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(54) **HEALTH MONITORING USING A NON-INVASIVE, MULTI-BAND BIOSENSOR**

GESUNDHEITSÜBERWACHUNG MIT EINEM NICHTINVASIVEN MEHRBAND-BIOSENSOR  
SURVEILLANCE DE LA SANTÉ À L'AIDE D'UN BIOCAPTEUR MULTIBANDE NON-INVASIF

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**US-A- 5 137 023 US-A- 5 515 847**  
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**Description****FIELD**

5 **[0001]** This application relates to a system of non-invasive, autonomous health monitoring, and in particular a health monitoring sensor that monitors a patient's vitals and detects concentration levels or indicators of substances in blood vessels.

**BACKGROUND**

10 **[0002]** A patient's vitals, such as temperature, blood oxygen levels, blood pressure, etc., may need to be monitored periodically typically using one or more instruments. For example, instruments for obtaining vitals of a patient include blood pressure cuffs, thermometers,  $\text{SaO}_2$  measurement devices, glucose level meters, etc. Often, multiple instruments must be brought to a patient's room by a caretaker, and the measurements collected using the multiple instruments.

15 This monitoring process can be time consuming, inconvenient and is not always continuous. It may also disrupt sleep of the patient. The measurements of the vitals must then be manually recorded into the patient's electronic medical record.

**[0003]** In addition, detection of substances and measurement of concentration level or indicators of various substances in a patient's blood vessels is important in health monitoring. Currently, detection of concentration levels of blood substances is performed by drawing blood from a blood vessel using a needle and syringe. The blood sample is then

20 transported to a lab for analysis. This type of monitoring is invasive, non-continuous and time consuming.

**[0004]** One current non-invasive method is known for measuring the oxygen saturation of blood using pulse oximeters. Pulse oximeters detect oxygen saturation of hemoglobin by using, e.g., spectrophotometry to determine spectral absorbencies and determining concentration levels of oxygen based on Beer-Lambert law principles. In addition, pulse oximetry may use photoplethysmography (PPG) methods for the assessment of oxygen saturation in pulsatile arterial

25 blood flow. The subject's skin at a 'measurement location' is illuminated with two distinct wavelengths of light and the relative absorbance at each of the wavelengths is determined. For example, a wavelength in the visible red spectrum (for example, at 660 nm) has an extinction coefficient of hemoglobin that exceeds the extinction coefficient of oxihemoglobin. At a wavelength in the near infrared spectrum (for example, at 940 nm), the extinction coefficient of oxihemoglobin exceeds the extinction coefficient of hemoglobin. The pulse oximeter filters the absorbance of the pulsatile fraction of

30 the blood, i.e. that due to arterial blood (AC components), from the constant absorbance by nonpulsatile venous or capillary blood and other tissue pigments (DC components), to eliminate the effect of tissue absorbance to measure the oxygen saturation of arterial blood. Such PPG techniques are heretofore been limited to determining oxygen saturation.

**[0005]** As such, there is a need for a patient monitoring system that includes a continuous and non-invasive biosensor that measures patient vitals and monitors concentration levels or indicators of one or more substances in blood flow.

35 US 5 515 847 A discloses a method and apparatus for monitoring glucose. US 5 137 023 A discloses a non-invasive system for measuring the concentration of an analyte. WO 2014/163583 A1 discloses a method and apparatus for determining  $\text{SpO}_2$ .

**SUMMARY**

40 **[0006]** According to a first aspect, a biosensor includes a PPG circuit and a processing circuit. The PPG circuit is configured to emit light having at least a first wavelength and a second wavelength directed at an outer epidermal layer of skin tissue of a patient. The PPG circuit is further configured to generate a first spectral response for light detected around the first wavelength from the outer epidermal layer of the skin tissue of the patient and generates a second

45 spectral response for light detected around the second frequency from the outer epidermal layer of the skin tissue of the patient. The processing circuit configured to isolate a systolic point and a diastolic point in the first spectral response and obtain a value  $L_{\lambda 1}$  using a ratio of the systolic point and the diastolic point in the first spectral response and isolate a systolic point and a diastolic point in the second spectral response and obtain a value  $L_{\lambda 2}$  using a ratio of the systolic point and diastolic point in the second spectral response. The processing circuit is further configured to obtain a value

50  $R_{\lambda 1, \lambda 2}$  from a ratio of the value  $L_{\lambda 1}$  and the value  $L_{\lambda 2}$ ; obtain a blood glucose concentration level from a calibration table using the value  $R_{\lambda 1, \lambda 2}$ ; and transmit the blood glucose concentration level for display.

**[0007]** According to a second aspect, a biosensor includes a PPG circuit, a processing circuit and a wireless transceiver. The PPG circuit is configured to generate at least a first spectral response for light reflected around a first wavelength from skin tissue of the patient and generate at least a second spectral response for light detected around a second

55 wavelength reflected from the skin tissue of the patient. The processing circuit is configured to obtain a value  $L_{\lambda 1}$  using the first spectral response, wherein the value  $L_{\lambda 1}$  isolates the first spectral response due to pulsating arterial blood flow and obtain a value  $L_{\lambda 2}$  using the second spectral response, wherein the value  $L_{\lambda 2}$  isolates the second spectral response due to pulsating arterial blood flow. The processing circuit is further configured to obtain a value  $R_{\lambda 1, \lambda 2}$  from a ratio of

the value  $L_{\lambda 1}$  and the value  $L_{\lambda 2}$  and obtain a base insulin resistance factor based on the value  $R_{\lambda 1, \lambda 2}$  that indicates a diabetic risk indicator. The wireless transceiver is configured to transmit the diabetic risk indicator to a remote device.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0008]

FIG. 1 illustrates a schematic block diagram of an exemplary embodiment of a biosensor.

FIG. 2 illustrates a schematic block diagram illustrating an embodiment of the PPG circuit in more detail.

FIG. 3 illustrates a schematic block diagram of another exemplary embodiment of the the PPG circuit.

FIG. 4 illustrates a logical flow diagram of an embodiment of a method for determining concentration of one or more substances using Beer-Lambert principles.

FIG. 5A and FIG. 5B illustrate schematic block diagrams of an embodiment of a method for photoplethysmography (PPG) techniques.

FIG. 6 illustrates a schematic diagram of a graph of actual clinical data obtained using PPG techniques at a plurality of wavelengths.

FIG. 7 illustrates a schematic block diagram of an embodiment of operation of the biosensor.

FIG. 8 illustrates a logical flow diagram of an embodiment of a method of determining concentration levels of one or more substances.

FIG. 9 illustrates a logical flow diagram of another embodiment of a method of determining concentration levels of one or more substances.

FIG. 10 illustrates a schematic block diagram of another embodiment of a biosensor using a broad spectrum light source.

FIG. 11A illustrates a graph of an embodiment of an output of a broad spectrum light source.

FIG. 11B illustrates a graph with an embodiment of an exemplary spectral response of detected light across a broad spectrum.

FIG. 12 illustrates a logical flow diagram of an exemplary method to determine blood concentration levels of a plurality of substances using the spectral response for a plurality of wavelengths.

FIG. 13 illustrates a logical flow diagram of an exemplary method to determine blood concentration levels of a single substance using the spectral response for a plurality of wavelengths.

FIG. 14 illustrates an exemplary graph of spectral responses of a plurality of wavelengths from clinical data using the biosensor.

FIG. 15 illustrates a logical flow diagram of an exemplary method to determine an absorption coefficients  $\mu$  of a substance at a wavelength  $\lambda$ .

FIG. 16 illustrates a logical flow diagram of an embodiment of a method of determining concentration levels of one or more substances.

FIG. 17A illustrates an exemplary embodiment of a form factor of the biosensor.

FIG. 17B illustrates an exemplary embodiment of another form factor of the biosensor.

FIG. 18A illustrates an exemplary embodiment of another form factor of the biosensor.

FIG. 18B illustrates an exemplary embodiment of another form factor of the biosensor.

FIG. 19A illustrates an exemplary embodiment of another form factor of the biosensor.

