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(54) **Title:** SYSTEMS AND METHODS FOR SPECTRAL ANALYSIS OF A TISSUE MASS USING AN INSTRUMENT, AN OPTICAL PROBE, AND A MONTE CARLO OR A DIFFUSION ALGORITHM

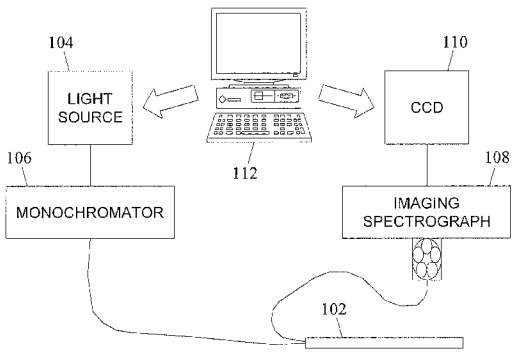

FIG. 1

(57) **Abstract:** Systems and methods for spectral analysis of a tissue mass using an instrument, an optical probe, and a Monte Carlo algorithm or a diffusion algorithm are provided. According to one method, an instrument is inserted into a tissue mass. A fiber optic probe is applied via the instrument into the tissue mass. Turbid spectral data of the tissue mass is measured using the fiber probe. The turbid spectral data is converted to absorption, scattering, and/or intrinsic fluorescence spectral data via a Monte Carlo algorithm or diffusion algorithm. Biomarker concentrations in the tissue mass are quantified using the absorption, scattering, and/or intrinsic fluorescence spectral data.

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DESCRIPTION

SYSTEMS AND METHODS FOR SPECTRAL ANALYSIS OF A TISSUE MASS USING AN INSTRUMENT, AN OPTICAL PROBE, AND A MONTE CARLO OR A DIFFUSION ALGORITHM

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/995,826, filed September 28, 2007, U.S. Provisional Patent Application Serial No. 61/047,273, filed April 23, 2008, and U.S. Provisional Patent Application Serial No. 61/047,270, filed April 23, 2008; the disclosure of each of which is incorporated herein by reference in its entirety.

GOVERNMENT INTEREST

This presently disclosed subject matter was made with U.S. Government support under Grant No. 1R01CA100559 awarded by NIH. Thus, the U.S. Government has certain rights in the presently disclosed subject matter.

TECHNICAL FIELD

The subject matter disclosed herein relates to optical spectroscopy and tissue physiology. More particularly, the subject matter disclosed herein relates to systems and methods for using a fiber optic probe to determine biomarker concentrations in a tissue mass.

BACKGROUND

Presently, optical spectroscopy may be used in some applications to serve as a diagnostic tool to detect various diseases. Notably, optical spectroscopy is sensitive to a number of biological scatterers, absorbers and fluorophores that exist in tissue. Absorbers include hemoglobin, adipose, water, beta carotene and melanin and other proteins. Scatterers include cellular and subcellular organelles. Fluorophores include metabolic electron carriers and structural proteins. Namely, these biological scatterers, absorbers, and fluorophores may be used to indicate the existence of certain diseases. Optical spectroscopy can therefore be used to provide early diagnosis of diseases, such as Alzheimer's disease, cardiovascular disease, breast cancer, and the

like. The use of such technology for early detection of diseases is invaluable. For example, each year in the United States, numerous women are diagnosed with breast cancer. While this disease takes many lives, the likelihood of survival is greatly increased with early treatment of abnormalities that are discovered via breast examinations and mammograms.

In the field of breast cancer diagnosis, current methods for determining whether an abnormality is cancerous include performing an open surgical biopsy or a needle biopsy. Of the two, needle biopsy is less invasive, faster, less expensive, and requires a shorter recovery time. However, there are drawbacks to the needle biopsy procedure due to the limited sampling accuracy associated with the technique. Because only a few samples of tissue are taken from the abnormality, the possibility that a biopsy will either provide a false negative or will be inconclusive (and require a repeat biopsy) exists.

One solution to overcome these shortcomings is to utilize optical spectroscopy to probe the abnormality. Namely, research has been conducted that indicates that ultra violet-visible-near infrared (UV-VIS-NIR) spectroscopic methods show distinct differences between the spectra of normal, benign, and malignant tissues. For example, various fluorescence studies have investigated the fluorescence emission and excitation spectra to differentiate malignant tissue from benign and some normal tissue in the breast. Other studies have used fluorescence to strictly differentiate between malignant and normal fibrous tissues. While fluorescence has been used to identify several types of breast tissue, it is difficult to distinguish malignant tissues from benign tissues using fluorescence alone.

One way to compensate for the deficiency in fluorescence techniques is to use diffuse reflectance spectroscopy. Diffuse reflectance spectroscopy (e.g., visible (400-600nm) and VIS-NIR (650-1000nm)) takes advantage of the non-fluorescent absorbers and scatterers in breast tissue to distinguish between benign tissues and malignant tissues. Past studies have demonstrated that diffuse reflectance spectra can be measured during breast cancer surgery to identify malignant and normal tissues.

Recently, researchers have investigated the use of fluorescence spectra and diffuse reflectance spectra in combination to diagnose breast cancer *ex*

vivo. From these studies, researchers discovered that the diffuse reflectance spectra coupled with the fluorescence emission spectra provided for distinguishing between malignant and nonmalignant tissues. Additionally, other studies have utilized a fiber optic probe to take fluorescence and diffuse reflectance spectra for the investigation of *ex vivo* breast tissue samples.

Despite the advances in the area of optical spectroscopy, there still remains a need for an effective method and apparatus for an *in vivo* optical probe that combines fluorescence and diffuse reflectance spectroscopy to improve biopsy procedures. Difficulties involved with providing an optical probe access to the tumor, form factor considerations, and the like have presented problems that hinder the implementation of such medical devices or methods. These difficulties may also present obstacles for other applications of optical spectroscopy in the medical arena, such as diagnostic monitoring, therapeutic monitoring, drug discovery and analysis, tissue oxygenation monitoring in surgical procedures, and the like.

Thus, there remains a need for an improved system and method for conducting spectral analysis of a tissue mass using an insertable instrument, an optical probe, and a Monte Carlo or diffusion algorithm.

SUMMARY

The subject matter described herein includes systems and methods for spectral analysis of a tissue mass using an instrument (such as a biopsy needle, an endoscope, or a catheter), an optical probe, a Monte Carlo algorithm or a diffusion algorithm. According to one aspect, an instrument, such as a biopsy needle is inserted into a tissue mass. A fiber optic probe is applied via the instrument into the tissue mass. Turbid spectral data of the tissue mass is measured using the fiber optic probe. The turbid spectral data is converted to absorption, scattering, and/or intrinsic fluorescence spectral data via a Monte Carlo algorithm or a diffusion algorithm. Biomarker concentrations in the tissue mass are quantified using the absorption, scattering, and/or intrinsic fluorescence spectral data. In an alternate embodiment, where the tissue is visible, the optical probe may be placed directly on the mass without the aid of an instrument.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the subject matter described herein will now be described with reference to the accompanying drawings, of which:

Figure 1 is a block diagram of an optical spectrometer system for determining biomarker concentrations in a tissue mass according to an embodiment of the subject matter described herein;

Figure 2A is a block diagram of an exemplary frequency-domain near-infrared spectrometer for determining biomarker concentrations in a tissue mass according to an embodiment of the subject matter described herein;

Figure 2B is a diagram of an exemplary side firing fiber optic probe that is interfaced with a tissue mass according to an embodiment of the subject matter described herein;

Figure 2C is a diagram of an exemplary forward firing fiber optic probe with a single collection ring that is interfaced with a tissue mass according to an embodiment of the subject matter described herein;

Figure 2D is a diagram of an exemplary probe tip of a forward firing fiber optic probe with a single collection ring according to an embodiment of the subject matter described herein;

Figure 2E is a diagram of vertical fiber arrays positioned at the termini of a forward firing fiber optic probe with a single collection ring according to an embodiment of the subject matter described herein;

Figure 2F is a diagram of an exemplary forward firing fiber optic probe with multiple collection rings that is interfaced with a tissue mass according to an embodiment of the subject matter described herein;

Figure 2G is a diagram of an exemplary probe tip of a forward firing fiber optic probe with multiple collection rings according to an embodiment of the subject matter described herein;

Figure 2H is a diagram of vertical fiber arrays positioned at the termini of a forward firing fiber optic probe with multiple collection rings according to an embodiment of the subject matter described herein;

Figure 3 is a flow chart of an exemplary process for quantifying biomarker concentrations according to an embodiment of the subject matter described herein;

Figure 4 is a flow chart of an exemplary process for measuring biomarker concentrations for therapeutic applications according to an embodiment of the subject matter described herein; and

Figure 5 is a flow chart of an exemplary process for measuring biomarker concentrations for diagnostic applications according to an embodiment of the subject matter described herein.

DETAILED DESCRIPTION

The subject matter described herein includes systems and methods for spectral analysis of a tissue mass using an instrument, an optical probe, and a Monte Carlo algorithm or a diffusion algorithm. According to one aspect, a fiber optic probe may be used to measure biomarkers in a tissue mass. As used herein, biomarkers may be defined as quantifiable components naturally found associated with tissue, and include, but are not limited to, oxygenated and deoxygenated hemoglobin, adipose, protein, beta carotene, myoglobin, nicotinamide adenine dinucleotide (NADH), nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), and collagen. Other biomarkers may include blood volume, drug uptake, lipid content, water content, Redox ratio, cytochrome oxidase (CtOx), drug uptake, and contrast agent uptake in the tissue mass. Notably, biomarkers can be utilized to monitor physiological conditions in a human subject or patient since changes in biomarker concentrations may serve as an indicator of tissue disease. For example, cancer may be detected by an increase in blood vessel growth and a decrease in blood oxygenation, both of which may be indicated by changes in certain biomarker concentrations, such as oxygenated and deoxygenated hemoglobin.

In one embodiment of the present subject matter, biomarkers may be measured by taking optical measurements with a fiber optic probe. For example, a fiber optic probe must initially interface (e.g., placed in contact) with a tissue mass to be analyzed. If the measurement is to be conducted *ex vivo*, there are relatively few difficulties involved with the acquisition of the optical measurements needed to yield biomarker concentrations. For example, if a tissue mass (e.g., a tumor) is visible, an insertable instrument may not be

required since the fiber optic probe may be placed directly on the tissue mass. Alternatively, if the optical measurement is to be made *in vivo*, then additional steps may be taken to position the probe in contact with the internal tissue mass or surrounding biopsy site.

In one embodiment, for *in vivo* spectral measurements, a small incision may be made into the skin (e.g., by a cutting needle) to accommodate an instrument. Exemplary instruments include, but are not limited to, biopsy needles, cannulas, endoscopic instruments, laparoscopic instruments, or any combination thereof. For example, the instrument, such as a biopsy needle-cannula device (e.g., a Bard Vacora 10G or 14G biopsy needle and coaxial cannula or a Cardinal Achieve 14G biopsy needle and coaxial cannula) may be inserted through the incision and guided via ultrasound to the tissue site of interest. The biopsy needle is subsequently extracted, thus leaving the cannula in place and in contact with the tissue site. A fiber optic probe (e.g., a forward firing fiber optic probe) is then inserted through the hollow cannula to interface with the tissue site. Once in contact with the tissue mass, the probe is used to take optical measurements, which are interpreted by an algorithm (executed by a processor) that yields biomarker concentrations. A biopsy needle may then be used to remove a tissue sample. In embodiments that specifically use a side firing fiber optic probe, the probe is adapted to fit within the biopsy needle (e.g., a Suros 9G or Mammotome biopsy needle) itself. For example, a side-firing fiber optic probe may be directly inserted into the bore of the biopsy needle and aligned to the side aperture on the biopsy needle.

In one embodiment, the optical measurements include turbid spectral data, such as reflectance spectral data and fluorescence spectral data. The fiber optic probe is ultimately retracted so a biopsy of interrogated tissue may be made through the cannula if necessary.

In one embodiment, an optical spectrometer system may be used to obtain optical measurements via a fiber optic probe and process the measurement data in order to yield biomarker concentrations. Figure 1A depicts an exemplary optical spectrometer system **100** that includes a fiber optic probe **102**. Spectrometer system **100** may also include a light source **104** (e.g., a xenon lamp), a monochromator **106** (e.g., a scanning double-excitation

monochromator), an imaging spectrograph **108**, a charged-couple device (CCD) unit **110**, and a processing unit **112** (e.g., a computer).

In one aspect of the present subject matter, fiber optic probe **102** may be adapted to fit any instrument. Possible probe adaptations include, but are not limited to, side firing probes and forward firing probes. One embodiment of probe **102** may be found in Zhu *et al.*, "Use of a multiseparation fiber optic probe for the optical diagnosis of breast cancer," *Journal of Biomedical Optics* 10(2), 024032 (March/April 2005). Other exemplary embodiments of fiber optic probes are shown below in Figures 2B, 2C, and 2F.

Probe geometry can be optimized for measurement of spectroscopic data in turbid media. Optimizing probe geometry may include selecting the numbers and geometry of collection and illumination fibers. One exemplary method for optimizing probe geometry is found in U.S. patent application publication number 2007/0019199 to Palmer *et al.*, the disclosure of which is hereby incorporated herein by reference in its entirety. For example, the probe geometry to be optimized may include at least one emitting probe fiber for emitting electromagnetic radiation into a turbid medium and at least one collecting probe fiber for collecting the electromagnetic radiation that has interacted with the turbid medium. A simulation may be performed with inputs of the probe geometry and a plurality of sets of optical property values associated with the turbid medium to generate output comprising optical parameter values measured by the probe geometry for each set of input optical property values. The measured optical parameter values are input to an inversion algorithm to produce corresponding optical properties as output. The produced optical properties are compared with optical properties known to correspond to the measured optical parameter values and a degree of matching between the produced optical properties and the known optical properties is determined. The simulation and inversion steps are repeated for a plurality of additional probe geometries. Each additional probe geometry differs from the previously tested probe geometry in at least one property. For example, the property may be a quantity of collecting entities, a diameter of at least one emitting or collecting entity, a linear distance between the emitting and collecting entities, or combinations thereof. An optimization algorithm is applied at each iteration to

select a probe geometry such that the resulting degree of matching will converge to an optimum value. An optimal geometry is selected based on the degree of matching determined for each geometry.

The aforementioned inversion algorithm used to interpret the turbid spectral data may extract the optical properties from the probe measurements. In one embodiment, the algorithm may include a Monte Carlo algorithm that is executed by processing unit **112**. Similarly, the Monte Carlo algorithm may also include an inverse Monte Carlo reflectance algorithm or an inverse Monte Carlo fluorescence algorithm. An exemplary Monte Carlo algorithm suitable for use with the subject matter described herein is found in international patent application number PCT/US2007/006624 to Palmer and Ramanujam and U.S. patent application publication 2006/0247532 to Ramanujam et al. An exemplary scaling method for expediting calculations performed in the Monte Carlo algorithm is described in U.S. provisional patent application serial number 60/903,177, filed February 23, 2007.

As mentioned above, fiber optic probe measurements may include optical spectra data. Possible probe measurements include, but are not limited to, measuring the turbid spectral data, such as fluorescence and diffuse reflectance spectra. Diffuse reflectance may be used to measure only the absorption and scattering properties in tissue. Fluorescence spectra data may be obtained by applying excitation light to the tissue sample in order to measure the intrinsic fluorescence emission properties of biomarkers, corrected for the absorption and scattering properties in tissue. One embodiment may utilize fluorescence excitation and emission spectra, as well as diffuse reflectance spectra, in the ultraviolet and visible (UV-VIS) range. For example, a probe capable of measuring the fluorescent spectra with excitation wavelengths ranging from 300-460 nm and diffuse reflectance spectra measured from 300-800 nm may be used to detect cancer.

Additionally, more optimal measurements may be taken if the spectral resolution of the spectrometer collecting the reflectance data (e.g., imaging spectrograph **108** in Figure 1A) is narrower than the narrowest spectral band being investigated. In one embodiment a spectral resolution that is at least a factor of two narrower than the narrowest spectral band may be used. For

evaluating biological tissue, a spectrometer with a spectral bandpass of between about 2.5 nm and about 5 nm may be utilized.

In another embodiment, a frequency-domain near-infrared optical spectrometer system may be used to obtain optical measurements via a side firing fiber optic probe and process the measurement data in order to yield biomarker concentrations. Figure 2A depicts an exemplary frequency-domain near-infrared optical spectrometer system **200** and Figure 2B depicts an exemplary side firing fiber optic probe **211** to be used with the spectrometer system **200**. System **200** may include a network analyzer **201**, a radio frequency (RF) switch **202**, a laser diode controller **203**, six bias T's **204**, six laser diodes **205**, an optical switch **206**, optical fiber cable **207** interfacing a fiber optic probe **211**, an avalanche photodiode (APD) **208**, a broadband amplifier **209**, and a laptop computer **210**. In one embodiment, network analyzer 201 may be replaced by a RF source with a sweep range from 50 – 500 MHz and a lock-in amplifier. Similarly, possible probe adaptations include, but are not limited to, side firing probes and forward firing probes. One embodiment of probe **211** may be found in U.S. patent application publication number 2005/0203419 to Ramanujam et al. In one embodiment, the frequency-domain near-infrared optical spectrometer system **200** may comprise a frequency domain photon migration (FDPM) instrument when a side firing probe is used.

Figure 2B shows a diagram of an exemplary side firing fiber optic probe **211** that interfaces with a tissue mass (e.g., a tumor). In one embodiment, probe **211** has an outer diameter of 1 to 3 mm that includes two side firing illumination fibers **212** and **213**, and a side firing collection fiber **214**, all inside an end-sealed stainless steel tube **217**. Notably, the two side firing illumination fibers and side firing collection fiber forms two source-detector separations, wherein, each of the source-detector separations range between 3 to 15 millimeters. In one embodiment, the side firing fiber optic probe uses the illumination fibers and collection fiber to achieve a sensing depth (i.e., depth of tissue which may be inspected) ranging from 0.5 to 10 millimeters. Steel tube **217** may include a side aperture a few millimeters from the sealed end, from which diffuse reflectance measurements can be made. The tips of fibers **212**,

213 and **214** are polished to a 45 degree angle and are coated with a reflective film. An absorptive coating **215** is applied on the outer surface of collection fiber **214** a few millimeters (e.g., 2-3 mm) away from the angle fiber tip to prevent any light from leaking directly from illumination fibers **212** and **213** into collection fiber **214**. A thin layer of biocompatible optical epoxy **216** can be used to seal the aperture on the stainless steel tube **217** and to protect the fibers from any scratch. An adaptor **218** can be used to align probe **211** to an instrument, such as a biopsy core needle. Fiber optic cable **207** interfaces probe **211** to spectrometer **200** (see Figure 2A). In one embodiment, the side firing fiber optic probe may be adapted for inserting into the tissue mass in order to measure turbid spectral data of the tissue mass. For example, the sealed end of the side firing fiber optic probe may be sharpened to be used as a needle for insertion into the tissue mass.

Figure 2C depicts a diagram of an exemplary forward firing fiber optic probe **220** including a single collection ring that may be interfaced with a tissue mass. In one embodiment, forward firing fiber optic probe **220** comprises a flexible steel sheathed tubing that contains a plurality of optical fibers. Fiber optic probe includes a portion **222** that comprises a rigid probe tip **223** on one end and a breakout tube **235** on the opposite end. Breakout tube **235** allows for the bifurcation of portion **222** into two different optical fiber groupings (e.g., an illumination fiber "leg" **251** and a collection fiber "leg" **252**). Fiber optic probe **220** may also include rigid members **224-228** (e.g., t-tubes and ferrules) that provide stability and interfacing capability for fiber optic probe **220**. Probe tip **223** may include a plurality of fibers arranged in a configuration as shown in pattern **221** (see Figure 2D), which comprises 19 illumination fibers **230** centrally grouped to form an illumination core. Although 19 illumination fibers are depicted in Figure 2D, any number of fibers may be used. For example, the illumination core may include any number of fibers to obtain an illumination core diameter that maximizes the coupling efficiency for the light source, and the (signal-to-noise ration) SNR for the fluorescence measurements. As shown in Figure 2D, the illumination core may also be surrounded by a single ring of collection fibers **231**. In one embodiment, the illumination fibers are used to emit light on the tissue sample to be examined. The light may be generated by

light source **104** and provided to fiber optic probe **220** via monochromator **106**. Specifically, light is emitted into one end of illumination fibers **230** (i.e., into vertical illumination fiber array **226**, which is located on the open-ended terminus of ferrule **225**). Fiber array **226** (shown in Figure 2E) is one possible arrangement in which the fibers can be coupled to monochromator **106**. Notably, each end of illumination fiber **230** in fiber array **226** corresponds to a terminus of illumination fiber **230** in probe tip **223** (i.e., each individual optical fiber runs the entire length of probe **220**). After the light is emitted by the illumination fibers **230** on a tissue mass, at least one collection fiber **231** captures the reflected light which is ultimately provided to imaging spectrograph **108** (via the interface created by fiber array **229** which is located on the open-ended terminus of ferrule **228** as shown in Figure 2E). In one embodiment, probe tip **223** is 9.3 cm long and has a diameter of 2.1 mm in order to fit within the lumen of a 14 gauge biopsy needle cannula. In one embodiment, forward firing fiber optic probe **220** uses the illumination fibers and collection fibers to achieve a sensing depth (i.e., depth of tissue which may be inspected) ranging from 0.5 to 10 millimeters.

Figure 2F depicts a diagram of an exemplary forward firing fiber optic probe **240** with multiple collection rings that may be interfaced with a tissue mass. In one embodiment, forward firing fiber optic probe **240** may be nearly identical to fiber optic probe **220** in Figure 2C with the exception of the diameter of probe tip **223**, the arrangement of fibers in pattern **241** (see Figure 2G), and the number and types of fibers contained in fiber array **249** (see Figure 2H). For example, probe tip **223** may be configured to include 19 illumination fibers centrally grouped and surrounded by three concentric layers of fibers (i.e., collection rings). Each collection ring includes a plurality of dead fibers and a plurality of live collection fibers, wherein each of the collection fibers may be distinguished by its collection ring placement. In other words, collection fibers located in the outermost collection ring are distinguished (i.e., for data collection purposes) from the collection fibers positioned in the innermost collection ring. The dead fibers **248** may be the same size as illumination fibers **244** and live collection fibers **245** for the purpose of bundle packing. The output signals from the three concentric rings of collection fibers are spatially separated by CCD

unit **110** (see Figure 1A), thereby enabling fluorescence and diffuse reflectance spectra to be measured at three illumination-collection separations simultaneously. As shown in Figure 2G, the outermost collection ring comprising 8 outer layer collection fibers **245** interspersed among and separated by 22 dead fibers **248**. Similarly, the middle collection ring includes 6 middle layer collection fibers **246** interspersed among and separated by 18 dead fibers **248**. Lastly, the innermost collection ring includes 4 inner layer collection fibers **247** interspersed among and separated by 15 dead fibers **248**. One advantage of arranging the collection fibers in this manner is that fiber optic probe **240** is capable of taking measurements at three different sensing depths within the tissue mass. In one embodiment, the probe tip **223** is 9.3 cm long and has a diameter of 3.4 mm in order to fit within the lumen of a 10 gauge biopsy needle cannula. In one embodiment, forward firing fiber optic probe **240** uses the illumination fibers and collection fibers to achieve a sensing depth (i.e., depth of tissue which may be inspected) ranging from 0.5 to 10 millimeters.

Figure 3 is a flow diagram illustrating the steps of an exemplary method **300** for determining biomarker concentrations in a tissue mass according to an embodiment of the subject matter described herein. Referring to Figure 3, in block **302**, an instrument is inserted in a tissue mass. In one embodiment, a biopsy needle-cannula instrument is inserted into or interfaces a tissue mass, such as a tumor, using ultrasound for guidance.

In block **304**, a fiber optic probe is applied into the tissue mass via the instrument. In one embodiment, the needle is first retracted from the cannula (i.e., the hollow cannula remains in the tumor while the biopsy needle is withdrawn) and is subsequently replaced by fiber optic probe **102** (see Figure 1). Essentially, fiber optic probe **102** uses the cannula as a guide to access the tumor. It is appreciated that fiber optic probe **102** may be placed in proximity, in contact, or within the tumor depending on the particular application. In another embodiment, a biopsy core needle is first fired into a tissue mass with guidance from mammography or ultrasound and the cutter in the needle is retracted such that the side-facing aperture on the needle is open. Then side firing fiber optic probe **211** may be inserted into the needle and oriented to face the aperture and diffuse reflectance spectroscopy measurements are made from the tissue

site adjacent to the side facing aperture. In an alternate embodiment, an insertable instrument may not be required if the tissue mass is visible. Rather the fiber optic probe may be applied directly to the tissue mass.

In block **306**, turbid spectral data is measured. In one embodiment, turbid spectral data is measured using fiber optic probe **102**. For example, fiber optic probe **102** may be used to make optical measurements, such as fluorescence spectra measurements and diffuse reflectance measurements, of the tumor. In another embodiment, turbid spectral data is measured using fiber optic probe **211**. For example, fiber optic probe **211** may be used to make optical measurements, such as diffuse reflectance measurements, of the tumor.

In block **308**, the turbid spectral data is converted to absorption, scattering, and/or intrinsic fluorescence data. In one embodiment, the measured turbid spectral data is used as input for a Monte Carlo algorithm. Using the turbid spectral data and the Monte Carlo algorithm, a processing unit (e.g., processing unit **112** in Figure 1) may convert the data into absorption, scattering, and intrinsic fluorescence data that can be easily interpreted and analyzed. In another embodiment, the measured turbid spectral data is used as input for a diffusion algorithm, a processing unit (e.g., laptop computer **210** in Figure 2A) may convert the data into absorption and scattering data that can be interpreted and analyzed. An exemplary diffusion algorithm can be found in Yu *et. al.* "Feasibility of near-infrared diffuse optical spectroscopy on patients undergoing image-guided core-needle biopsy," *Optics Express* 15, 7335-7350 (2007).

In block **310**, biomarker concentrations are quantified using the combined spectral data (i.e., absorption, scattering, and/or intrinsic fluorescence data). In one embodiment, the combined spectral data may be analyzed and processed to quantify the biomarker concentrations existing in the tissue mass (i.e., the tumor). Once the biomarker concentrations are quantified, specific physiological conditions can be determined. Method **300** then ends.

Although Figure 3 describes a general method for determining biomarker concentrations, it is appreciated that method **300** may be modified for specific medical applications. For example, Figure 4 depicts an exemplary method **400**

for determining biomarker concentrations in order to provide therapeutic screening. Referring to Figure 3, in block **402**, known biomarkers are measured. In one embodiment, known biomarkers of cancer may be measured by using an instrument that positions a fiber optic probe **102** or **211** on a tissue mass, such as a tumor, *in vivo*. Probe **102** or **211** may then obtain diffuse reflectance and/or fluorescence spectra measurements of the tumor, and an algorithm may be used to extract the optical properties (i.e., determine absorption, scattering, and/or intrinsic fluorescence data properties). These properties may be associated with quantities of biomarkers present in the tumor, and may be used to determine tumor characteristics including, but not limited to, tumor size or shape. For example, biomarkers present in tumor tissue may be quantitatively measured to determine the current oxygen depletion and blood vessel growth of the tumor.

In block **404**, the biomarker measurements are analyzed. In one embodiment, the biomarker measurements may be used to make a prognostic assessment of the tumor. If the size of a tumor can be identified, the best course of therapy to treat the tumor may then be determined. One example is utilizing the data on the current oxygen depletion and blood vessel growth to identify a tumor and select a favorable treatment/therapy, e.g., chemotherapy (or regimen thereof) or radiotherapy.

In block **406**, the chosen therapy is initiated. In one embodiment, various cancer fighting drugs may be prescribed in order to possibly reduce the size of the tumor (e.g., chemotherapy).

In block **408**, the progress of the therapy may be monitored through the measurement of known biomarkers. Monitoring may occur through taking current measurements of the biomarkers which were initially measured. These measurements may allow for a comparison between the current biomarker concentrations and the initial biomarker concentrations. In one embodiment, an instrument (e.g., a cannula) may be used to position probe **102** (or probe **211**) on the tumor *in vivo* in a similar manner described in block **402**. Probe **102** (or probe **211**) may subsequently obtain the fluorescence and diffuse reflectance (or diffuse reflectance only) spectra measurements of the tumor and the algorithm may extract the optical properties (i.e., obtain absorption, scattering,

and/or intrinsic fluorescence data) from the spectra data. For example, this may include measuring the current biomarker concentrations of the tumor to determine the present oxygen depletion levels and blood vessel growth associated with the tumor.

In block **410**, a determination may be made as to whether the chosen therapy has produced positive results. This determination may be made by comparing the current biomarker concentrations to the initial biomarker concentrations and analyzing the results with respect to the anticipated response. If positive results have been produced, then method **400** continues to block **412**. If positive results have not been produced, then method **400** continues to block **414**. In one embodiment, the concentrations of biological markers may be used to determine whether the tumor has decreased in size. For example, it may be determined that the tumor has decreased by identifying an indication of a decrease in blood vessel growth and oxygen depletion in comparison with the measurements obtained in block **402**.

In block **412**, the original therapy form may be continued. In one embodiment, the patient may continue to follow with his currently prescribed treatment if a decrease in tumor size has been detected. One example is to continue treating a patient with currently prescribed cancer fighting drugs.

Additionally, if therapy has been determined to produce successful results in block **410**, method **400** may loop back to block **408** where the therapy form may be continued and monitored again. It may also be beneficial to continue to monitor the progress of therapy via biomarker concentration measurement, as described above, to determine if the positive response continues during the course of treatment. One embodiment may include monitoring the patient several times during treatment to assess the size of a tumor at different time intervals during treatment. Examples may include the monitoring and assessing the progress of treatment every two weeks as a patient undergoes therapy.

In block **414**, the current therapy form may be discontinued. Possible examples of non-positive results include, but are not limited to, no change in condition or a worsening in condition. In one embodiment, the current therapy method may be abandoned in favor of another if no decrease in tumor size has

been detected. One example is to abandon the currently prescribed cancer fighting drugs if biological markers indicate these drugs have no effect on the tumor.

In block **416**, the biomarker measurements may be re-evaluated, and a new form of therapy may be chosen to treat the tumor. In one embodiment, the data on the biological markers may be re-evaluated in order to determine a different form of therapy that is likely to decrease the presence of these biomarkers. One example is to choose a different cancer drug combination which may result in a decrease of the tumor. Additionally, if the original therapeutic method has been deemed unsuccessful, therapy may begin again with the new chosen therapeutic method, per block **406**. In one embodiment, a new form of therapy may be implemented and the progress of the therapy is monitored to determine if the new therapeutic method will be successful in decreasing the size of the tumor. One exemplary scenario may involve a beginning a new therapeutic method involving different cancer fighting drugs to decrease a tumor which had been unresponsive to the original drug combination.

In addition to the therapeutic applications afforded, the present subject matter may also be utilized for diagnostic applications. Figure 5 depicts one embodiment where the present subject matter may include a method **500** for diagnostic screening. Referring to Figure 5, in block **502**, biomarker measurements are taken at a tissue site of interest. In one embodiment, biomarker measurements are taken at a tissue site using an optical fiber probe. One example is to measure the biomarkers present at a tissue site which may appear suspicious on an ultrasound or X-ray image.

In block **504**, the biomarker concentration may be analyzed. In one embodiment, the biomarker concentration may be analyzed by taking the measured data from probe **102** or **211**, applying an algorithm to the data, and retrieving the optical properties. One example is to determine the concentration of a biomarker known to be associated with cancer by applying the measured data to a Monte Carlo or a diffusion algorithm and determining the optical properties (i.e., the absorption, scattering, and/or intrinsic fluorescence data) which can then yield concentrations.

In block **506**, a determination may be made as to whether the tissue site is diseased. If the tissue is diseased, then method **500** continues to block **508**. If the tissue is not diseased, then method **500** proceeds to block **510**. Diseased sites may be characterized by several biomarker indicators including, but not limited to, abnormally high or low concentration levels in certain biomarkers. One embodiment may be determining whether the tissue at the site possesses biomarkers in concentrations which would indicate the tissue is not healthy. For example, the biomarker concentration data is used to determine if a suspicious tissue site originally viewed in an ultrasound or X-ray image is malignant, benign, or normal.

In block **508**, a sample of the site of interest may be removed. One embodiment may be to remove a sample of tissue from a diseased site using removal methods known in the art. For example, a tissue sample is removed if the biomarkers indicate the site is cancerous. The sample may then be further tested to confirm the diagnosis or discern additional properties related to the disease.

In block **510**, probe **102** (or **211**) may be moved to a new site of interest. One embodiment may be to move probe **102** (or **211**) to a different location on the tissue being investigated. If the site is determined to not be diseased or if a sample of the diseased site has already been removed, probe **102** (or **211**) may be moved to a new site of interest. Method **500** may then be repeated several times to further survey the site. Such surveys may allow for the diagnosis of the extent of the disease present in the site, and may also allow for the identification of non-diseased areas which may then be spared from treatment. One example is to move probe **102** (or **211**) to a different location on a suspicious tissue mass located via ultrasound or at the physican's discretion.

Additional sites may be investigated by returning to block **502**. One embodiment may be to make several measurements on and around a site of interest to determine the extent of a disease. One example is to measure biomarker concentrations that are indicative of cancer on and around a tumor to determine the size of the tumor.

The methods described by the present subject matter may be used for additional purposes and applications. In addition to therapeutic and diagnostic

monitoring, the present subject matter may be used for applications such as monitoring tissue oxygenation in reconstructive/plastic/cosmetic surgery, drug discovery, cancer detection, monitoring response to therapy, measuring prognostic biomarkers, monitoring blood loss, providing biopsy guidance, evaluating trauma patients, transplant organ perfusion, and the like.

In an alternate embodiment, the aforementioned fiber optic probe may also be used for obtaining *in vivo* measurements of blood parameters. For example, the fiber optic probe may be used to quantitatively determine the concentration of "total hemoglobin" (i.e., the total hemoglobin content in a tissue mass), blood loss, dilutional effects from fluid intake, porphyrin levels, cellular metabolism, and the hemoglobin saturation of a tissue mass *in vivo*. In addition, the constituents of hemoglobin, which include oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin, may also be readily quantified using the present subject matter. The fiber optic probe may also measure the concentration of the hemoglobin analyte by being placed in an oral mucosa, under the tongue, or taped to any exposed surfaces (such as an arm), thereby providing real-time measurements of the analyte of interest. Applications of this technology include, but are not limited to, a quick non-invasive screening test for total hemoglobin, quantifying tissue blood loss *in vivo*, quantifying dilutional effects of fluids in the tissue, and quantifying tissue oxygenation *in vivo*. One other advantage of the present subject matter includes eliminating the need for all handling and disposal of blood and sharp medical equipment (e.g., syringes).

In one embodiment, the fiber optic probe may be used to perform intraoperative margin assessments of a tissue mass *in vivo*. Due to the fact that cancerous mass specimens removed from numerous patients can be characterized as having "positive margins." The existence of a positive margin in an excised tissue mass serves as an indication that cancerous tissue most likely remains in the patient. As a result, a repeat surgery is oftentimes required. In one embodiment, the present subject matter serves as an intraoperative instrument that ensures that a cancerous tissue mass is completely excised at the time of the surgery. One advantage of the present subject matter is that unlike existing techniques for evaluating tissue margins

during surgery (e.g., cytology and frozen section), an on-site pathologist is not required.

The technology development for this application is an optical margin assessment device (e.g., a fiber optic probe), which permits surgeons to identify and correct "positive tumor margins" that exist during surgery. In order to enhance the effectiveness of identifying positive tumor margins utilizing optical spectroscopy, one or more contrast agents (e.g., acetic acid, Acriflavin, 2-[N-(7-nitrobenz-2-oxa-l,3-diazol-4-yl) amino]-2-deoxy-D-glucose (NBDG), fluorescin, and the like) may be used in conjunction with the fiber optic probe. For example, acetic acid may be used during colposcopic examination to identify atypical areas of the cervix that require biopsy. Application of acetic acid in a concentration ranging from 3-6% causes acetowhitening of cervical abnormalities, such as neoplasia, adenocarcinoma, and invasive squamous cell carcinoma. Specifically, the use of acetic acid may alter a tissue's protein structure such that light is prevented from passing through the epithelium, thereby enhancing light scattering. In another embodiment, the mere presence of the contrast agent in the tissue provides light scattering, fluorescence, or absorption contrast in the tissue mass. For example, 2-NBDG is a fluorescent optical analog of deoxyglucose (similar to 2-fluorodeoxyglucose used in Positron emission tomography (PET) imaging) and is taken up with increased glucose metabolism. In this scenario, the presence of the 2-NBDG in the tissue mass provides fluorescence contrast in the tissue mass. Likewise, Acriflavin intercalates with DNA and thus provides nuclear contrast. Acetic acid may be imaged via light scattering while Acriflavin and 2-NBDG fluoresce in the blue-green wavelengths. Notably, the present subject matter may use contrast agents to increase contrast between positive and negative margins in tissue, either *in vivo* or *ex vivo*.

In one embodiment, a contrast agent may be applied to internal tissue that is left exposed after the excision of a tumor tissue mass. For example, the tissue margins are "painted" with 3-6% acetic acid. The tissue margin surface is then imaged with a CCD camera, digital camera, or the like. The light source may be the surrounding ambient light or an illumination source that provides broadband illumination over the visible and near infrared wavelengths. The

images may be captured rapidly over a period of 30-60 seconds during which the acetowhitening affect decays. The images derived from optical spectroscopy imaging techniques can capture and quantify the contrast agent's brightness and kinetics of the brightness to indicate whether the tumor margin is positive or negative (e.g., the contrast agent enhances light scattering in the margins of the tissue mass). More specifically, the contrast achieved may be enhanced by the use of a specific optical contrast agent that is selectively taken up by positive tumor margins. This information (i.e., the enhanced light scattering) is captured and processed using special signal processing algorithms to delineate positive tumor margins.

In an alternate embodiment, other contrast agents that are applicable to intraoperative margin assessment may be used. For example, photosensitizers such as aminolevulinic acid, methylene blue, and other porphyrins may be utilized. These contrast agents can also be used with a high dose of light to treat residual tumors in the cavity after resection.

It will be understood that various details of the presently disclosed subject matter may be changed without departing from the scope of the presently disclosed subject matter. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation.

CLAIMS

What is claimed is:

1. A system for determining biomarker concentrations in a tissue mass, the system comprising:

an instrument for inserting into to the tissue mass;

a fiber optic probe for interfacing the tissue mass via the instrument and measuring turbid spectral data of the tissue mass; and

a processing unit for converting the turbid spectral data to at least one of absorption, scattering, and intrinsic fluorescence spectral data via a Monte Carlo algorithm or a diffusion algorithm and quantifying biomarker concentrations in the tissue mass using the absorption, scattering, and intrinsic fluorescence spectral data.

2. The system of claim 1 wherein the fiber optic probe comprises at least one of a forward firing fiber optic probe and a side firing fiber optic probe.

3. The system of claim 2 wherein the side firing fiber optic probe is adapted to fit within a biopsy needle.

4. The system of claim 3 wherein the biopsy needle includes at least one of a Suros 9G biopsy needle, a Mammotome biopsy needle, a Bard Vacora 10G biopsy needle, a Bard Vacora 14G biopsy needle, and a Cardinal Achieve 14G biopsy needle.

5. The system of claim 2 wherein the forward firing fiber optic probe is adapted to fit within a biopsy cannula.

6. The system of claim 1 wherein the instrument comprises a cannula, a biopsy needle, an endoscopic instrument, and a laparoscopic instrument.

