Harrison only teaches: FIG. 4A illustrates an example 400 of a stylus input object 404 in a hover state with respect to a phone interactive interface 406 projected onto a notepad interface object 402. The stylus input object 404 and notepad interface object 402 may be identified and/or tracked within an environment with respect to one another. The phone interactive interface 406 may be projected onto the notepad interface object 402…col. 9, lines 5-11; FIG. 6A illustrates an example 600 of a finger input object

604 in a hover state 606. The finger input object 604 may be indentified and tracked as an input object within an environment. Similarly, a palm interface object 602 may be indentified and tracked as an interface object within the environment. The palm interface object 602 and the finger input object 604 may be tracked with respect to one another in the environment…col.10, lines 10-17.

Claims 2-6, 8-15 and 17-20 are allowable due to their dependencies.

The closest references, Harrison et al. and Bailey et al. (US 9915726 B2) alone or in combination disclose some features of the claimed invention but do not disclose the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MD M RAHMAN whose telephone number is (571)272-9175. The examiner can normally be reached on Mon-Thur.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, TARIFUR CHOWDHURY can be reached on 571-272-2287. 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.

MD M. RAHMAN
Primary Patent Examiner
Art Unit 2886

/MD M RAHMAN/
Primary Examiner, Art Unit 2877

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

109543 7590 09/04/2024
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

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 transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Sharon Kaiser	(Typed or printed name)
/Sharon Kaiser/	(Signature)
December 3, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/438,144	02/09/2024	Mohammed N. ISLAM	OMNI0101PUSA10	6361

TITLE OF INVENTION: WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	12/04/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAHMAN, MD M	2877	250-341800

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 Brooks Kushman P.C.
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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: OMNI MEDSCI, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): ANN ARBOR, MICHIGAN

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 02-3978

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 /Kevin J. Heinl/ Date December 3, 2024

Typed or printed name Kevin J. Heinl Registration No. 29,805

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/438,144	**12/03/2024 04:41:09 PM Z ET**	**OMNI0101PUSA10**

Title of Invention

WEARABLE DEVICES COMPRISING SEMICONDUCTOR DIODE LIGHT SOURCES WITH IMPROVED SIGNAL-TO-NOISE RATIO

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6361	FILED BY	Sharon Kaiser
PATENT CENTER #	68206964	FILING DATE	02/09/2024
CUSTOMER #	109543	FIRST NAMED INVENTOR	Mohammed N. ISLAM
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kevin Heinl

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Issue-Fee-PTOL85.pdf	1	Issue Fee Payment (PTO-85B)	1108 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Issue-Fee-PTOL85.pdf	88A516B5F68A80E0610AEB078B7A06D4920025171CD8DAB3D D084F77F812180E1AB3D1CEEC10E25591FAD0360D5137A1D0 C801655E63DC5BE2035B169A221291

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 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.

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ELECTRONIC PAYMENT RECEIPT

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18/438,144	**12/03/2024 04:41:09 PM Z ET**	**OMNI0101PUSA10**

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CUSTOMER #	109543	FILING DATE	02/09/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Mohammed N. ISLAM

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 023978	**E2024B3G44289504**	**Sharon Kaiser**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
023978	**37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	**$480.00**

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.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/438,144	01/14/2025	12193790	OMNI0101PUSA10	6361

109543 7590 12/25/2024
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

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 0 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 Center (https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Mohammed N. ISLAM, Ann Arbor, MI;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

OMNI MEDSCI, INC., Ann Arbor, MI;

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/438,144	02/09/2024	Mohammed N. ISLAM	OMNI0101PUSA10	6361

109543 7590 01/14/2025
Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

EXAMINER
RAHMAN, MD M

ART UNIT	PAPER NUMBER
2877	

NOTIFICATION DATE	DELIVERY MODE
01/14/2025	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):

docketing@brookskushman.com

PTOL-90A (Rev. 04/07)

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/438,144	14-Jan-2025	12193790

Brooks, Kushman P.C./Cheetah Omni MedSci
150 W 2nd St., Suite 400N
Royal Oak, MI 48067

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants