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Title of Invention

NEAR-INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF BREAST AND OTHER CANCERS

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NEAR-INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF BREAST AND OTHER CANCERS

TECHNICAL FIELD

[0001] This disclosure relates to lasers and light sources for use in near-infrared spectroscopy for early detection of various kinds of cancers, including breast cancer, and to systems and methods for using near-infrared or short-wave infrared light sources for early detection of breast cancer using, for example, a fiber-based super-continuum source.

BACKGROUND AND SUMMARY

[0002] 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.

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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.

[0007] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] 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:

[0009] FIGURE 1 illustrates the optical absorption of pure water, hemoglobin without oxygen, and hemoglobin saturated with oxygen.

[0010] FIGURE 2 shows examples of various absorption bands of chemical species in the wavelength range between about 1200-2200nm.

[0011] FIGURE 3 depicts the structure of a female breast.

[0012] FIGURE 4 illustrates particular embodiments of imaging systems for optically scanning a breast.

[0013] FIGURE 5 shows the normalized absorption spectra of main tissue absorbers in the NIR for breast cancer, between about 600-1100nm.

[0014] FIGURE 6 illustrates the normalized absorption coefficient in the wavelength range between about 500-1600nm for many of the components of breast tissue.

[0015] FIGURE 7 shows the typical spectra of the cancerous site of a treated rat and the corresponding site of a normal rat. (A) Logarithm of the inverse of reflection spectra; and (B) second derivative spectra.

[0016] FIGURE 8 shows the second derivative of spectral changes over several weeks between about 1600-1800nm in rats with breast cancer.

[0017] FIGURE 9 illustrates the second derivative spectra for cholesterol, collagen and elastin.

[0018] FIGURE 10 shows the absorption coefficient as a function of wavelength between about 1000nm and 2600nm for water, adipose and collagen.

[0019] FIGURE 11 illustrates the absorbance for four types of collagen: collagen I, collagen II, collagen III, and collagen IV.

[0020] FIGURE 12 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.

[0021] FIGURE 13 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.

[0022] FIGURE 14 illustrates the optical absorption or density as a function of wavelength between approximately 700nm and 1300nm for water, hemoglobin and oxygenated hemoglobin.

[0023] FIGURE 15 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.

[0024] FIGURE 16 presents histology of renal arteries comprising endothelium, media and adventitia layers and some renal nerves in or below the adventitia. (A) No laser exposure. (B) After focused laser exposure, with the laser light near 1708nm.

[0025] FIGURE 17 illustrates the experimental set-up for *ex vivo* skin laser treatment with surface cooling to protect the epidermis and top layer of the dermis.

[0026] FIGURE 18 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 (A and B) corresponding to ~70 J/cm² average fluence and 830mW (C and D) corresponding to ~80 J/cm² average fluence.

[0027] FIGURE 19 illustrates a block diagram or building blocks for constructing high power laser diode assemblies.

[0028] FIGURE 20 shows a platform architecture for different wavelength ranges for an all-fiber-integrated, high powered, super-continuum light source.

[0029] FIGURE 21 illustrates one embodiment for a short-wave infrared super-continuum light source.

[0030] FIGURE 22 shows the output spectrum from the SWIR SC laser of FIGURE 21 when about 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.

[0031] 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).

DETAILED DESCRIPTION

[0032] 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 and 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.

[0033] 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 1 illustrates the optical absorption 100 of pure water (dotted line) 101, hemoglobin without oxygen (thinner solid line) 102, and hemoglobin saturated with oxygen (thicker solid line) 103. 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.

[0034] FIGURE 2 shows examples of various absorption bands of chemical species 200 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 201 between about 1000nm and 1700nm, the first overtone region 202 between about 1500nm and 2050nm, and the combination band region 203 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 2 that overlap with the absorption valleys in Figure 1. These are likely to be the wavelengths of interest for spectroscopic analysis of cancerous regions.

[0035] In women, the breasts (FIGURE 3) 300 overlay the pectoralis major muscles 302 and cover much of the chest area and the chest walls 301. The breast is an apocrine gland that produces milk to feed an infant child; the nipple 304 of the breast is surrounded by an areola 305, which has many sebaceous glands. The basic units of the breast are the terminal duct lobules 303, which produce the fatty breast milk. They give the breast its function as a mammary gland. The lobules 303 feed through the milk ducts 306, and in turn these ducts drain to the nipple 304. The superficial tissue layer (superficial fascia) may be separated from the skin 308 by about 0.5-2.5cm of adipose of fatty tissue 307.

[0036] Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts 306, the lobules 303 that supply the ducts with milk, and/or the connective tissue between the lobules. Cancers originating from ducts 306 are known as ductal carcinomas, while those originating from lobules 303 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.

[0037] Several particular embodiments of imaging systems 400, 450 for optically scanning a breast are illustrated in FIGURE 4. In these particular embodiments, the patient 401, 451 may lie in a prone position with her breasts inside a box 402, 452 with probably a transparent window on the detector side. A compression plate 403, 453 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 402, 452 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 4 may also have one or more detectors 404, 455, one or more light sources 404, 454, various electronics, and even an imaging system based on charge coupled devices 405. As illustrated in FIGURE 4, the light sources 404, 454 and detectors 404, 455 may be coupled to the box 402, 452 through one or more fibers 406, 456. Also, the imaging may be in reflection mode (top of FIGURE 4), transmission mode (bottom of FIGURE 4), or some combination.

[0038] Beyond the geometry and apparatus of FIGURE 4, 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.

[0039] Although particular embodiments of imaging architectures are illustrated in FIGURE 4, 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 304. 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 304 and areola 305 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 303 and connective tissue. Both non-invasive and minimally invasive optical imaging methods are intended to be covered by this disclosure.

OPTICAL WAVELENGTH RANGES FOR CANCER DETECTION

[0040] 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 5 shows the normalized absorption spectra 500 of main tissue absorbers in the NIR between about 600nm and 1100nm: deoxy-hemoglobin, Hb, 501, oxy-hemoglobin, HbO₂, 502, water 503, lipids 504 and collagen 505. 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.

[0041] Based on FIGURE 1 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 100 in FIGURE 1, the absorption between approximately 1000-1300nm may be comparable to the 600-1000nm window described in FIGURE

5. 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.

[0042] 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 6 illustrates the normalized absorption coefficient μ_a in the wavelength range between about 500nm and 1600nm for Hb 601, HbO₂ 602, beta-carotene 603, water 604, lipid 605 and collagen 606.

COLLAGEN AND ADIPOSE SIGNATURES IN NEAR-IR

[0043] 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.

[0044] 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.

[0045] 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 7 shows the typical spectra of the cancerous site of the treated rat and the corresponding site of the normal rat. FIGURE 7A shows the logarithm of the inverse of reflection spectra 700, while FIGURE 7B shows their second derivative spectra 750. The curves 701, 751 correspond to the spectra of the cancerous sites, while 702, 752 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 7B may be used for interpretation of the spectral changes.

[0046] In FIGURE 7B 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 7 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.

[0047] 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 8, the second derivative spectral changes 800 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 801 to the 7th 802 week. The cancer's temporal progression through the 8th 803, 9th 804, 10th 805 and 11th 806 week are shown in the various curves in FIGURE 8. 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 806 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.

[0048] Moreover, in the data of FIGURE 8 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 11). 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.

[0049] 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 9 illustrates the second derivative spectra 900 for cholesterol (similar to one embodiment of lipids) 901, collagen 902, and elastin 903. The left curve 925 shows the second derivative data over the wavelength range of about 1150nm to 1300nm, while the right curve 950 shows the second derivative data over the wavelength range of about 1600nm to 1850nm. These wavelengths show numerous features for cholesterol/lipid 901, collagen 902, and elastin 903, which again emphasizes the added value of using wavelengths longer than about 1000nm for cancer diagnostics.

[0050] 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 1000 are shown in FIGURE 10 as a function of wavelength between about 1000nm and 2600nm. FIGURE 10 overlaps the absorption coefficient for water 1001, adipose 1002 (forms of adipose include fatty tissue and acids, lipids, and cholesterol), and collagen type I 1003. One may note that particular absorption peaks for adipose 1002 and collagen type I 1003 align at wavelengths near 1210nm 1004 and 1720nm 1005, which also correspond to local minima in water absorption.

[0051] Moreover, the NIR spectra for collagen also depend on the type of collagen. As an example, FIGURE 11 illustrates the absorbance 1100 for four types of collagen: collagen I 1101, collagen II 1102, collagen III 1103, and collagen IV 1104. 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.

[0052] 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.

[0053] Comparing these absorption features with the data in FIGURES 6-11 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.

[0054] 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 9 to measure the cholesterol/lipid peak below 1200nm in 901 versus the collagen peak above 1200nm in 902. In yet another embodiment, the absorption features in FIGURE 6 may be relied upon to monitor the lipid content 605 by measuring near 1200nm and the collagen content 606 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] LASER EXPERIMENTS: PENETRATION DEPTH, FOCUSING, SKIN COOLING

[0060] 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.

[0061] An exemplary set-up 1200 for testing chicken breast samples using collimated light is illustrated in FIGURE 12. The laser light 1201 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 1202. The resulting beam 1203 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 1206 were mounted in a sample holder 1205, and the sampler holder 1205 was mounted in turn on a translation stage 1204 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.

[0062] For these particular experiments, the measured depth of damage (in millimeters) versus the incident laser power (in Watts) is shown 1300 in FIGURE 13. In this embodiment, laser diodes were used at wavelengths near 980nm, 1210nm and 1700nm. The curve 1301 corresponds to about 980nm, the curve 1302 corresponds to about 1210nm, and the curve 1303 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., 1001 in FIGURE 10). Part of the difference in threshold powers may also arise from the absorption of proteins such as collagen (e.g., 1003 in FIGURE 10). After a certain power level, the damage depth appears to saturate: i.e., the slope flattens out as a function of increasing pump power.

[0063] In one embodiment, if the penetration depth is defined as the depth where damage begins to approximately saturate, then for wavelengths of about 980nm 1301 the penetration depth 1306 may be defined as approximately 4mm, for wavelengths of about 1210nm 1302 the penetration depth 1305 may be defined as approximately 3mm, and for wavelengths of about 1700nm 1303 the penetration depth 1304 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 1303 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., 1001 in FIGURE 10). On the other hand, at the highest power point 1301 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., 1001 in FIGURE 10). Based on data 1300 such as in FIGURE 13, it may be possible to select the particular wavelength for the laser beam to be used in the non-invasive procedure.

[0064] Even near wavelengths such as described in FIGURE 13, 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 14 shows the optical absorption or density as a function of wavelength 1400 between approximately 700nm and 1300nm. Curves are shown for the water absorption 1401, hemoglobin Hb absorption 1402, and oxygenated hemoglobin HbO₂ 1403. In this example, two particular wavelengths are compared: 980nm 1404 and 1075nm 1405. 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 1405 may be preferred, since it falls near a local minimum in water 1401, hemoglobin 1402, and oxygenated hemoglobin 1403 absorption. On the other hand, if the penetration depth at 980nm 1404 is adequate and the problem is to generate heat through water absorption, then 980nm 1404 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.

[0065] 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 15 illustrates the set-up 1500 used for the focused infrared experiments. In this embodiment, a lens 1501 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 1504 is placed between two microscope slides 1502 and 1503 for in vitro experiments. The tissue 1504 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 1505 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.

[0066] For a particular embodiment, histology of the renal artery is shown in FIGURE 16A for no laser exposure 1600 and shown in FIGURE 16B with focused infrared laser exposure 1650. 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 16A with no laser exposure, the layers of the artery wall may be identified: top layer of endothelium 1601 that is about 0.05mm thick, the media comprising smooth muscle cells or tissue 1602 that is about 0.75mm thick, and the adventitia 1603 comprising some of the renal nerves 1604 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.

[0067] The histology with focused infrared light exposure 1650 is illustrated in FIGURE 16B. 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 1651, the media 1652, and the adventitia 1653. With this type of histology, the non-damaged regions remain darker (similar to FIGURE 16A), while the laser induced damaged regions turn lighter in color. In this example, the endothelium 1651 and top layer of the media 1652 remain undamaged – i.e., the top approximately 0.5mm is the undamaged region 1656. The laser damaged region 1657 extends for about 1mm, and it includes the bottom layer of the media 1652 and much of the adventitia 1653. The renal nerves 1654 that fall within the damage region 1657 are also damaged (i.e., lighter colored). On the other hand, the renal nerves beyond this depth, such as 1655, may remain undamaged.

[0068] 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 1656 and 1657). 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.

[0069] 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 1700 is illustrated in FIGURE 17. The skin sample 1704, or more generally sample under test, is placed in a sample holder 1703. The sample holder 1703 has a cooling side 1701 and a heating side 1702. The heating side 1702 comprises a heater 1705, which may be adjusted to operate around 37 degrees Celsius – i.e., close to body temperature. The cooling side 1701 is coupled to an ice-water bath 1707 (around 2 degrees Celsius) and a warm-water bath 1706 (around 37 degrees Celsius) through a switching

valve 1708. The entire sample holder 1703 is mounted on a linear motor 1709, so the sample can be moved perpendicular 1710 to the incoming light beam.

[0070] In this embodiment, the light is incident on the sample 1704 through a sapphire window 1711. The sapphire material 1711 is selected because it is transparent to the infrared wavelengths, while also being a good thermal conductor. Thus, the top layer of the sample 1704 may be cooled by being approximately in contact with the sapphire window 1711. The laser light 1712 used is near 1708nm from a cascaded Raman oscillator (described in greater detail herein), and one or more collimating lenses 1713 are used to create a beam with a diameter 1714 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.

[0071] Experimental results obtained using the set-up of FIGURE 17 are included in FIGURE 18. In this example, FIGURE 18 shows the MTT histochemistry of human skin 1800 treated with ~1708 nm laser (5 seconds pre-cool; 2mm diameter spot exposure for 3 seconds) at 725 mW (A 1801, B 1802) corresponding to about 70 J/cm² average fluence, and 830 mW (C 1803, D 1804) corresponding to about 80 J/cm² average fluence. The images in FIGURE 18 show that the application of a cold window was effective in protecting the epidermis 1805 (darker top layer) and the top approximately 0.4 or 0.5mm of the dermis 1806. 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.

[0072] 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 10), such as collagen 1003, adipose 1002 and elastin 1004, are to be minimized. The water absorption 1001 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. 1001 in FIGURE 10) is desired. Any of FIGURES 1, 6, 9, 10, or 11 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.

LASER SYSTEMS FOR THERAPEUTICS OR DIAGNOSTICS

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] Different light sources may be selected for the infrared 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 (SC) sources 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), photonic crystal fibers, or a hybrid of these fibers.

[0082] In one embodiment, LED's can be used that have a higher power level in the infrared wavelength range. LED's 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.

[0083] In yet another embodiment, various types of laser diodes may be used in the infrared 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. A plurality of 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 (DBR) 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.

[0084] 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 5nm to 100nm wide, preferably in the 60nm to 100nm range for some applications. 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 infrared.

[0085] 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.

[0086] 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 a particular 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 diameters of approximately 100 microns 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.

INFRARED SUPER-CONTINUUM LASERS

[0087] 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.

[0088] 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.

[0089] 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 (DFB) laser diode with a wavelength near 1542nm or 1550nm, with approximately 0.5–2.0ns pulsed output, and with a pulse repetition rate between one kilohertz and 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 a particular 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.

[0090] The SC generation 2007 may occur in the relatively short lengths of fiber that follow the pump laser. Exemplary SC fiber lengths 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 occurs primarily, followed by a second fiber 2009 where the SC generation and spectral broadening occurs primarily.

[0091] 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 0.5ps 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] In one embodiment, one example of the SC laser that operates in the short wave infrared (SWIR) 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 microns 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 0.5nsec 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.

[0096] 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.

[0097] If an approximately 10m length of output fiber 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 about 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.

[0098] Although one particular example of a 5W SWIR-SC implementation 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 1060nm 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. A mode field adapter may be included in the mid-stage, 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. The pump 2112 for the power amplifier may be up to six pump diodes providing 30W each near 915nm. For this much pump power, the output power in the SC may be as high as 50W or more.

[0099] In one embodiment, it may be desirable 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.

[0100] In one embodiment, the top of FIGURE 23 illustrates a block diagram for an SC source 2300 capable of generating light between approximately 1400nm 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 1542nm 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.

[0101] In yet another embodiment, the bottom of FIGURE 23 illustrates a block diagram for an SC source 2350 capable of generating light exemplary between approximately 1900nm 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 1542nm 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 exemplary lengths between approximately 5 meters and 50 meters. 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.

[0102] FIGURES 20-23 are examples of SC light sources that may 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.

[0103] 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 desirable 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.

[0104] Although the present disclosure has been described in several embodiments, a myriad of changes, variations, alterations, transformations, and modifications may be suggested to one skilled in the art, and it is intended that the present disclosure encompass such changes, variations, alterations, transformations, and modifications as falling within the spirit and scope of the appended claims. 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.

ABSTRACT

A system and method for using near-infrared or short-wave infrared (SWIR) light sources for early detection and monitoring of breast cancer, as well as other kinds of cancers may detect decreases in lipid content and increases in collagen content, possibly with a shift in the collagen peak wavelengths and changes in spectral features associated with hemoglobin and water content as well. Wavelength ranges between 1000-1400nm and 1600-1800nm may permit relatively high penetration depths because they fall within local minima of water absorption, scattering loss decreases with increasing wavelength, and they have characteristic signatures corresponding to overtone and combination bands from chemical bonds of interest, such as hydrocarbons. Broadband light sources and detectors permit spectroscopy in transmission, reflection, and/or diffuse optical tomography. High signal-to-noise ratio may be achieved using a fiber-based super-continuum light source. Risk of pain or skin damage may be mitigated using surface cooling and focused infrared light.

FIGURE 1

100

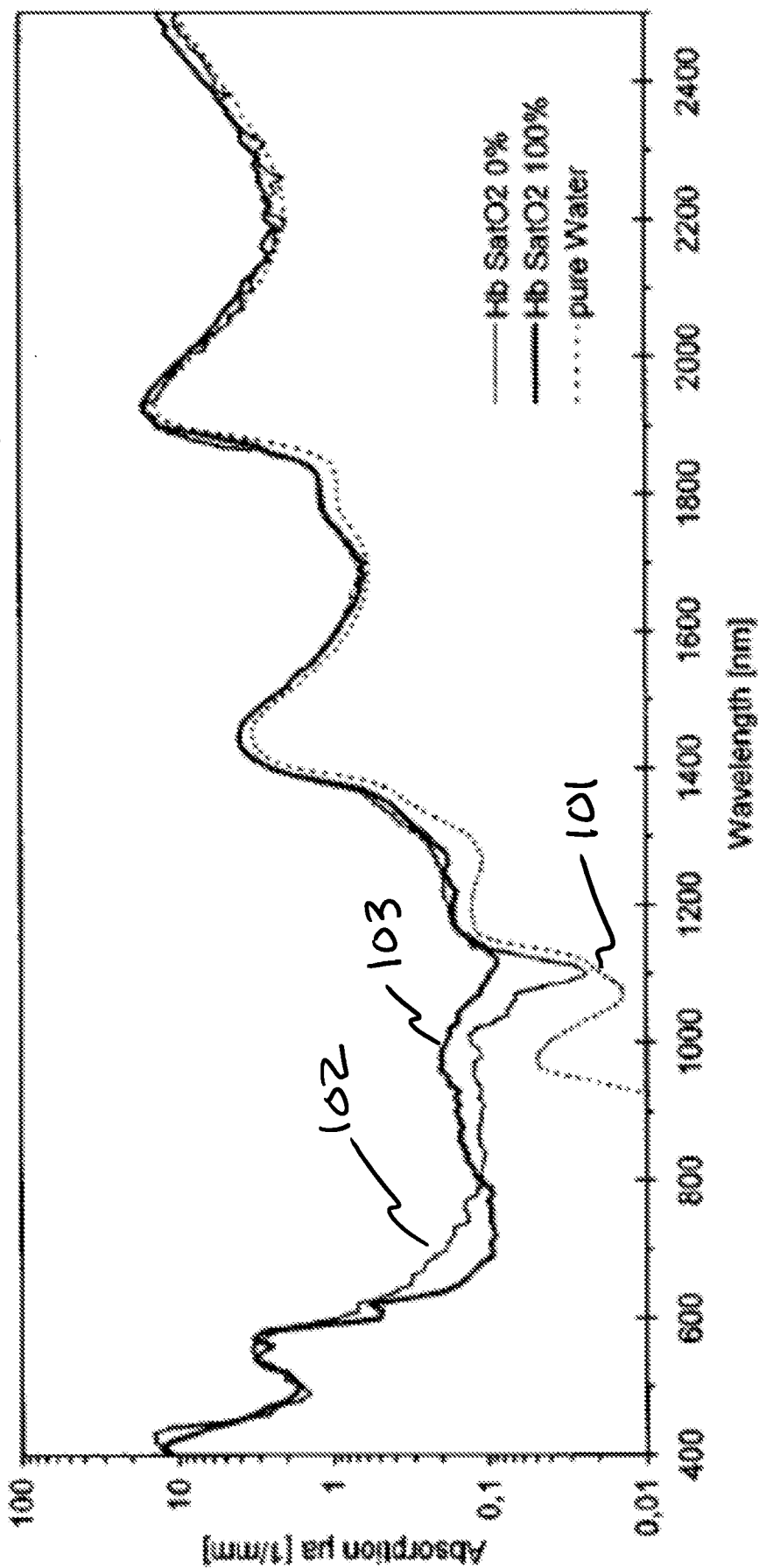


FIGURE 2

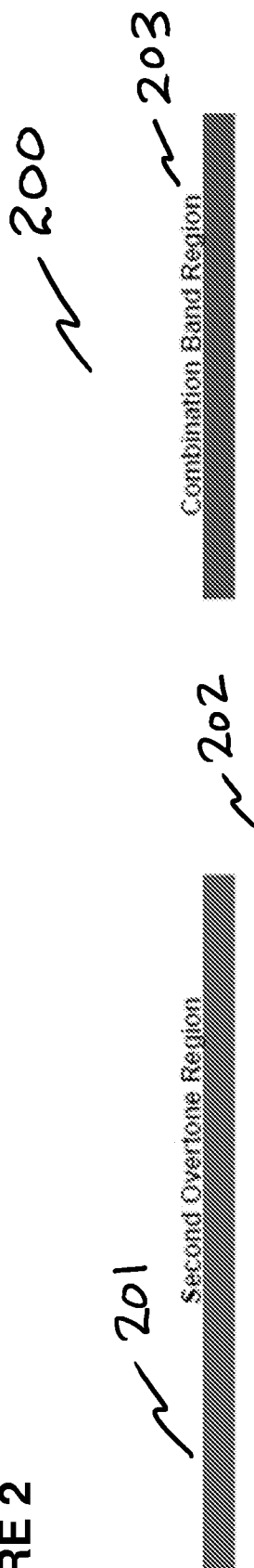
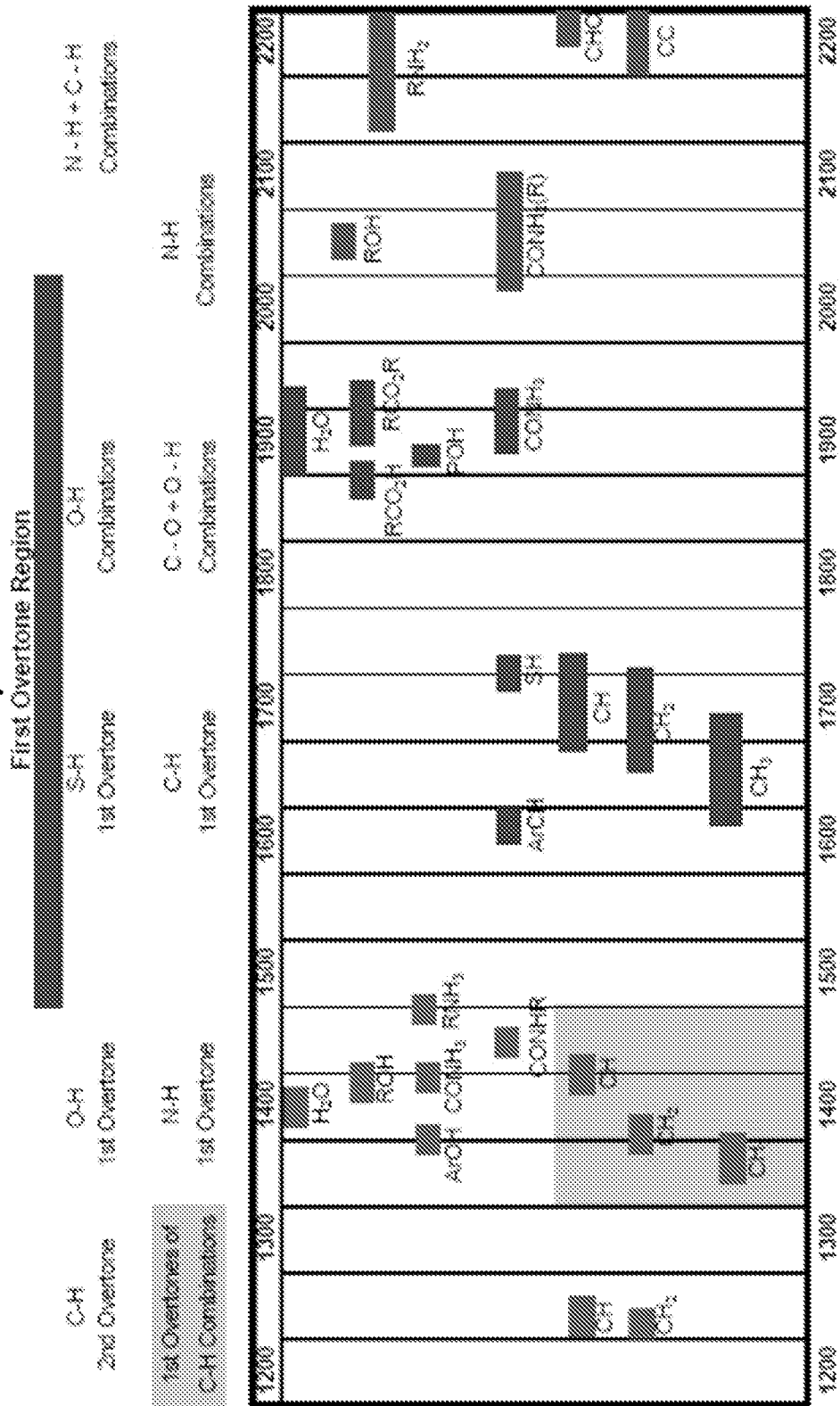
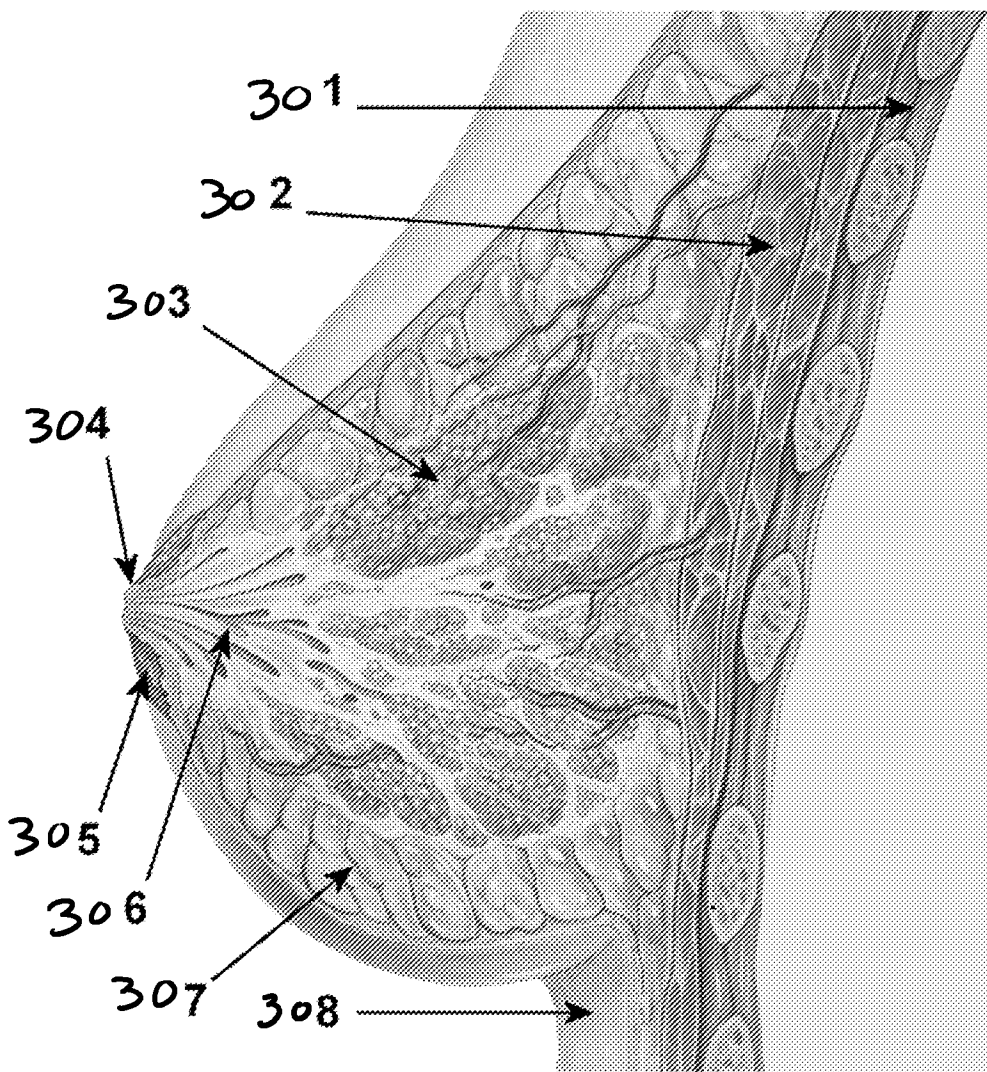


FIGURE 3



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

FIGURE 4

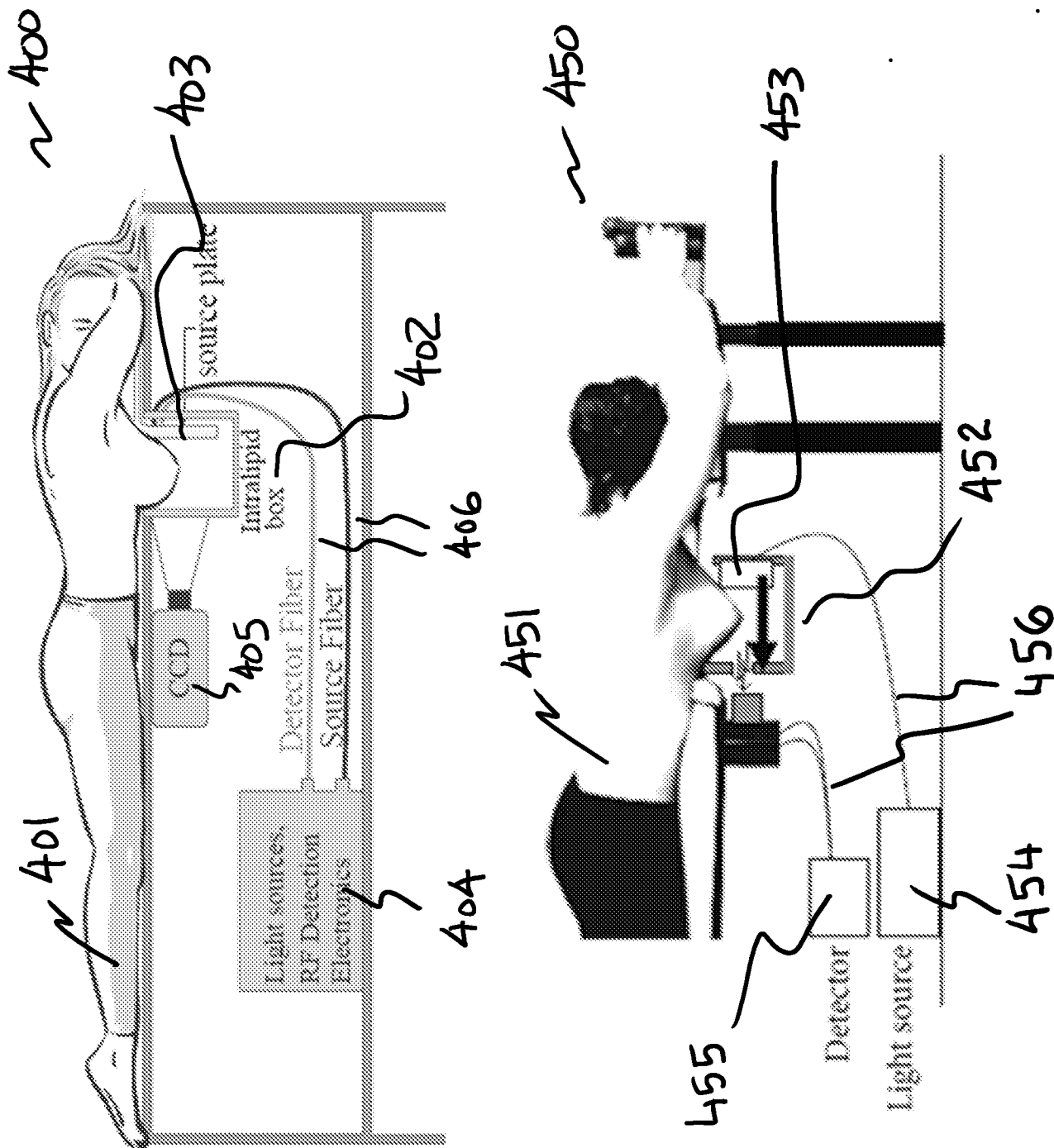


FIGURE 5

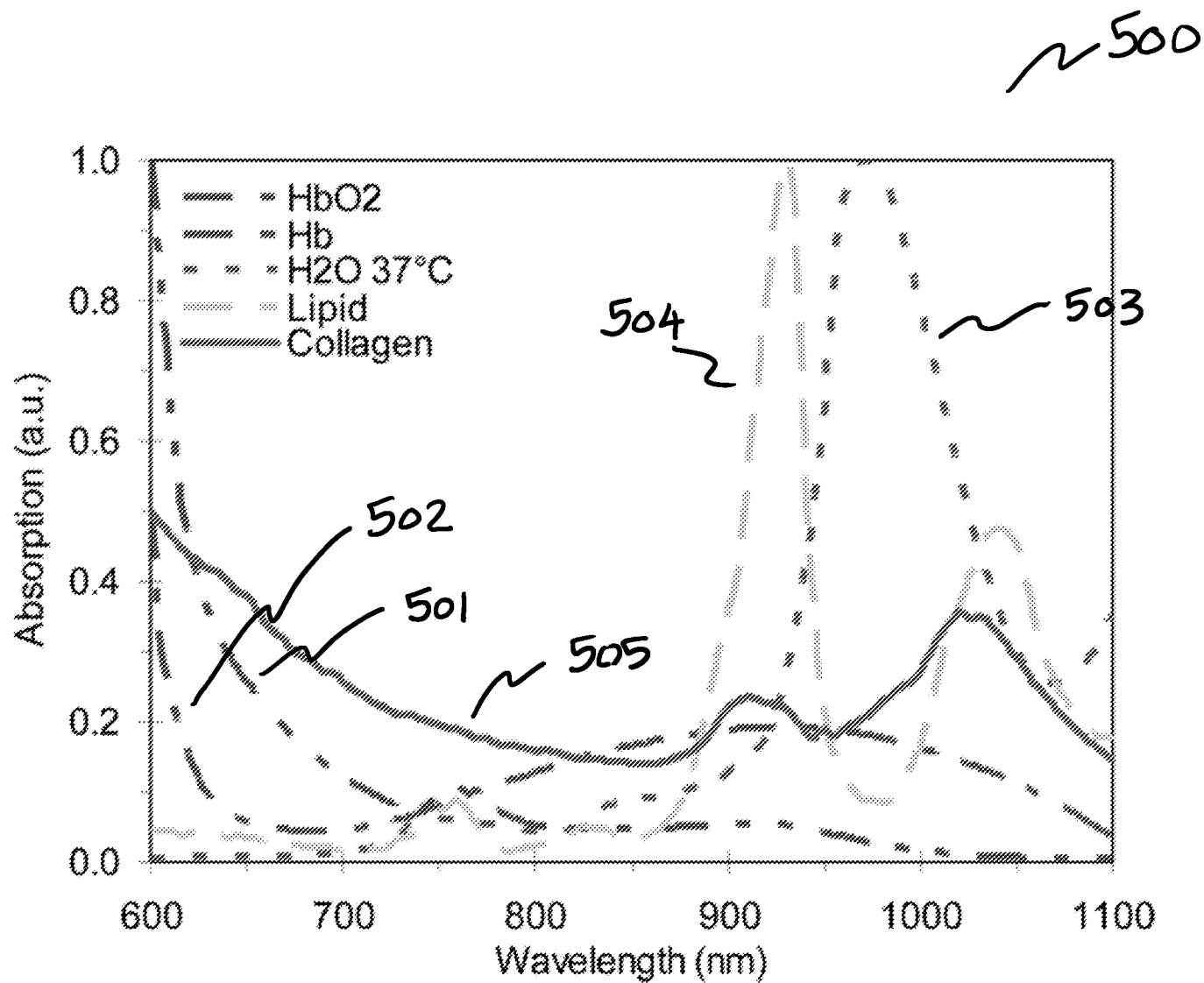


FIGURE 6

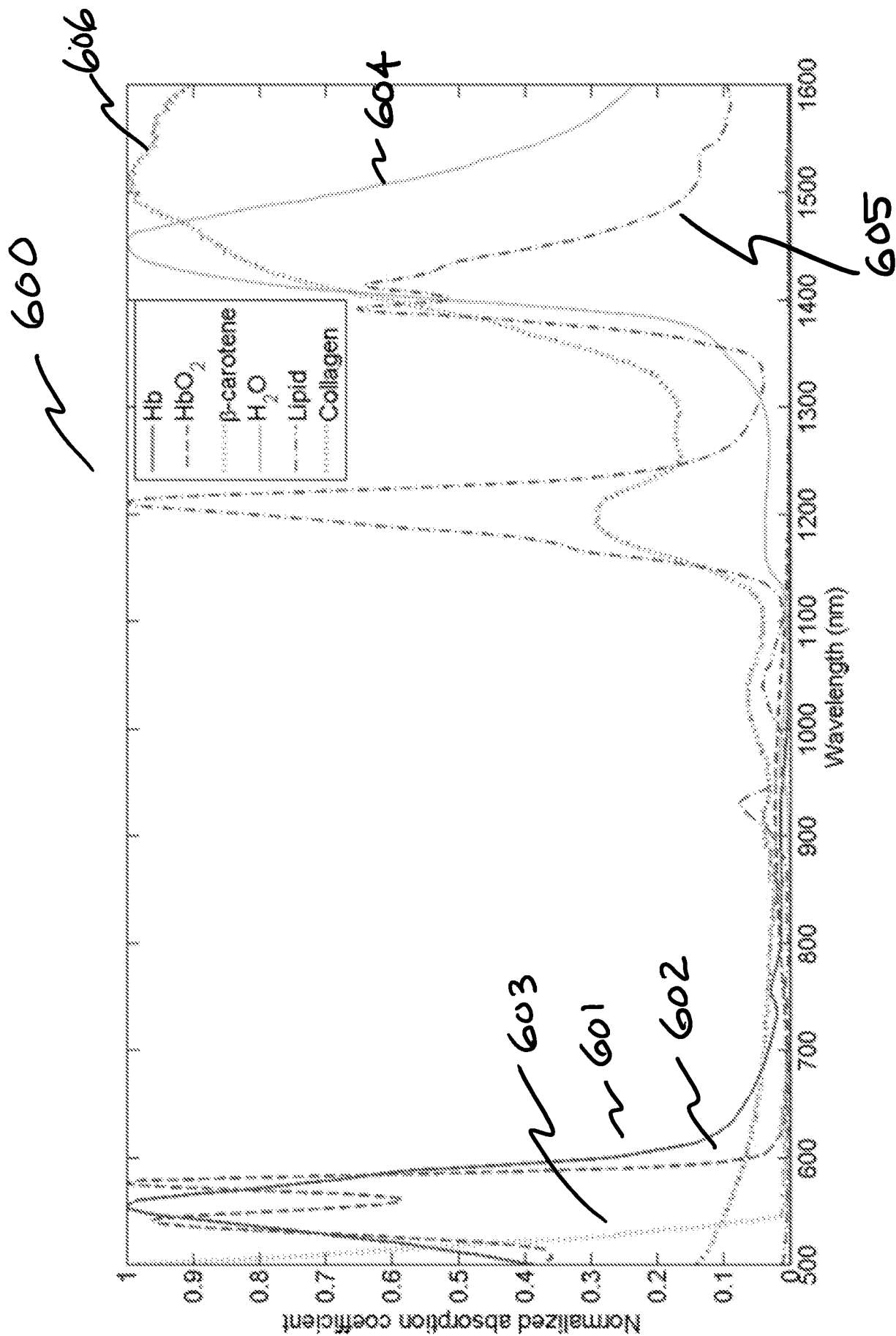


FIGURE 7

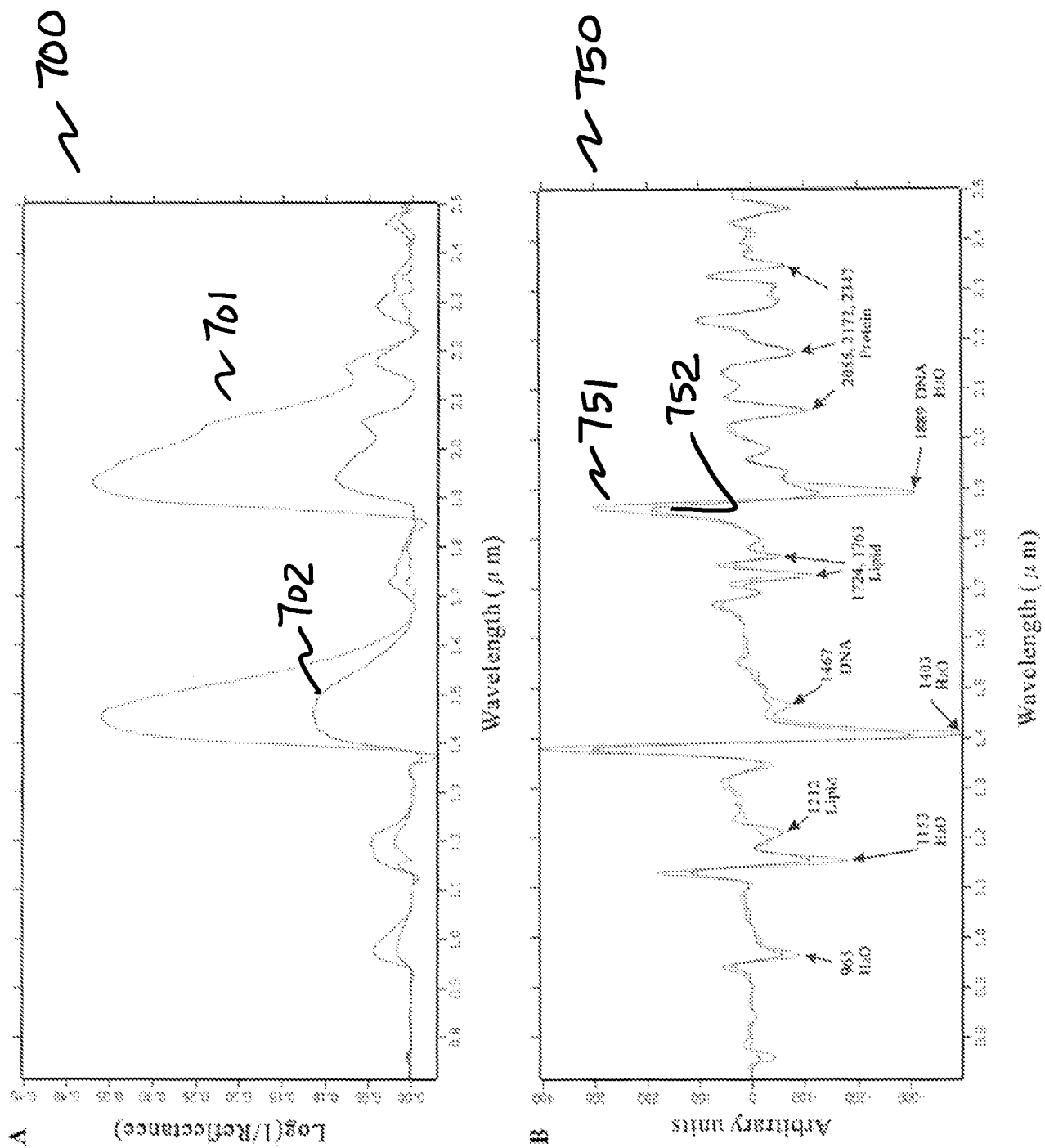


FIGURE 8

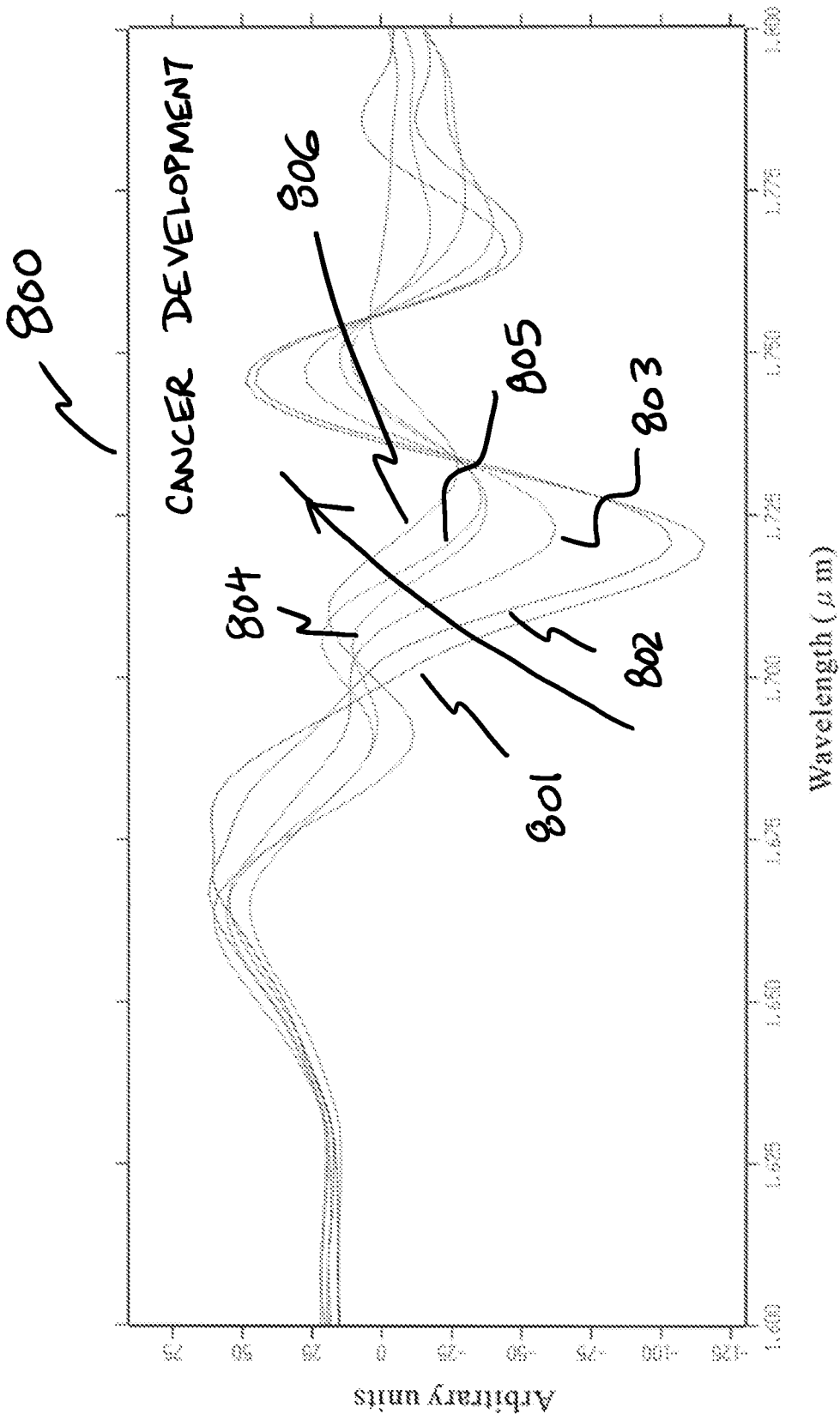


FIGURE 9

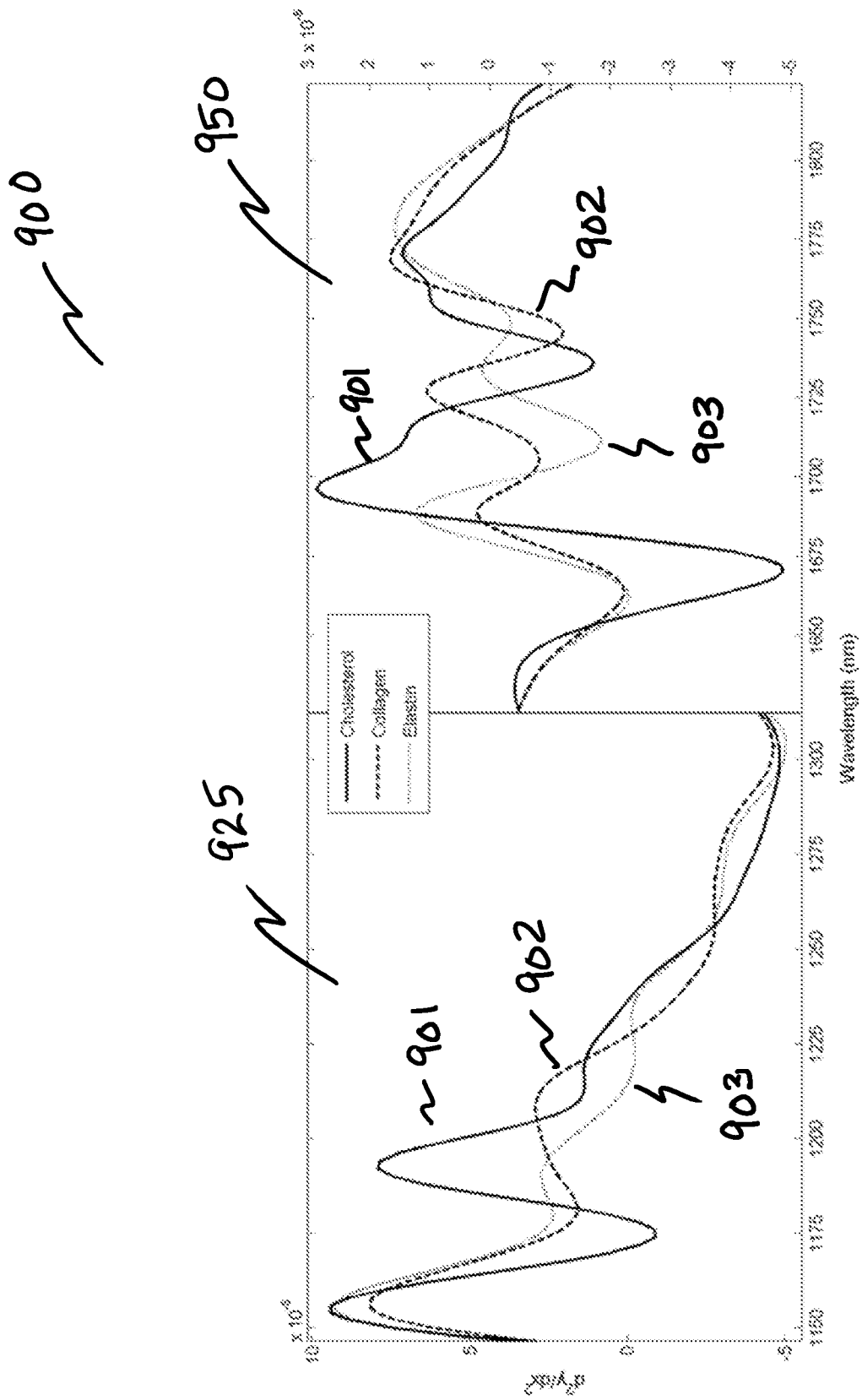
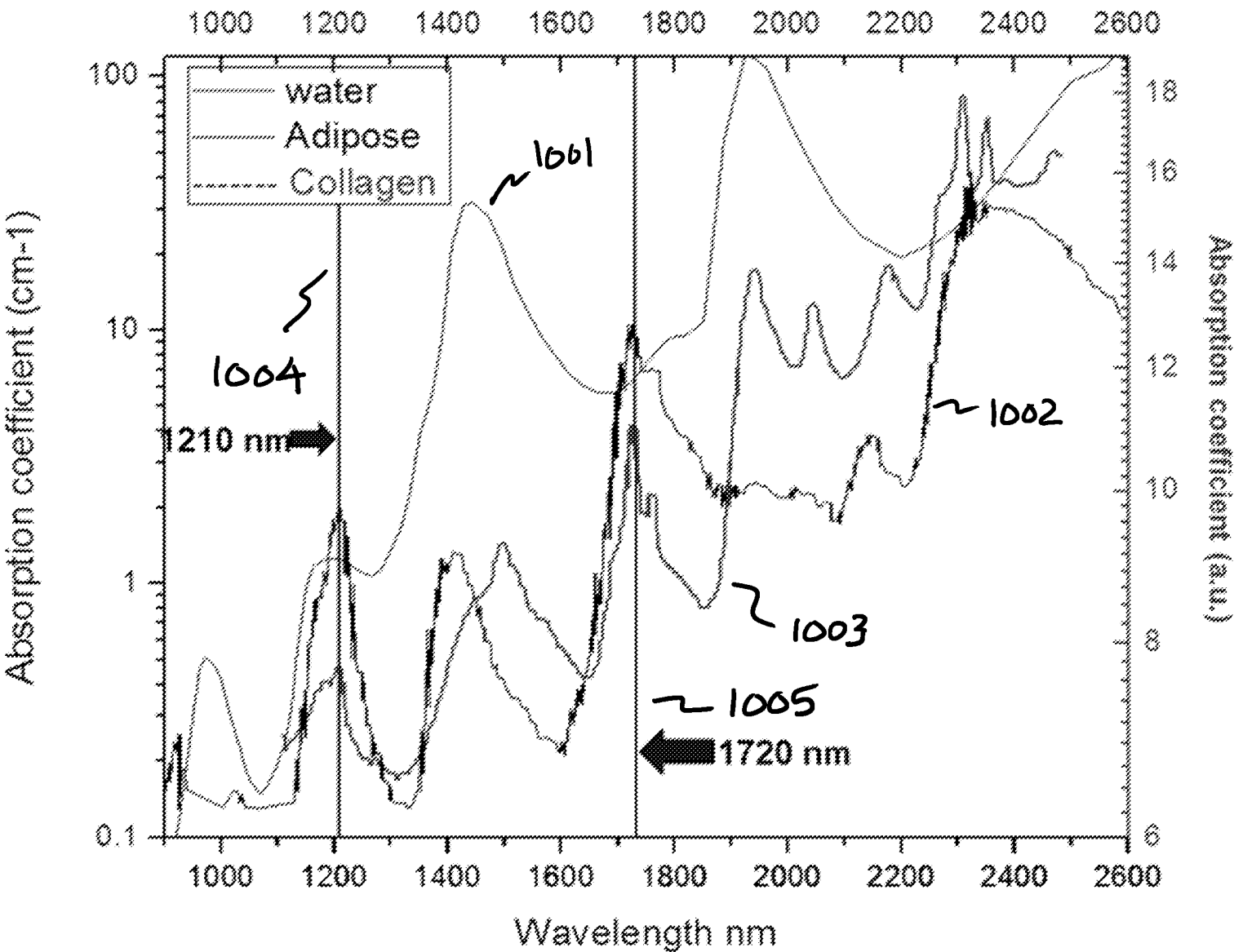


FIGURE 10



~1100

~1102

~1104

FIGURE 11

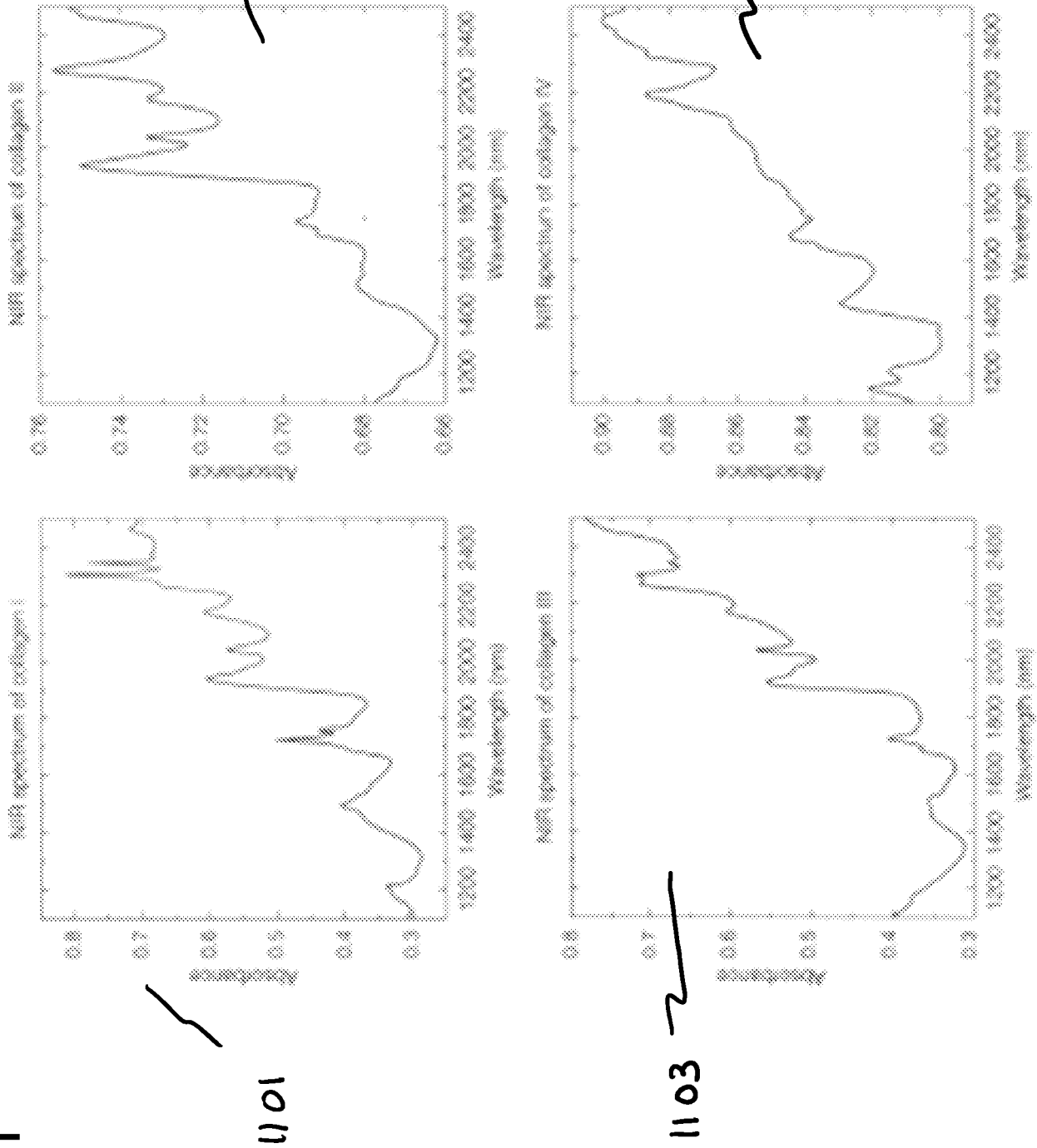
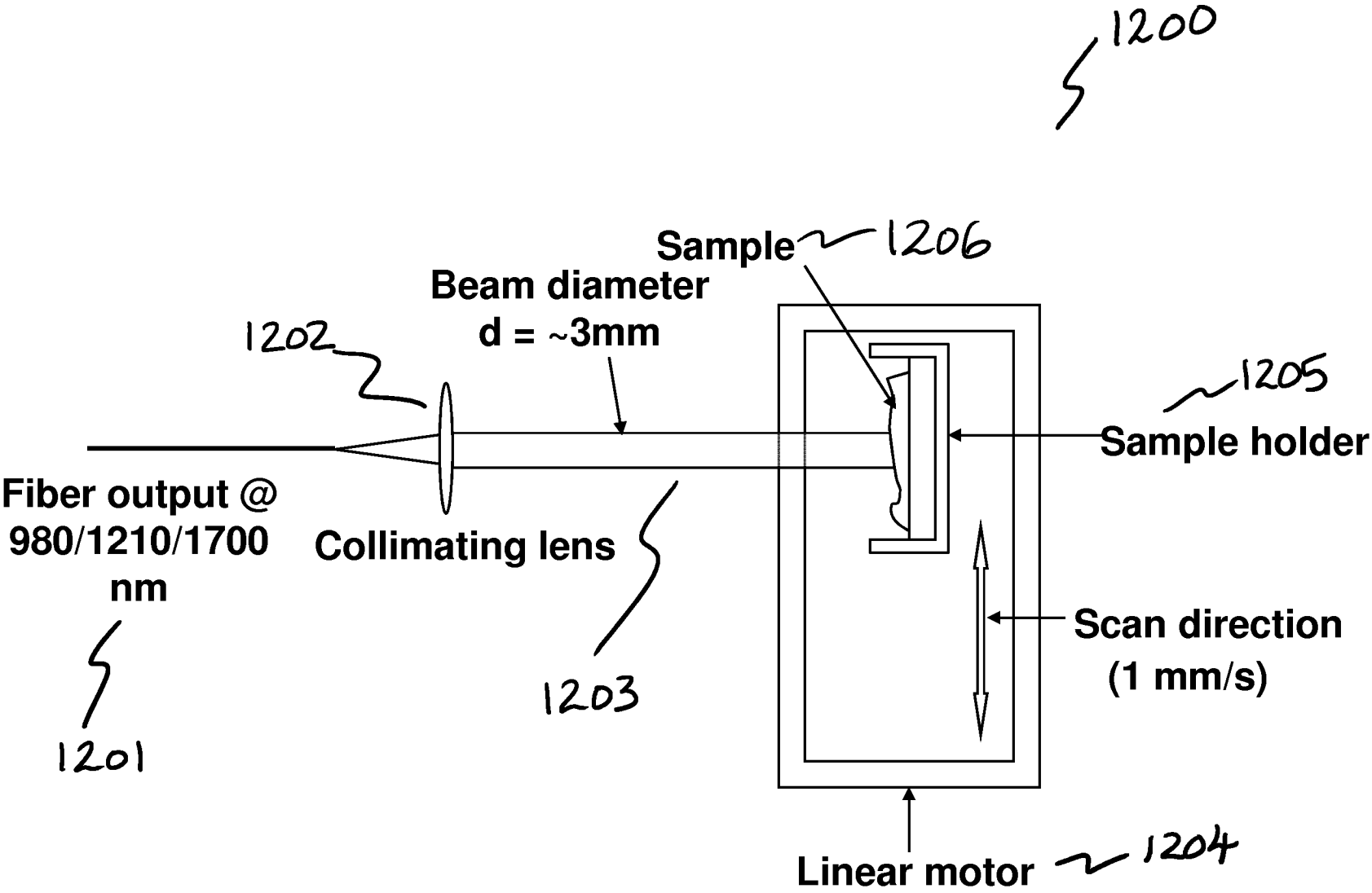
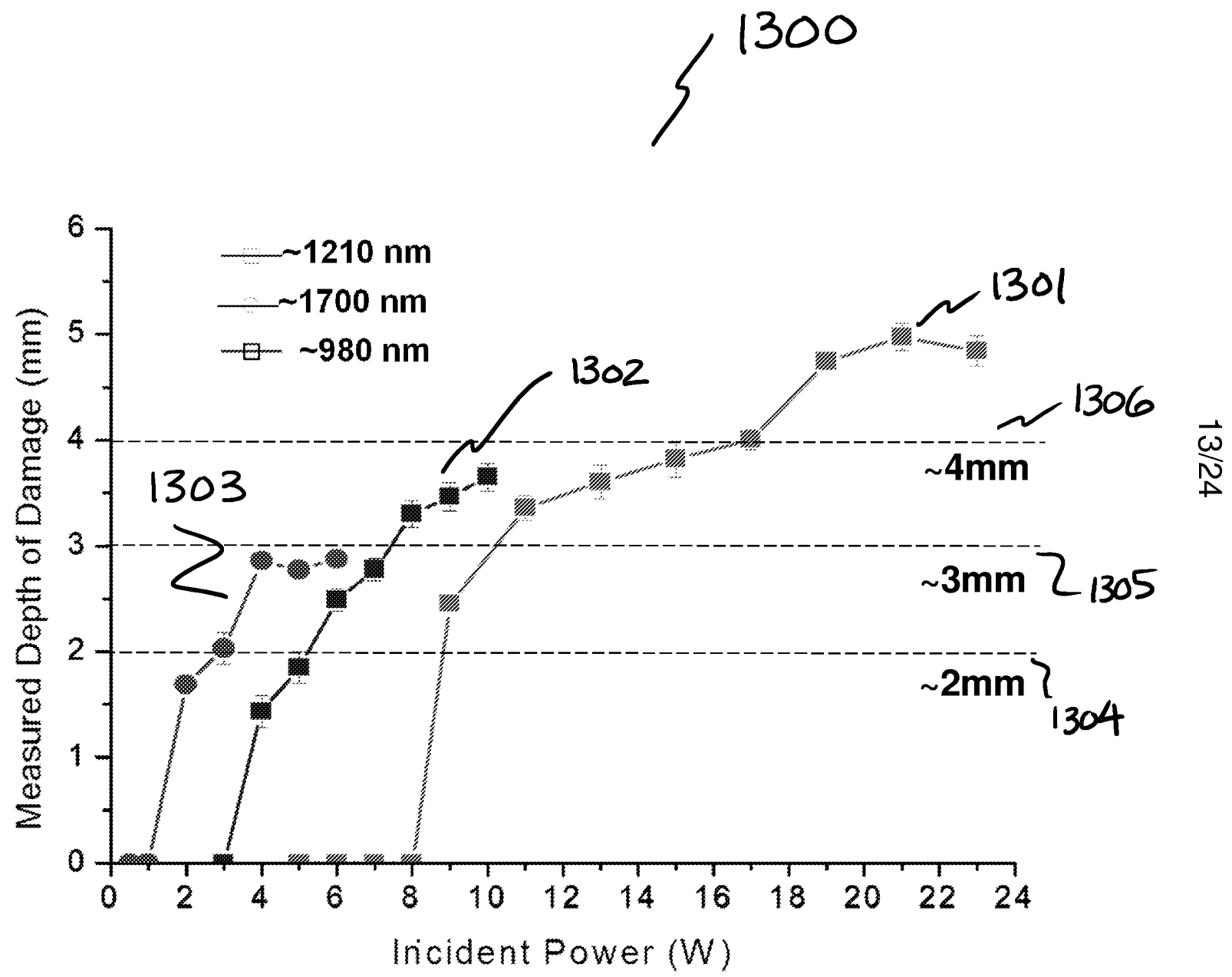


FIGURE 12



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FIGURE 13



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FIGURE 14

1400

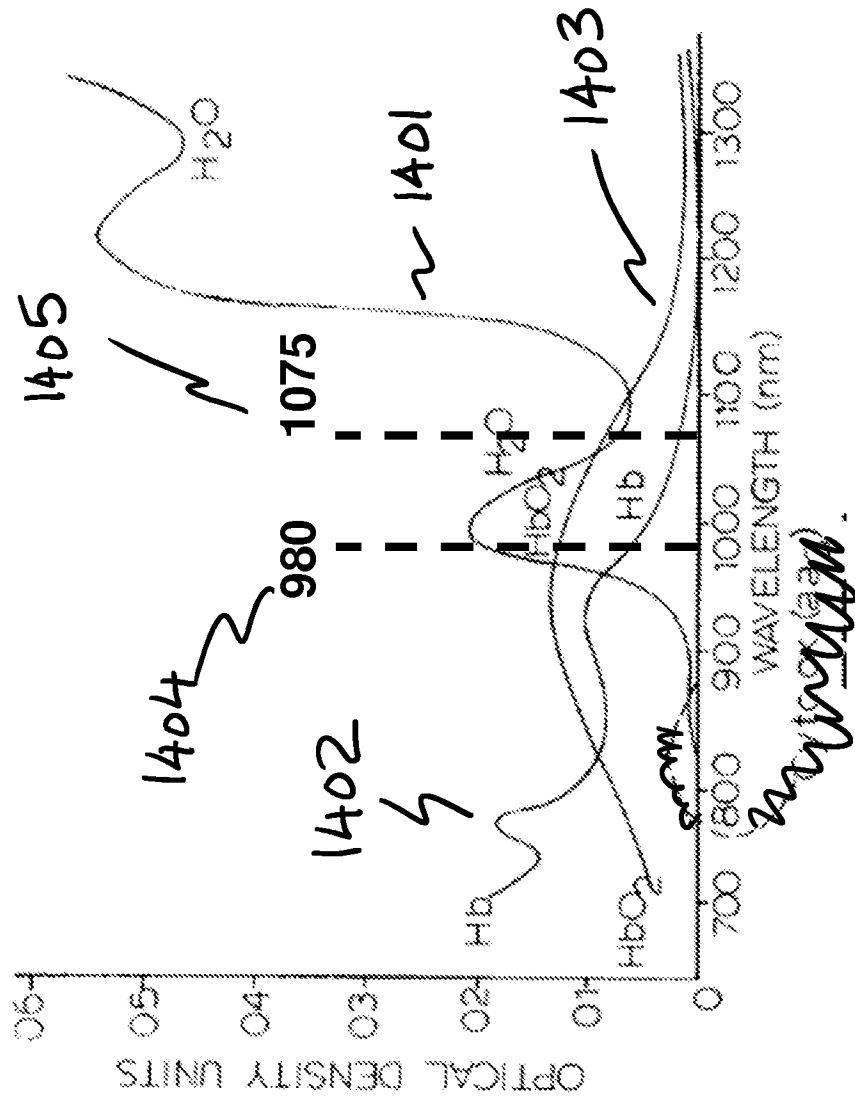


FIGURE 15

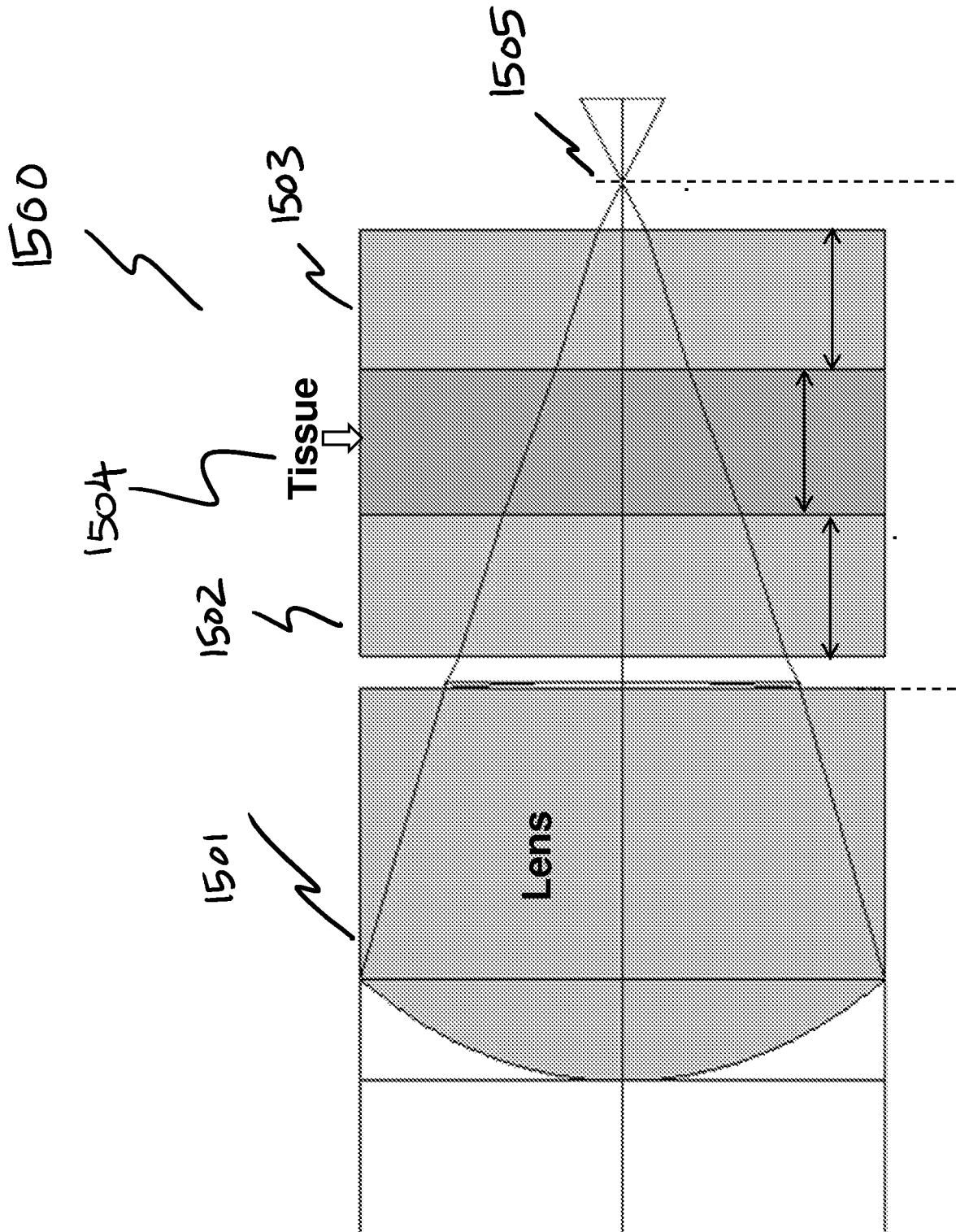


FIGURE 16A

1600

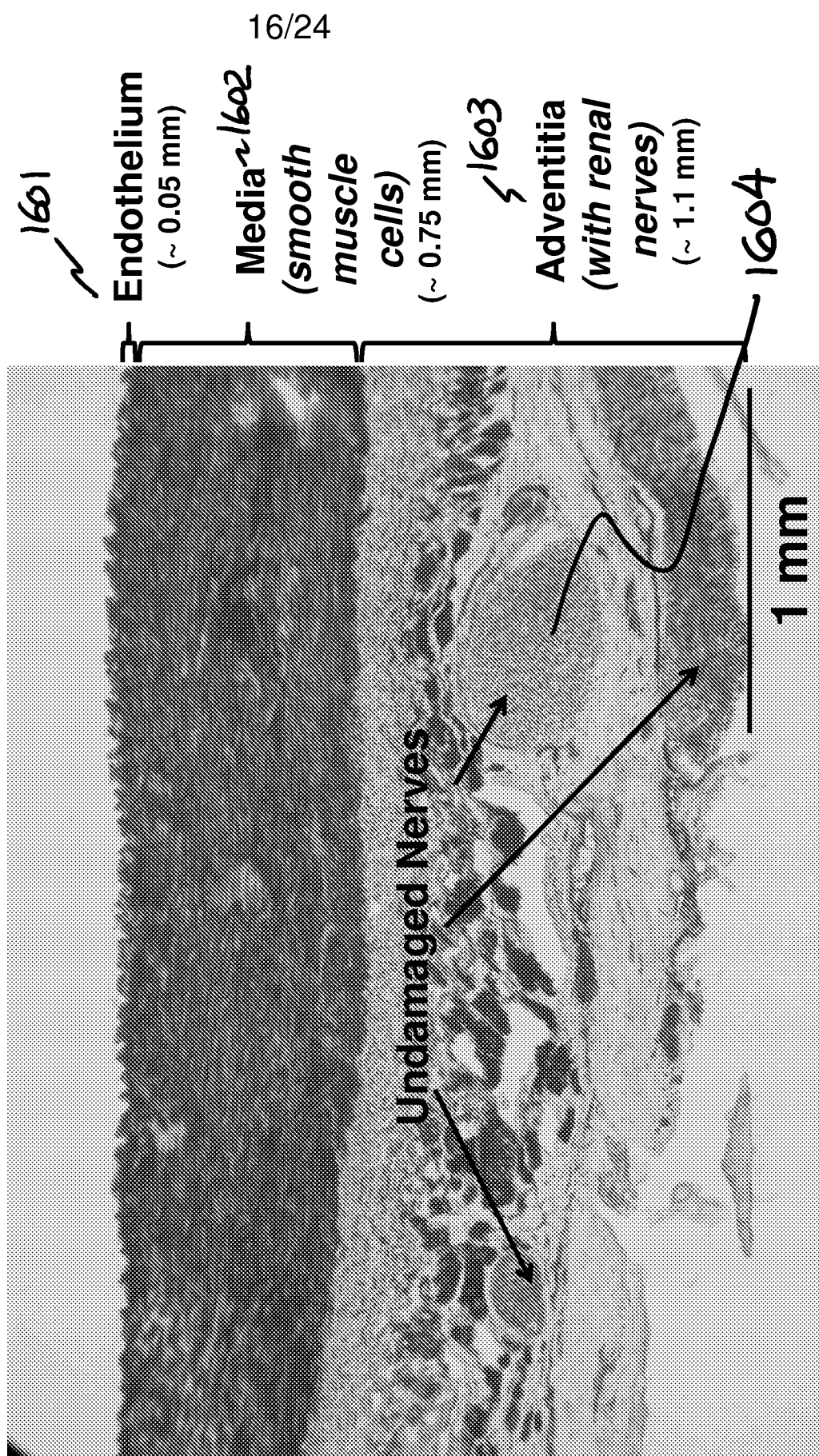


FIGURE 16B

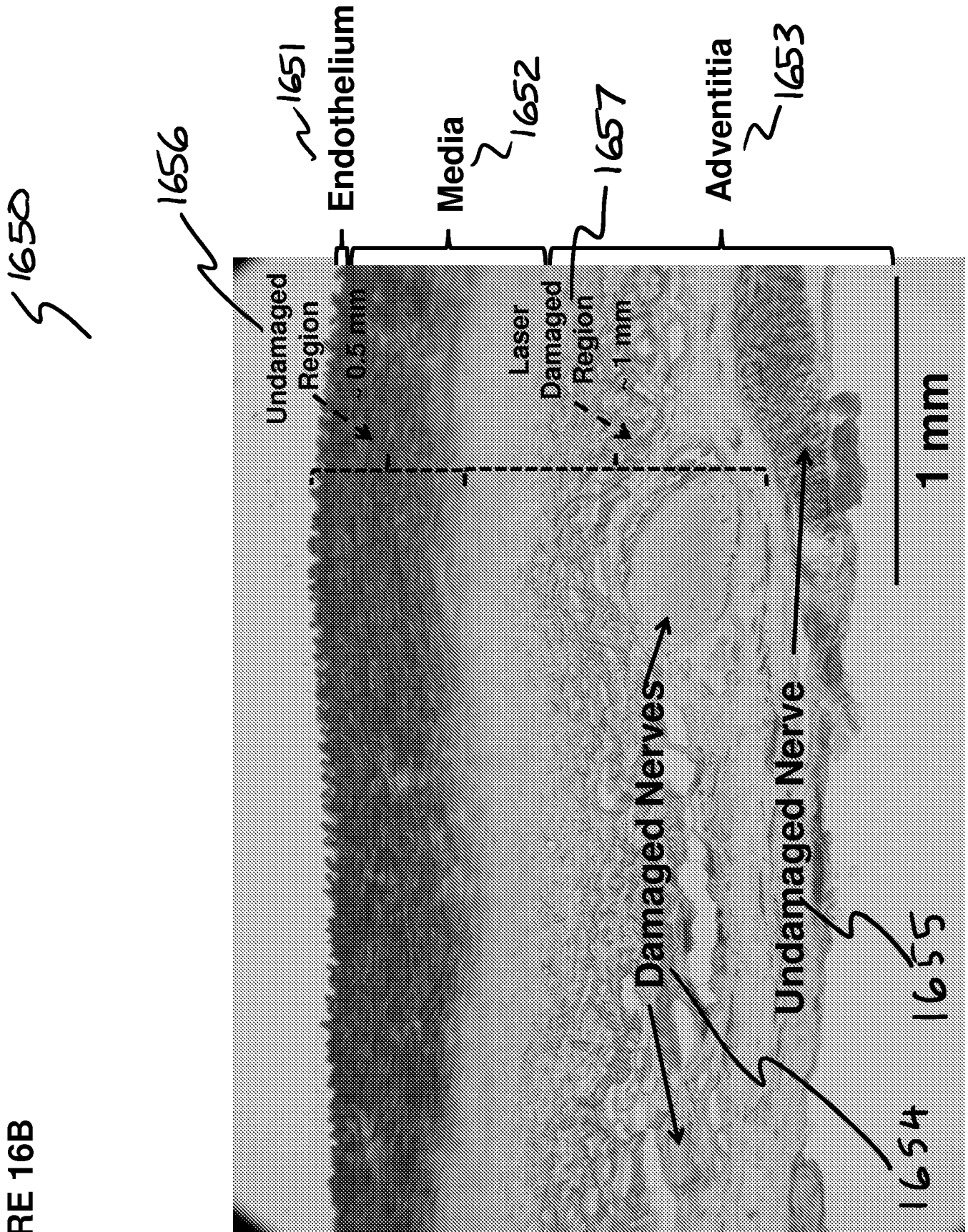


FIGURE 17

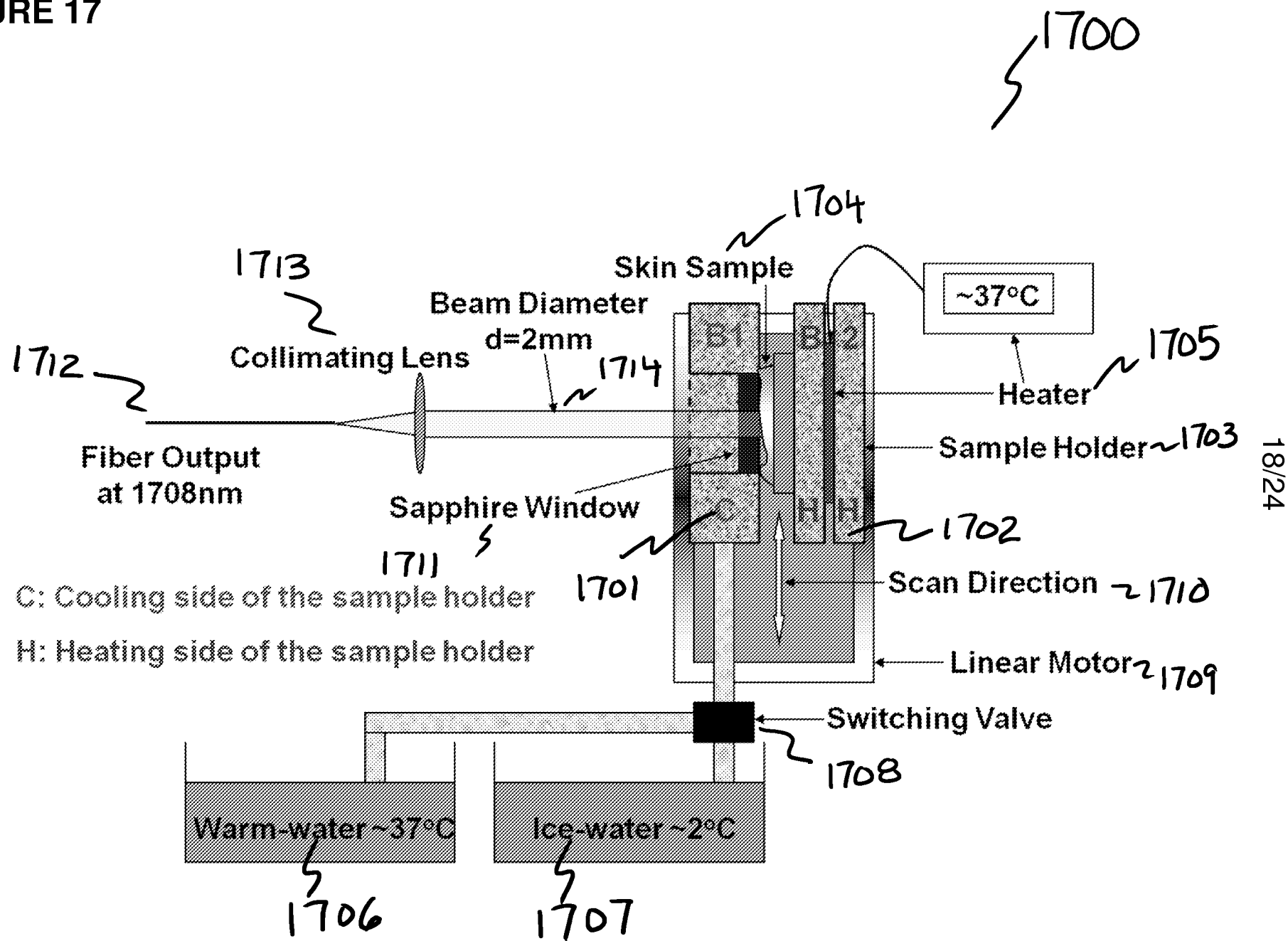
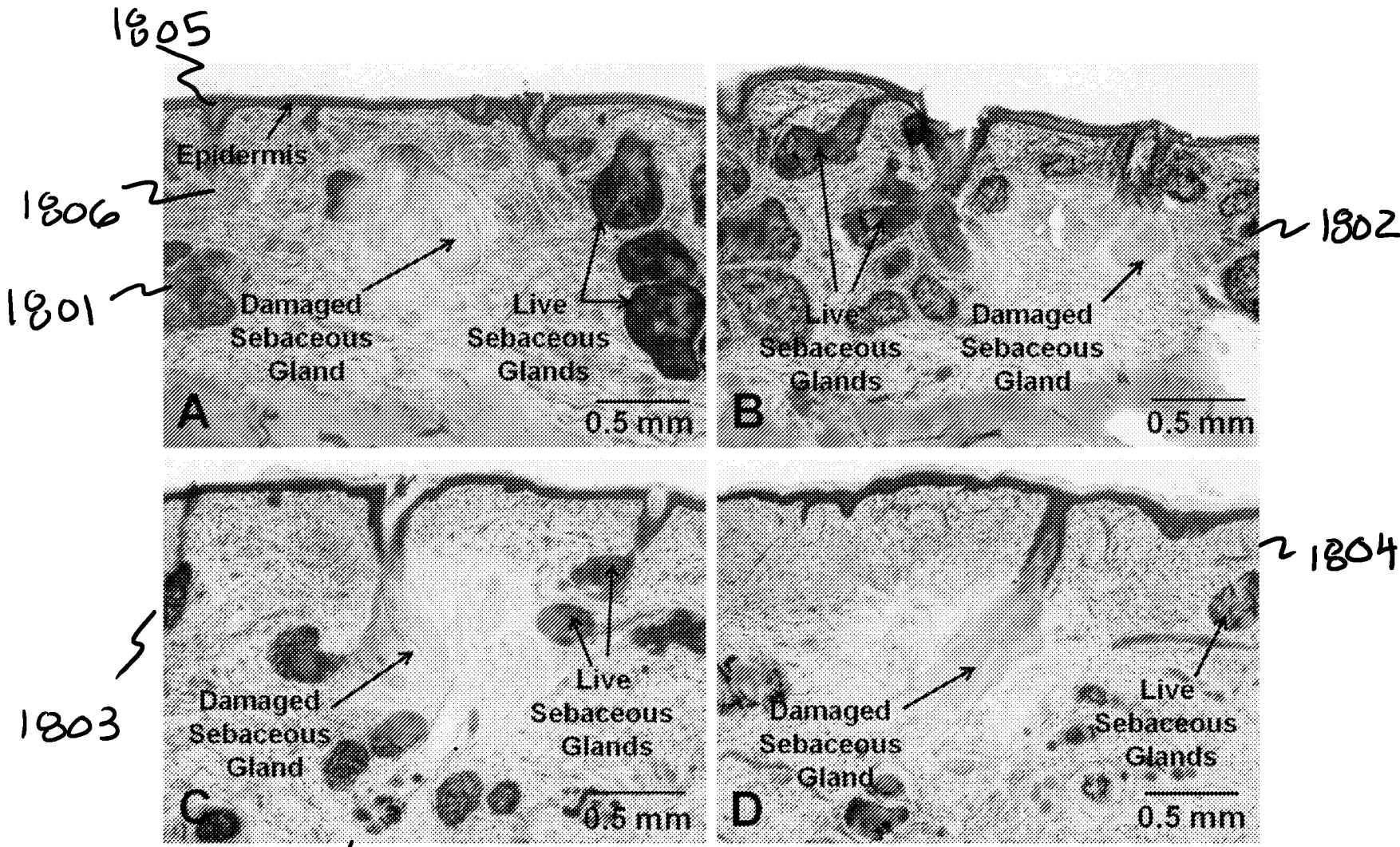


FIGURE 18

~ 1800



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FIGURE 19

1900

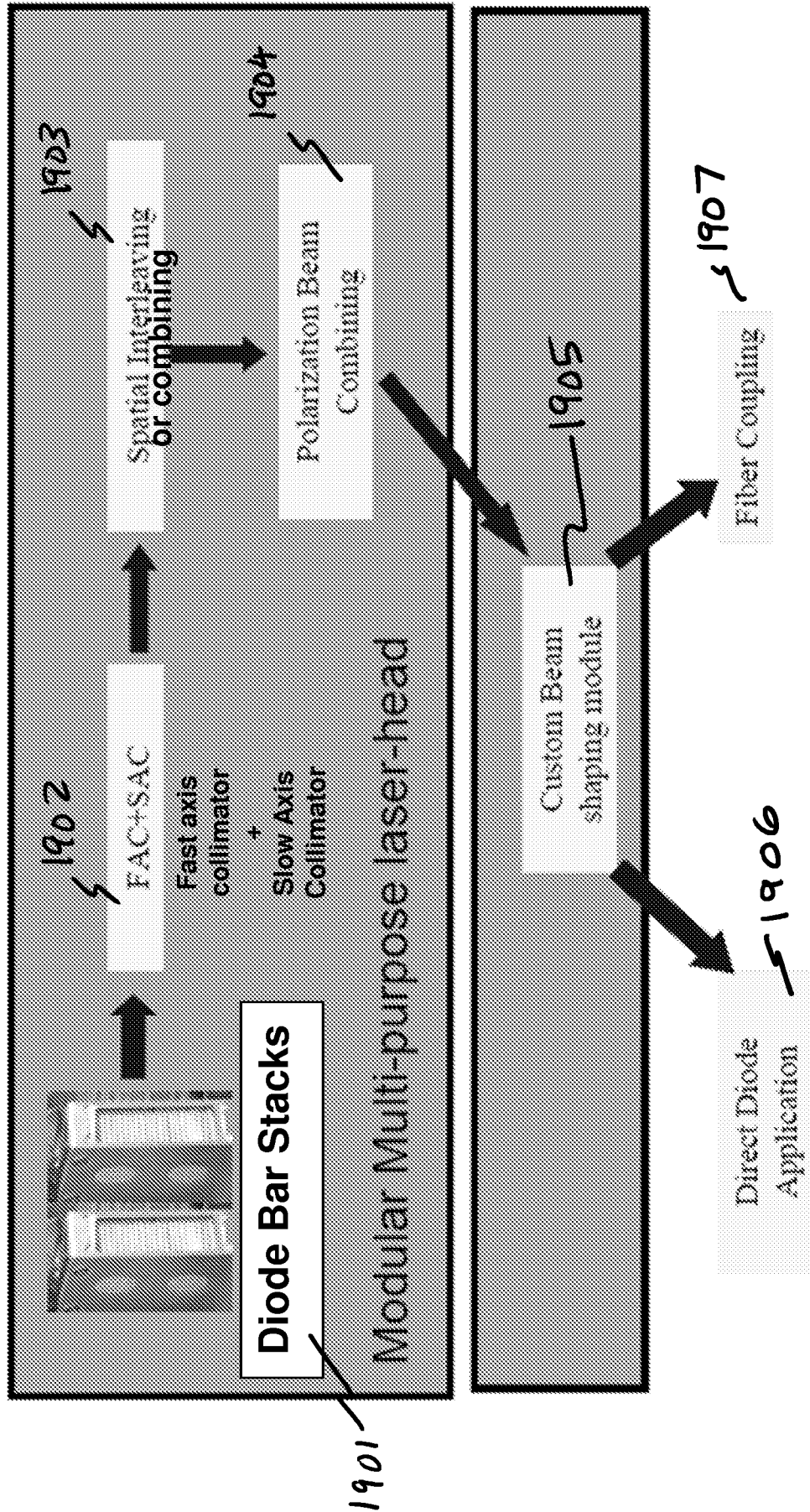


FIGURE 20

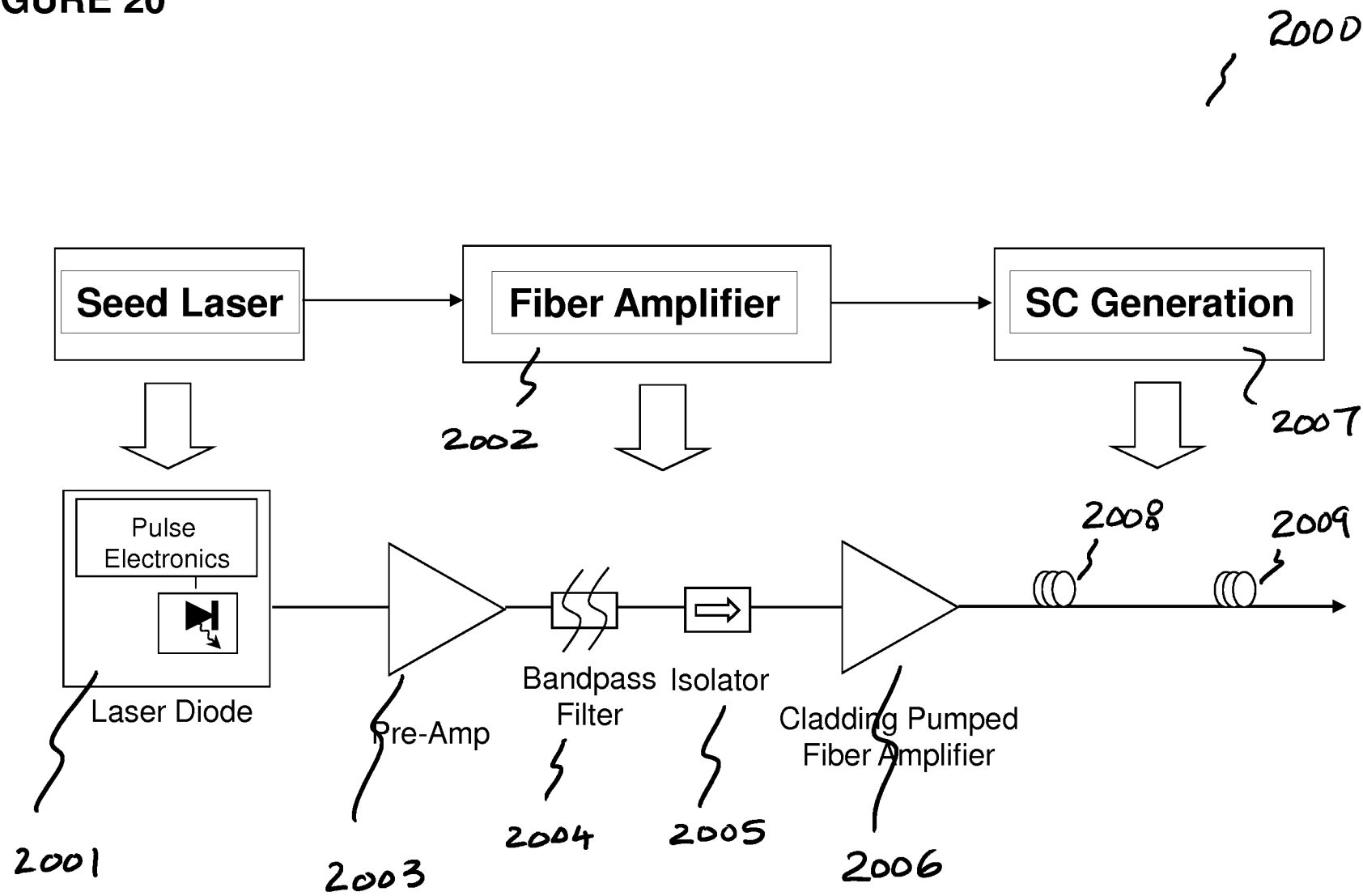


FIGURE 21

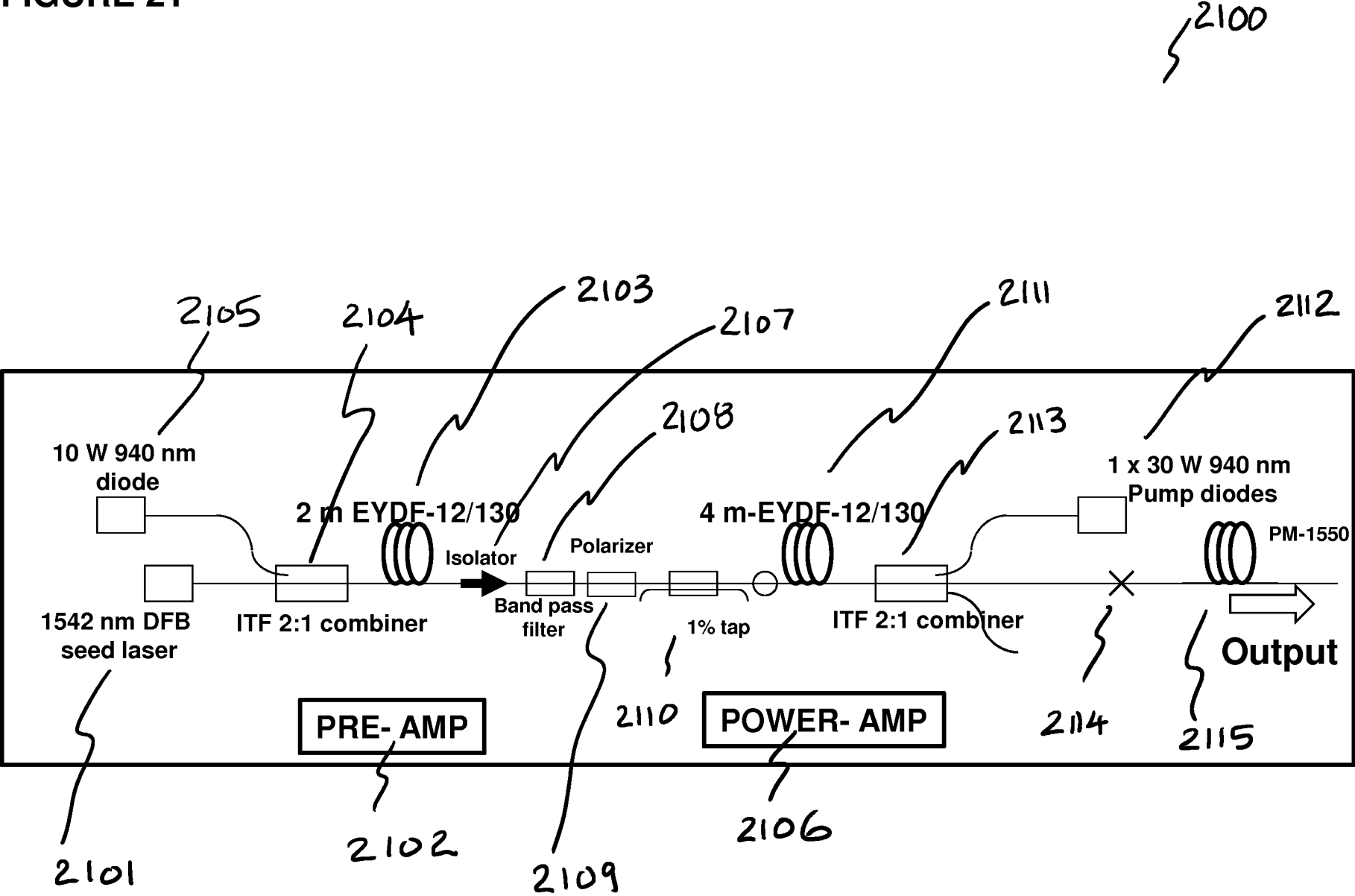


FIGURE 22

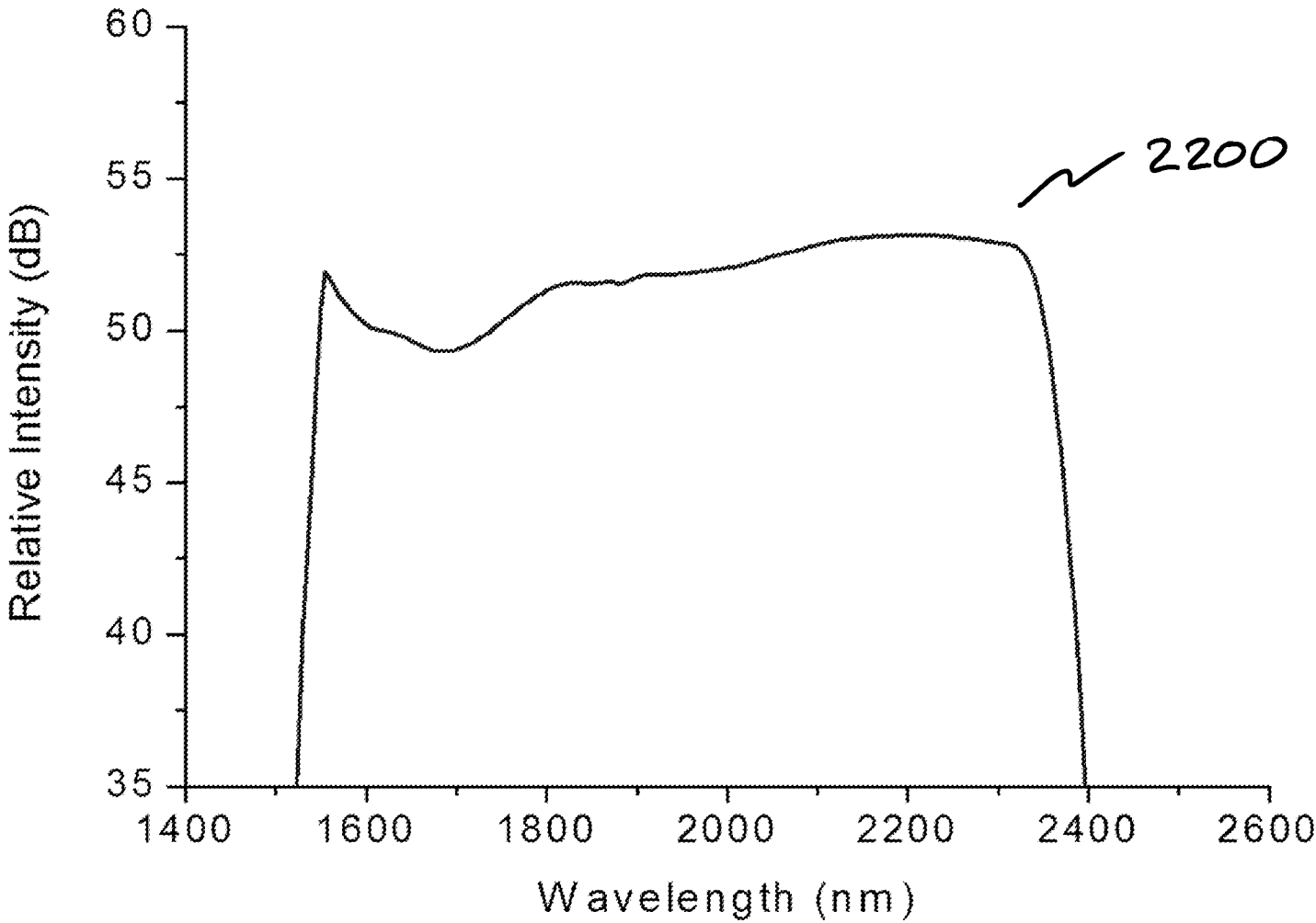
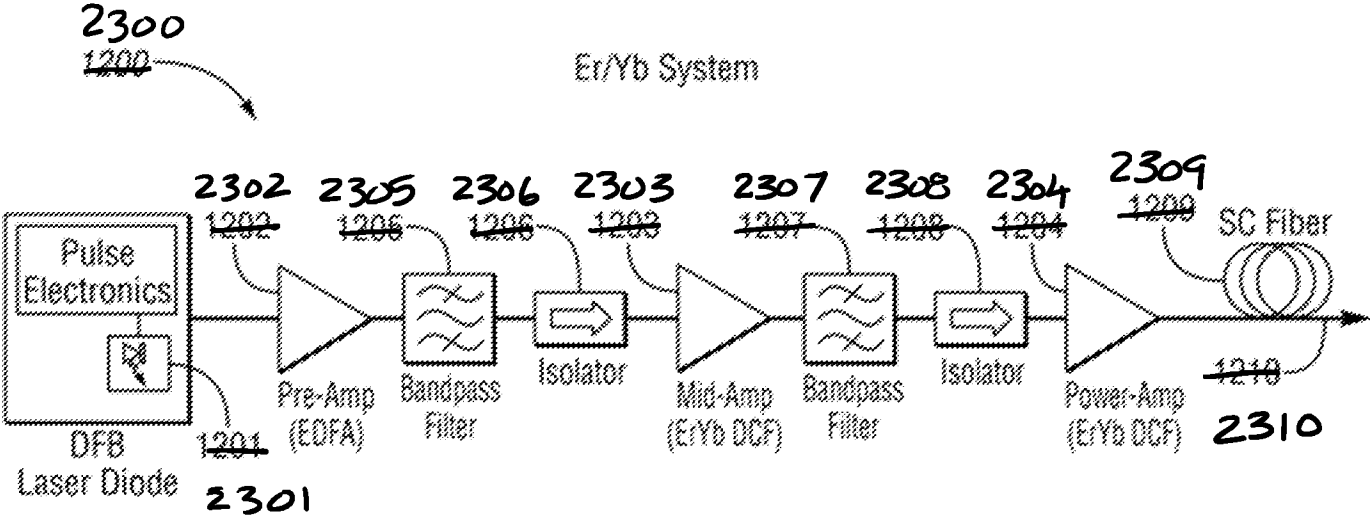
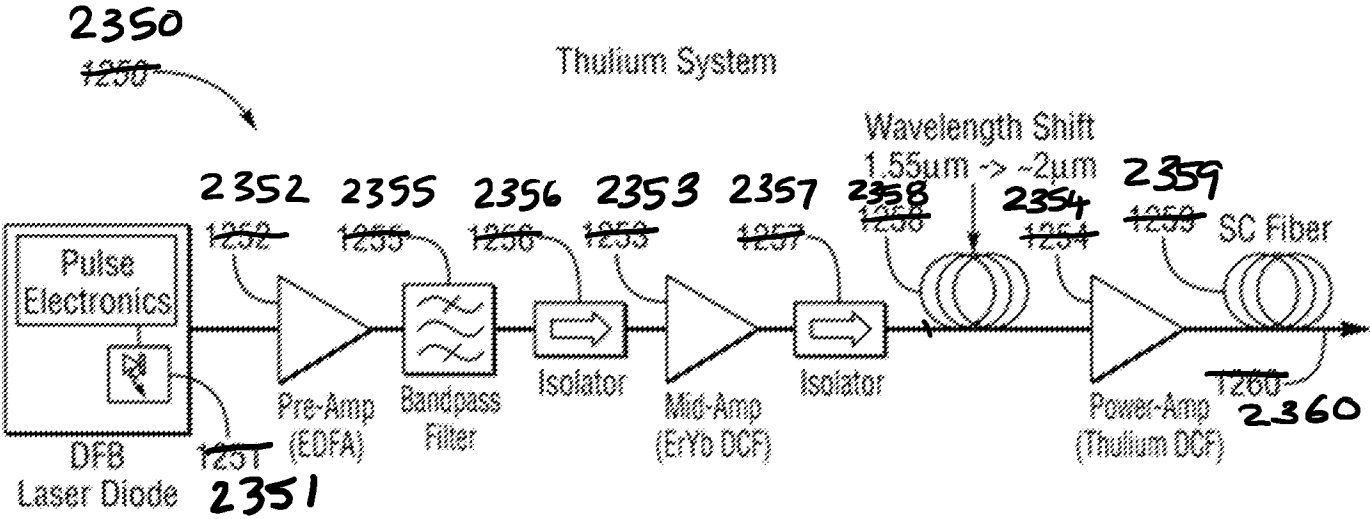


FIGURE 23



Entity Status

Applicant claims small entity status under 37 CFR 1.27

☒ Yes, applicant qualifies for small entity status under 37 CFR 1.27

☐ No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/David S. Bir/			Date (YYYY-MM-DD)	2012-12-28
First Name	David	Last Name	Bir	Registration Number (If appropriate)	38383

This collection of information is required by 37 CFR 1.51. 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 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	NEAR-INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF BREAST AND OTHER CANCERS			
First Named Inventor/Applicant Name:	Mohammed N. Islam			
Filer:	David S. Bir/Judy Noble			
Attorney Docket Number:	OMNI0107PRV			
Filed as Small Entity				
Provisional Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Provisional Application filing fee	2005	1	125	125
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				125

Electronic Acknowledgement Receipt

EFS ID:	14587201
Application Number:	61747553
International Application Number:	
Confirmation Number:	1174
Title of Invention:	NEAR-INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF BREAST AND OTHER CANCERS
First Named Inventor/Applicant Name:	Mohammed N. Islam
Customer Number:	109543
Filer:	David S. Bir/Judy Noble
Filer Authorized By:	David S. Bir
Attorney Docket Number:	OMNI0107PRV
Receipt Date:	31-DEC-2012
Filing Date:	
Time Stamp:	13:25:24
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$125
RAM confirmation Number	614
Deposit Account	023978
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Petitioner WHOOP, Inc. Ex1073

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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Specification	application-107.pdf	189461 b8417881a746d0f15710feeab915ac50819ba9fc	no	34
Warnings:					
Information:					
2	Drawings-only black and white line drawings	Figures-107.pdf	10046499 d5f4a41f7af49d090a95f404378c07bb2902d081	no	24
Warnings:					
Information:					
3	Provisional Cover Sheet (SB16)	ProvisionalSB-107.pdf	2071713 b1c85a7c37b93ed41096c5a8f8d617708394c919	no	3
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29633 f6aeddcc91d4e3f946eab7634138ee752bc3619c4	no	2
Warnings:					
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SCORE Placeholder Sheet for IFW Content

Application Number: 61747553

Document Date: 12/31/2012

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
61/747,553	12/31/2012		125	OMNI0107PRV		

CONFIRMATION NO. 1174

109543
Brooks, Kushman P.C./Cheetah Omni MedSci
1000 Town Center
Twenty Second Floor
Southfield, MI 48075

FILING RECEIPT



OC000000058612315

Date Mailed: 01/15/2013

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

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Applicant(s)

Mohammed N. Islam, Ann Arbor, MI;

Power of Attorney:

David Bir--38383

If Required, Foreign Filing License Granted: 01/11/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 61/747,553**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

NEAR-INFRARED SUPER-CONTINUUM LASERS FOR EARLY DETECTION OF BREAST AND OTHER CANCERS

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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