7. The system of claim 1 wherein the instrument is inserted in the tissue mass *in vivo*.

8. The system of claim 1 wherein the turbid spectral data comprises diffuse reflectance spectral data and fluorescence spectral data of the tissue mass.

9. The system of claim 1 wherein the biomarker concentrations are used to determine if tissue mass is malignant, benign, or normal.

10. The system of claim 9 wherein a biopsy is conducted on the tissue mass through a cannula or a biopsy needle if the tissue is malignant.

11. The system of claim 1 wherein the biomarker concentrations are used to quantify drug uptake by the tissue mass.

12. The system of claim 1 wherein the fiber optic probe is adapted to acquire the turbid spectral data using a spectrometer having a spectral bandpass of between about 2.5 nm and 5 nm.

13. The system of claim 1 wherein the Monte Carlo algorithm includes either an inverse Monte Carlo reflectance algorithm or an inverse Monte Carlo fluorescence algorithm.

14. The system of claim 1 wherein the fiber optic probe includes a side firing fiber optic probe adapted for interfacing the tissue mass and measuring turbid spectral data of the tissue mass, and wherein the side firing fiber optic probe comprises a one-end-sealed stainless steel tube with a side facing aperture, two side firing illumination fibers, and a side firing collection fiber, forming two source-detector separations.

15. The system of claim 14 wherein each of the two source-detector separations range between 3 to 15 millimeters.

16. The system of claim 14 wherein the diameter of the side firing fiber optic probe includes a diameter ranging between 1 to 3 millimeters.

17. The system of claim 14 wherein the side firing fiber optic probe includes a sensing depth ranging from 0.5 to 10 millimeters.

18. The system of claim 14 wherein each of the side firing fibers includes an angled fiber tip that includes a reflective coating.

19. The system of claim 14 wherein the side firing collection fiber includes an absorptive coating on its outer surface for blocking light leaks directly from illumination fibers or scattered lights inside the stainless steel tube.

20. The system of claim 18 wherein biocompatible epoxy is used for sealing the side facing aperture and for index-matching material between the fiber tips and the tissue mass.

21. The system of claim 1 wherein a contrast agent is applied to the tissue mass to enhance light scattering in the tissue mass.

22. The system of claim 21 wherein the enhanced light scattering aids with margin assessment.

23. The system of claim 1 wherein the presence of the contrast agent in the tissue provides light scattering, fluorescence, or absorption contrast in the tissue mass.

24. The system of claim 21 wherein the contrast agent includes at least one of acetic acid, Acriflavin, 2-[N-(7-nitrobenz-2-oxa-l,3-diazol-4-yl) amino]-2-deoxy-D-glucose (NBDG), fluorescin, aminolevulinic acid, and methlyene blue.

25. The system of claim 1 wherein the processing unit is further configured to determine the concentrations at least one of total hemoglobin, oxyhemoglobin concentration, deoxyhemoglobin concentration, beta carotene concentration, hemoglobin saturation, nicotinamide adenine dinucleotide (NADH), flavin adenine dinucleotide (FAD), collagen, porphyrins, retinol, tryptophan, tissue blood loss, dilutional effects of fluids, *in vivo*.

26. The system of claim 1 wherein the fiber optic probe includes a forward firing fiber optic probe adapted for interfacing the tissue mass and measuring turbid spectral data of the tissue mass, and wherein the forward firing fiber optic probe includes a probe tip comprised of a plurality of fibers.

27. The system of claim 26 wherein the plurality of fibers in the forward firing fiber optic probe are configured with a central core of illumination fibers surrounded by a single concentric ring of collection fibers.

28. The system of claim 27 wherein the plurality of fibers in the forward firing fiber optic probe are configured with a central core of illumination fibers encircled by a plurality of concentric rings of collection fibers, wherein each concentric ring includes a plurality of ring-specific collection fibers.

29. The system of claim 27 wherein the probe tip includes a length of 9.3 centimeters and a diameter of 2.1 millimeters.

30. The system of claim 28 wherein the probe tip includes a length of 9.3 centimeters and a diameter of 3.4 millimeters

31. The system of claim 28 wherein the fiber optic probe includes a sensing depth ranging from 0.5 to 10 millimeters.

32. A method for determining biomarker concentrations in a tissue mass, the method comprising:

inserting an instrument into the tissue mass; and

applying a fiber optic probe via the instrument into the tissue mass;

measuring turbid spectral data of the tissue mass using the fiber optic probe;

converting the turbid spectral data to at least one of absorption, scattering, and intrinsic fluorescence spectral data via a Monte Carlo algorithm or a diffusion algorithm; and

quantifying biomarker concentrations in the tissue mass using the at least one of absorption, scattering, and intrinsic fluorescence spectral data.

33. The method of claim 32 wherein the fiber optic probe comprises at least one of a forward firing fiber optic probe and a side firing fiber optic probe.

34. The method of claim 33 wherein the forward firing fiber optic probe is adapted to fit within a biopsy cannula.

35. The method of claim 33 wherein the side firing fiber optic probe is adapted to fit within a biopsy needle.

36. The method of claim 35 wherein the biopsy needle includes at least one of a Suros 9G biopsy needle, a Mammotome biopsy needle, a Bard Vacora 10G biopsy needle, a Bard Vacora 14G biopsy needle, and a Cardinal Achieve 14G biopsy needle.

37. The method of claim 32 wherein the instrument comprises a cannula, a biopsy needle, an endoscopic instrument, and a laparoscopic instrument.

38. The method of claim 32 wherein the instrument is inserted in the tissue mass *in vivo*.

39. The method of claim 32 wherein the turbid spectral data comprises

diffuse reflectance spectral data and fluorescence spectral data of the tissue mass.

40. The method of claim 32 wherein the biomarker concentrations are used to determine if tissue mass is malignant, benign, or normal.

41. The method of claim 40 wherein a biopsy is conducted on the tissue mass through a cannula or a biopsy needle if the tissue is malignant.

42. The method of claim 32 wherein the biomarker concentrations are used to quantify drug uptake by the tissue mass.

43. The method of claim 32 wherein the fiber optic probe is adapted to acquire the turbid spectral data using a spectrometer having a spectral bandpass of between about 2.5 nm and 5 nm.

44. The method of claim 32 wherein the Monte Carlo algorithm includes either an inverse Monte Carlo reflectance algorithm or an inverse Monte Carlo fluorescence algorithm.

45. The method of claim 32 wherein the fiber optic probe includes a side firing fiber optic probe adapted for interfacing the tissue mass and measuring turbid spectral data of the tissue mass, and wherein the side firing fiber optic probe comprises a one-end-sealed stainless steel tube with a side facing aperture, two side firing illumination fibers, and a side firing collection fiber, forming two source-detector separations.

46. The method of claim 45 wherein each of the two source-detector separations range between 3 to 15 millimeters.

47. The method of claim 45 wherein the diameter of the side firing fiber optic probe includes a diameter ranging between 1 to 3 millimeters.

48. The method of claim 45 wherein the side firing fiber optic probe includes a sensing depth ranging from 0.5 to 10 millimeters.

49. The method of claim 45 wherein each of the side firing fibers includes an angled fiber tip that includes a reflective coating.

50. The method of claim 45 wherein the side firing collection fiber includes an absorptive coating on its outer surface for blocking light leaks directly from illumination fibers or scattered lights inside the stainless steel tube.

51. The method of claim 49 wherein biocompatible epoxy is used for sealing the side facing aperture and for index-matching material between the fiber tips and the tissue mass.

52. The method of claim 32 further comprising: applying a contrast agent to the tissue mass to enhance light scattering, absorption, or fluorescence in the tissue mass.

53. The method of claim 52 wherein the enhanced light scattering, absorption, or fluorescence aids with margin assessment.

54. The method of claim 52 wherein the contrast agent includes at least one of acetic acid, Acriflavin, 2-[N-(7-nitrobenz-2-oxa-l,3-diazol-4-yl) amino]-2-deoxy-D-glucose (NBDG), fluorescin, aminolevulinic acid, and methlyene blue.

55. The method of claim 32 wherein the processing unit is further configured to determine the concentrations at least one of total hemoglobin, oxyhemoglobin concentration, deoxyhemoglobin concentration, beta carotene concentration, nicotinamide adenine dinucleotide (NADH), flavin adenine dinucleotide (FAD), collagen, retinol, porphyrin, hemoglobin saturation, tissue blood loss, dilutional effects of fluids *in vivo*.

56. The method of claim 32 wherein the fiber optic probe includes a forward firing fiber optic probe adapted for interfacing the tissue mass and measuring turbid spectral data of the tissue mass, and wherein the forward firing fiber optic probe includes a probe tip comprised of a plurality of fibers.

57. The method of claim 56 wherein the plurality of fibers in the forward firing fiber optic probe are configured with a central core of illumination fibers surrounded by a single concentric ring of collection fibers.

58. The method of claim 57 wherein the plurality of fibers in the forward firing fiber optic probe are configured with a central core of illumination fibers encircled by a plurality of concentric rings of collection fibers, wherein each concentric ring includes a plurality of ring-specific collection fibers.

59. The method of claim 57 wherein the probe tip includes a length of 9.3 centimeters and a diameter of 2.1 millimeters.

60. The method of claim 58 wherein the probe tip includes a length of 9.3 centimeters and a diameter of 3.4 millimeters

61. The method of claim 56 wherein the fiber optic probe includes a sensing depth ranging from 0.5 to 10 millimeters.

62. A system for determining biomarker concentrations in a tissue mass, the system comprising:

a side firing fiber optic probe for inserting into a tissue mass and measuring turbid spectral data of the tissue mass, wherein the side firing fiber optic probe includes a one-end-sealed stainless steel tube with a side facing aperture, two side firing illumination fibers, and a side firing collection fiber, forming two-source detector separations, wherein the sealed end of the stainless steel tube includes a sharpened point adapted for insertion into the tissue mass; and

a processing unit for converting the turbid spectral data to at least one of absorption and scattering spectral data via a diffusion algorithm and quantifying biomarker concentrations in the tissue mass using the absorption and scattering spectral data.

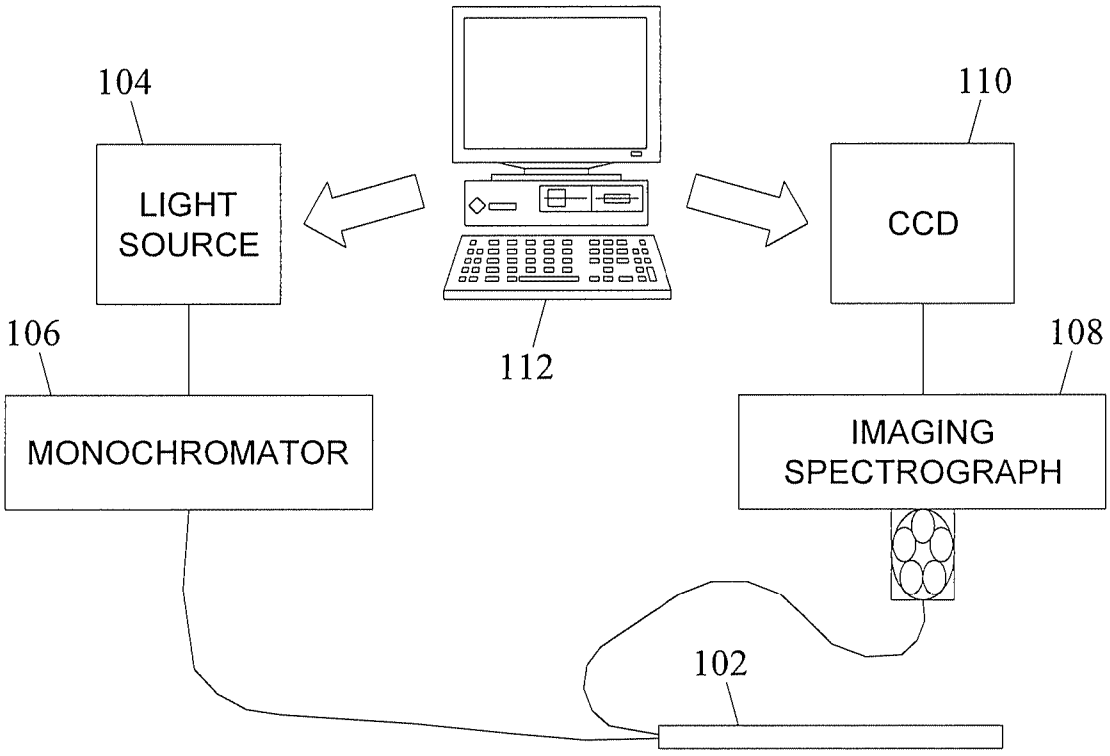
104
LIGHT SOURCE
110
CCD
106
MONOCHROMATOR
112
108
IMAGING SPECTROGRAPH
102

FIG. 1

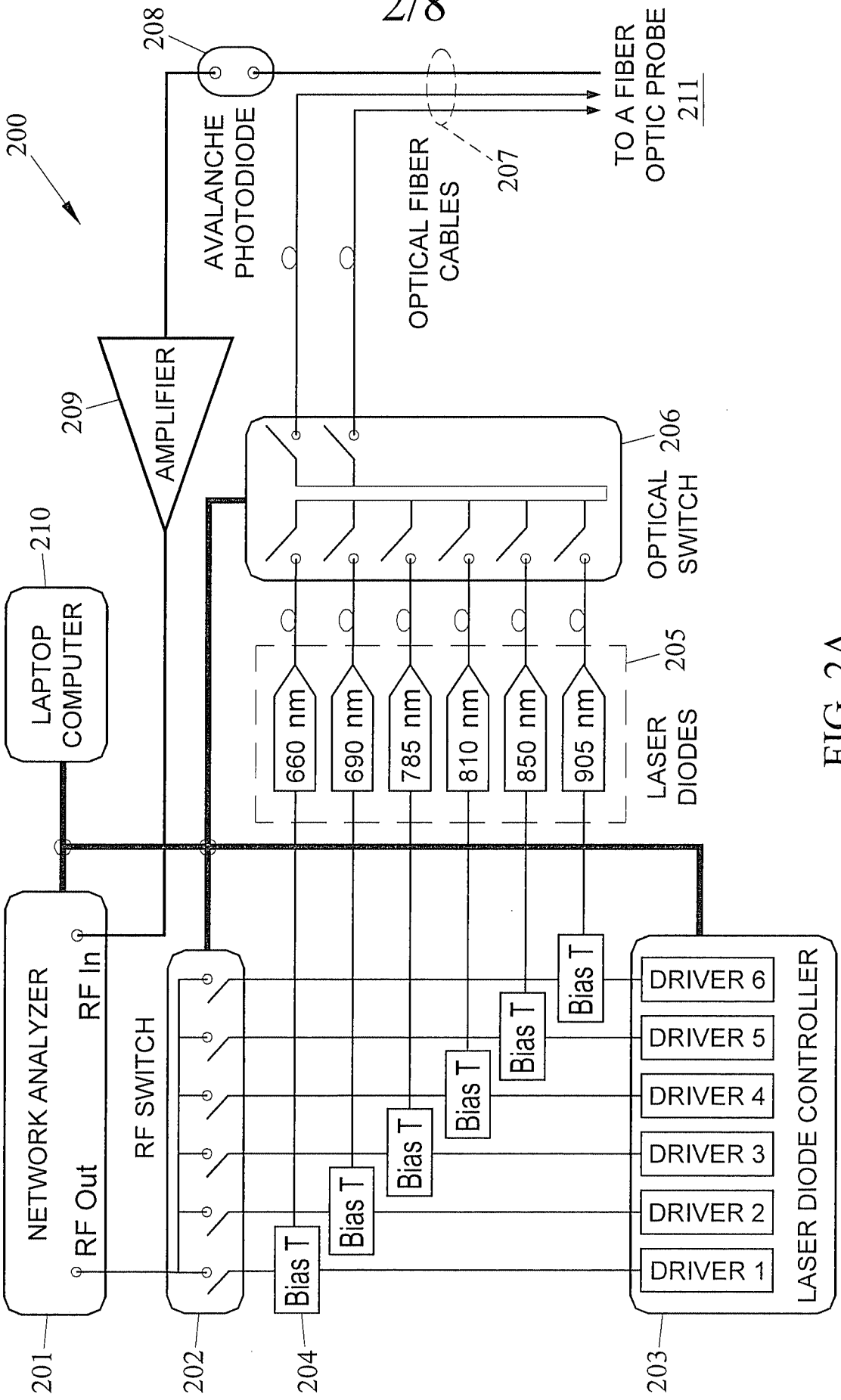
200
208
AVALANCHE PHOTODIODE
TO A FIBER OPTIC PROBE
211
OPTICAL FIBER CABLES
207
209
AMPLIFIER
206
OPTICAL SWITCH
210
LAPTOP COMPUTER
205
LASER DIODES
660 nm
690 nm
785 nm
810 nm
850 nm
905 nm
NETWORK ANALYZER
RF Out
RF In
RF SWITCH
Bias T
DRIVER 6
DRIVER 5
DRIVER 4
DRIVER 3
DRIVER 2
DRIVER 1
LASER DIODE CONTROLLER
201
202
204
203

FIG. 2A

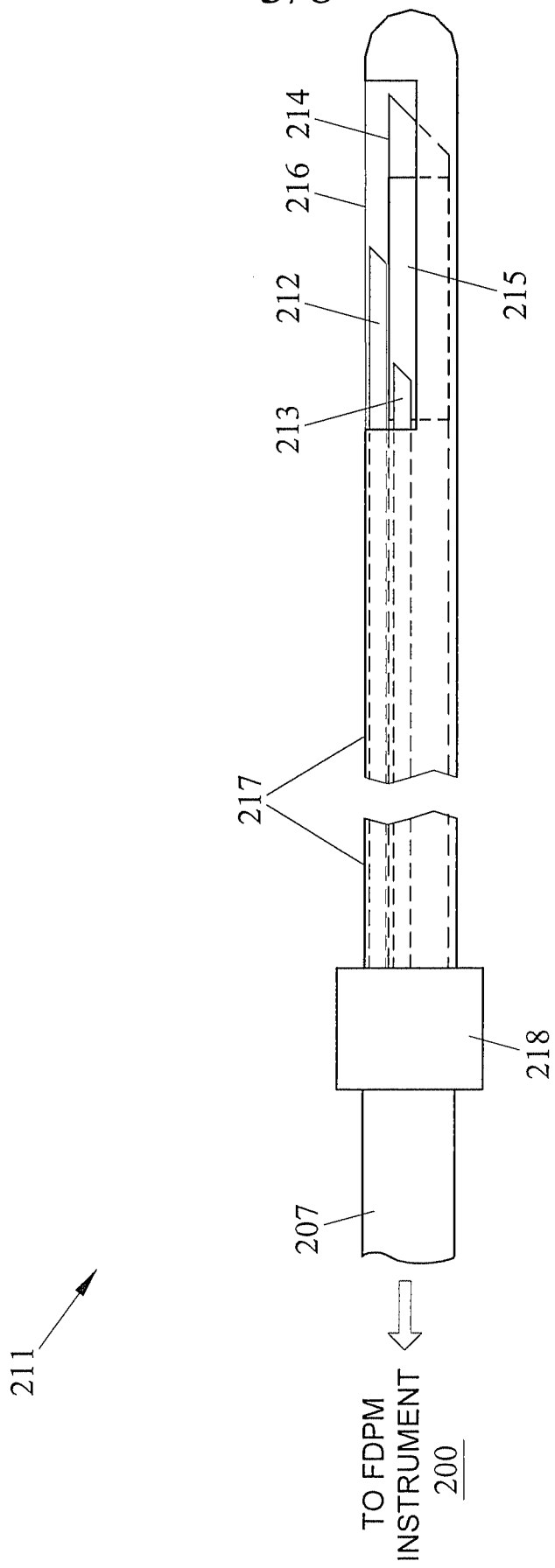

FIG. 2B

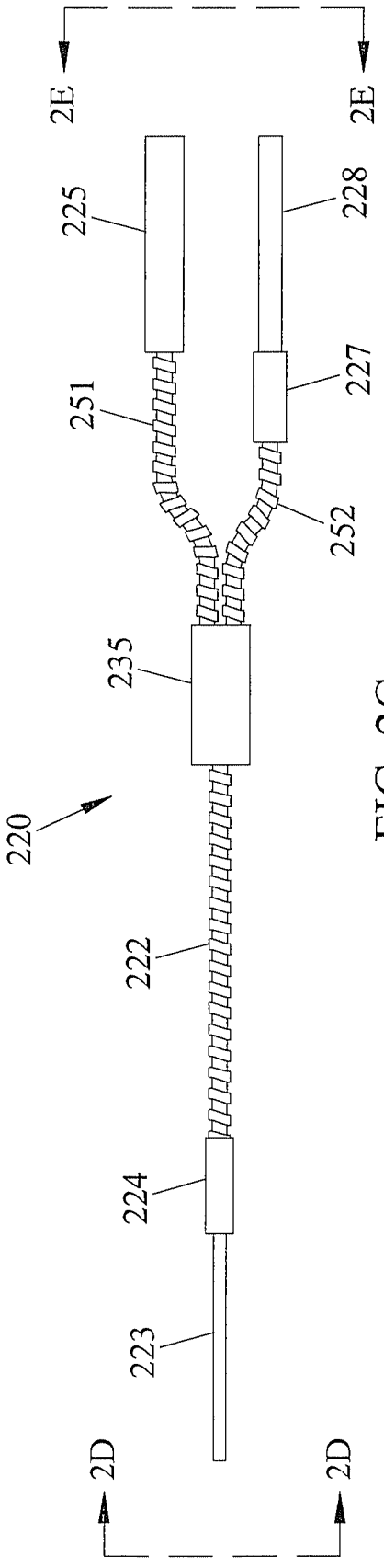

FIG. 2C

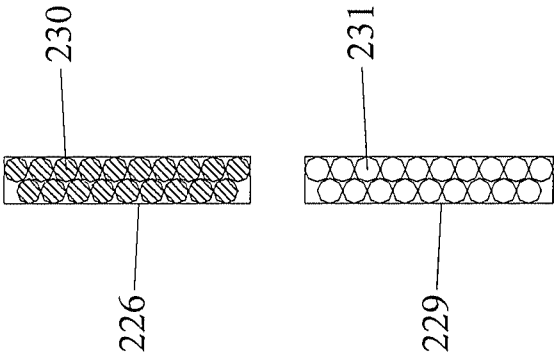

FIG. 2E

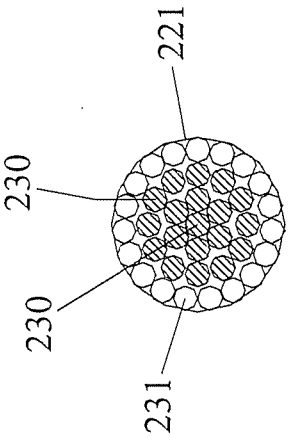

FIG. 2D

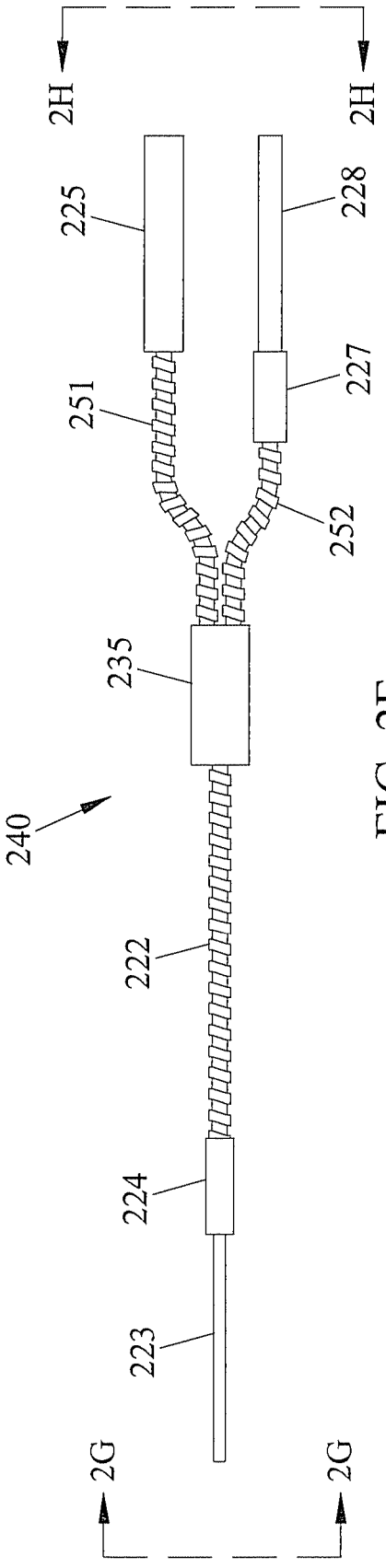

FIG. 2F

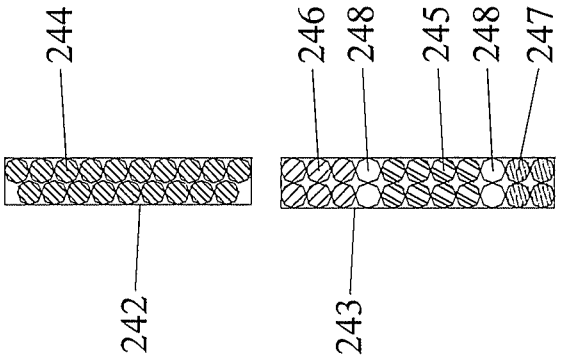

FIG. 2H

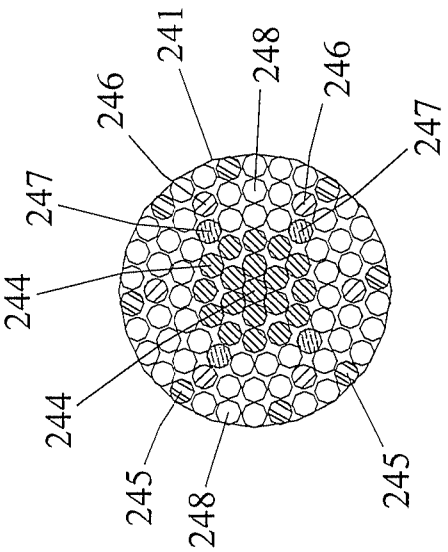

FIG. 2G

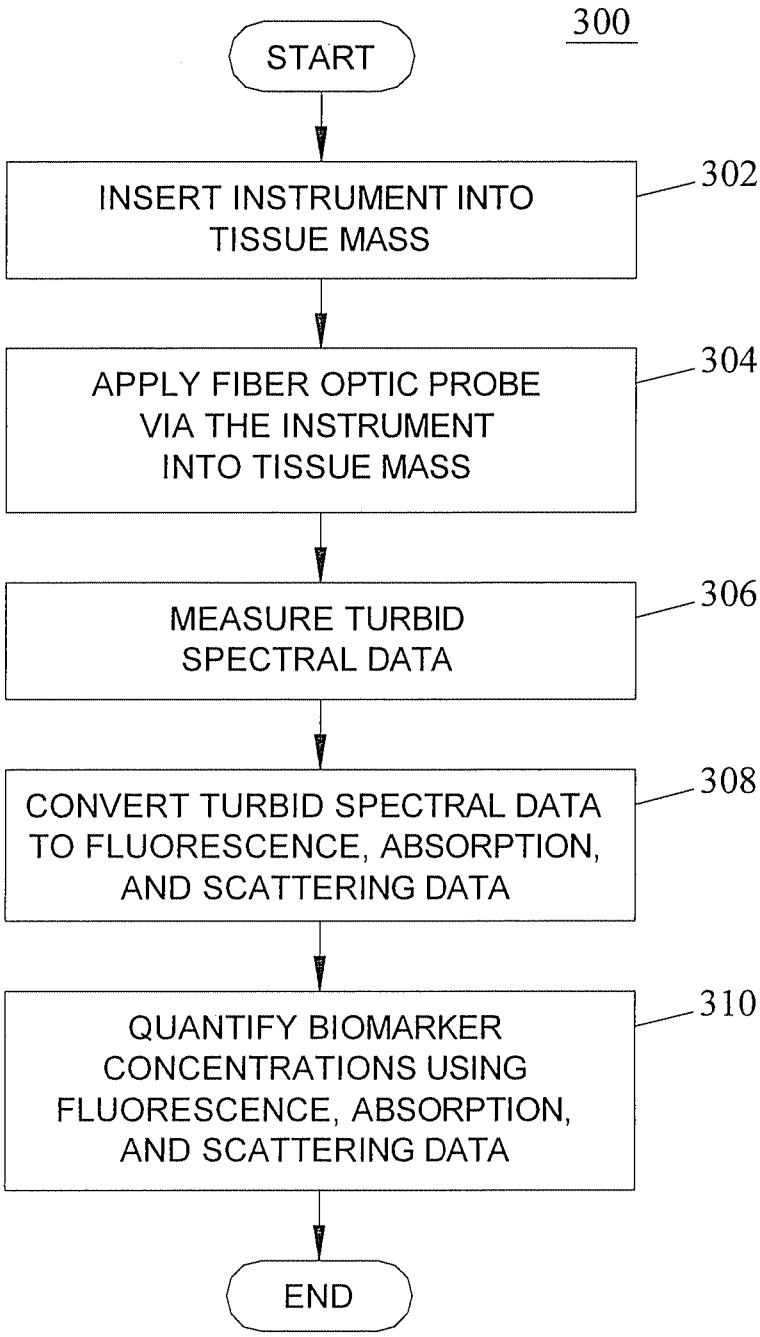
300
START
INSERT INSTRUMENT INTO TISSUE MASS
302
APPLY FIBER OPTIC PROBE VIA THE INSTRUMENT INTO TISSUE MASS
304
MEASURE TURBID SPECTRAL DATA
306
CONVERT TURBID SPECTRAL DATA TO FLUORESCENCE, ABSORPTION, AND SCATTERING DATA
308
QUANTIFY BIOMARKER CONCENTRATIONS USING FLUORESCENCE, ABSORPTION, AND SCATTERING DATA
310
END

FIG. 3

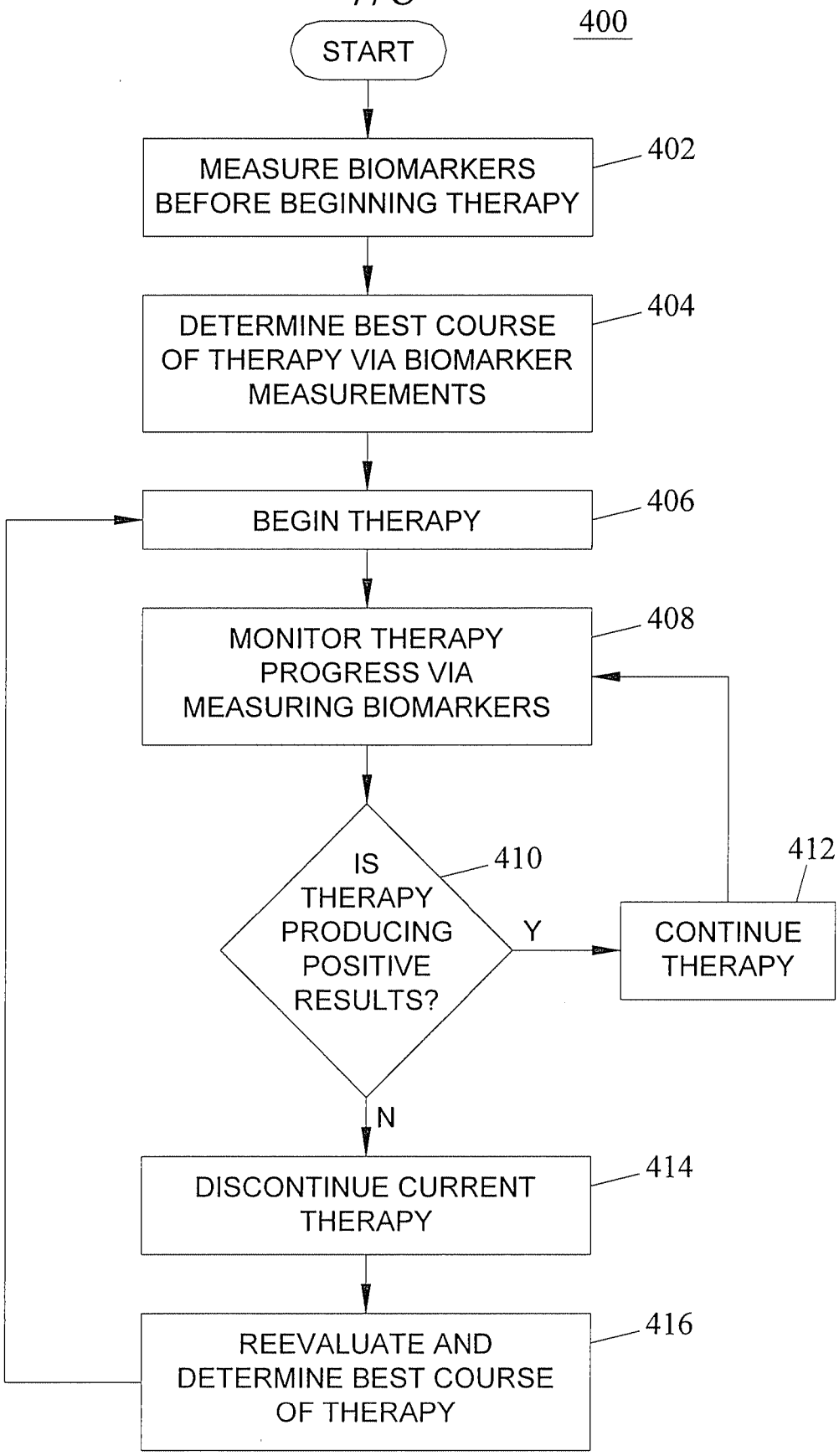
400
START
MEASURE BIOMARKERS BEFORE BEGINNING THERAPY
402
DETERMINE BEST COURSE OF THERAPY VIA BIOMARKER MEASUREMENTS
404
BEGIN THERAPY
406
MONITOR THERAPY PROGRESS VIA MEASURING BIOMARKERS
408
IS THERAPY PRODUCING POSITIVE RESULTS?
410
Y
CONTINUE THERAPY
412
N
DISCONTINUE CURRENT THERAPY
414
REEVALUATE AND DETERMINE BEST COURSE OF THERAPY
416

FIG. 4

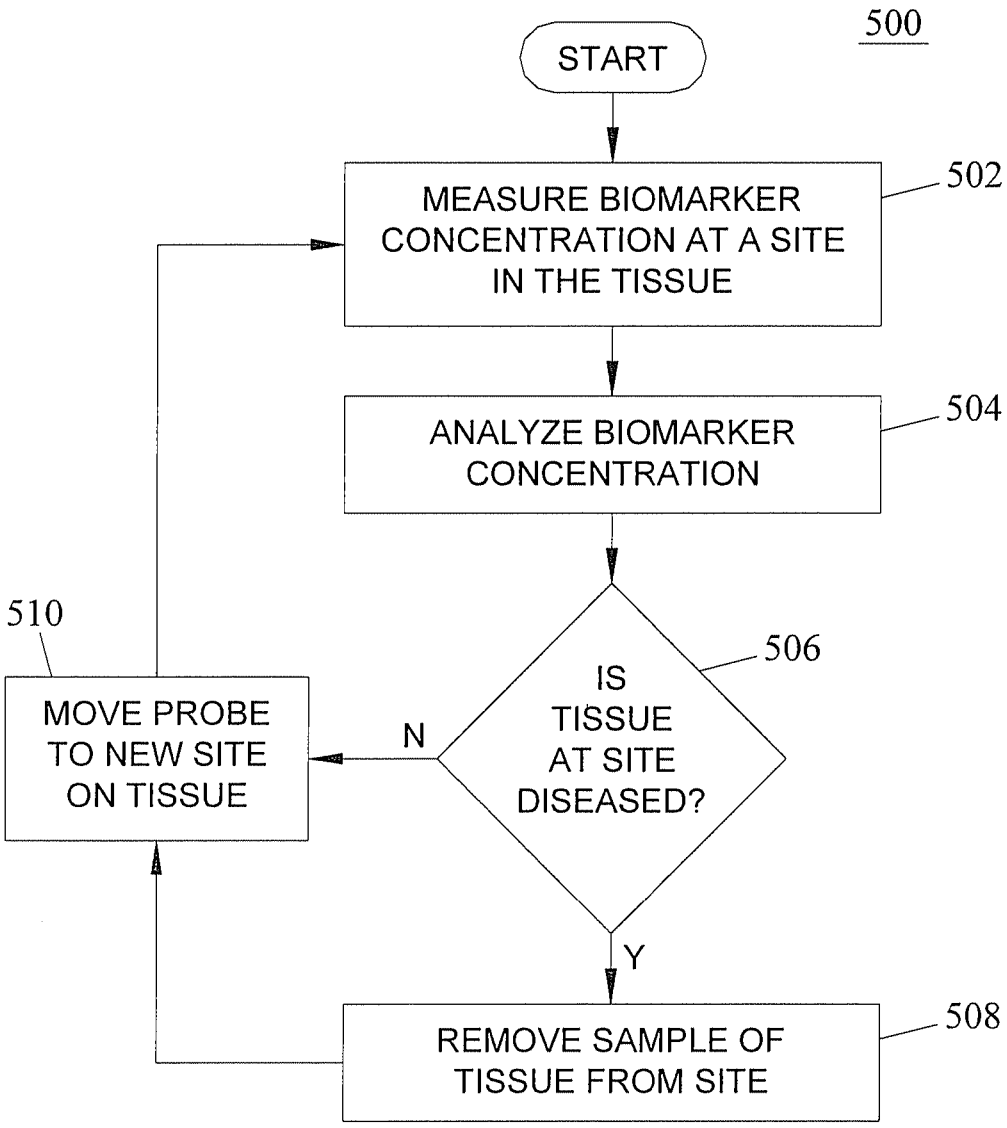
500
START
MEASURE BIOMARKER CONCENTRATION AT A SITE IN THE TISSUE
502
ANALYZE BIOMARKER CONCENTRATION
504
IS TISSUE AT SITE DISEASED?
506
N
Y
MOVE PROBE TO NEW SITE ON TISSUE
510
REMOVE SAMPLE OF TISSUE FROM SITE
508

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/078186

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 A61B

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKIPASS (KIPO internal) and keywords "spectral, analysis, tissue, mass, optical, probe, insert, and similar terms"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6219566 B1 (Photonics Research Ontario) 17 April 2001 See abstract, Figures 1-12 and claims 1-35	1-62
A	US 2002-0055671 A1 (Xiaomao Wu et al.) 9 May 2002 See abstract, Figures 1-7 and claims 1-22	1-62
A	US 6678541 B1 (The Governmemt of the United States of America) 13 January 2004 See abstract, Figures 1-12 and claims 1-46	1-62

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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专利名称(译)	使用仪器，光学探针和蒙特卡罗或扩散算法对组织块进行光谱分析的系统和方法		
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其他公开文献	EP2194848A4		
外部链接	Espacenet		

摘要(译)

提供了使用仪器，光学探针和蒙特卡罗算法或扩散算法对组织块进行光谱分析的系统和方法。根据一种方法，将器械插入组织块中。通过仪器将光纤探针施加到组织块中。使用光纤探针测量组织质量的混浊光谱数据。通过蒙特卡罗算法或扩散算法将混浊光谱数据转换成吸收，散射和/或固有荧光光谱数据。使用吸收，散射和/或内在荧光光谱数据量化组织块中的生物标记物浓度。