5 FIG. 19B illustrates an exemplary embodiment of another form factor of the biosensor.

FIG. 20 illustrates a schematic block diagram of an embodiment of an exemplary network in which the the biosensor described herein may operate.

10 FIG. 21A illustrates a schematic block diagram of an embodiment of a network illustrating interoperability of a plurality of biosensors.

FIG. 21B illustrates a logical flow diagram of an embodiment of a method for adjusting operation of the biosensor in response to a position of the biosensor.

15 FIG. 22 illustrates a schematic drawing of an exemplary embodiment of results of clinical data obtained using the biosensor from a first patient.

20 FIG. 23 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from the first patient.

FIG. 24 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from a second patient.

25 FIG. 25 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from the second patient.

FIG. 26 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from a third patient.

30 FIG. 27 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from a fourth patient.

35 FIG. 28 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from a fifth patient.

FIG. 29 illustrates a schematic drawing of another exemplary embodiment of results of clinical data obtained using the biosensor from the fifth patient.

40 FIG. 30 illustrates a schematic drawing of an exemplary embodiment of using the biosensor for measurements of a liver enzyme.

FIG. 31 illustrates a schematic block diagram of an embodiment of a method for determining concentration levels or indicators of substances in pulsating blood flow in more detail.

45 FIG. 32 illustrates a schematic block diagram of an exemplary embodiment of a graph 3200 illustrating the extinction coefficients over a range of frequencies for a plurality of hemoglobin compounds.

## DETAILED DESCRIPTION

50 **[0009]** The word "exemplary" or "embodiment" is used herein to mean "serving as an example, instance, or illustration." Any implementation or aspect described herein as "exemplary" or as an "embodiment" is not necessarily to be construed as preferred or advantageous over other aspects of the disclosure. Likewise, the term "aspects" does not require that all aspects of the disclosure include the discussed feature, advantage, or mode of operation.

55 **[0010]** Embodiments will now be described in detail with reference to the accompanying drawings. In the following description, numerous specific details are set forth in order to provide a thorough understanding of the aspects described herein. It will be apparent, however, to one skilled in the art, that these and other aspects may be practiced without some or all of these specific details. In addition, well known steps in a method of a process may be omitted from flow diagrams

presented herein in order not to obscure the aspects of the disclosure. Similarly, well known components in a device may be omitted from figures and descriptions thereof presented herein in order not to obscure the aspects of the disclosure.

## Overview

**[0011]** A non-invasive and continuous biosensor is implemented in a compact form factor, such as on a finger, patch, wrist band or ear piece. Due to its compact form factor, the biosensor may be configured for measurements on various skin surfaces of a patient, including on a forehead, arm, wrist, abdominal area, chest, leg, ear lobe, finger, toe, ear canal, etc. The biosensor includes one or more sensors for detecting biosensor data, such as a patient's vitals, activity levels, or concentrations of substances in the blood flow of the patient. For example, the biosensor may include a temperature sensor having an array of sensors positioned adjacent to the skin of the patient. The biosensor may also include an activity monitor to determine activity level and/or positioning of the patient. The biosensor may also include a photoplethysmography (PPG) sensor. The PPG sensor may be configured to detect oxygen saturation (SPO<sub>2</sub>) levels in blood flow, as well as heart rate and blood pressure.

**[0012]** In addition, the PPG sensor is configured to monitor concentration levels or indicators of one or more substances in the blood flow of the patient. In one aspect, the PPG sensor may non-invasively and continuously detect diabetic parameters, such as base insulin resistance, insulin response in response to caloric intake, nitric oxide (NO) levels, glucose levels, and predict diabetic risk or diabetic precursors, in pulsatile arterial blood flow. In another aspect, the PPG sensor may measure vascular health using NO levels. In another aspect, the PPG sensor may detect blood alcohol levels in pulsatile arterial blood flow. In another aspect, the PPG sensor may detect cytochrome P450 proteins or one or more other liver enzymes or proteins. In another aspect, the PPG sensor may detect digestive parameters, such as digestion phase 1 and 2 responses, and caloric intake. The PPG sensor may detect various electrolyte concentration levels or blood analyte levels, such as bilirubin and sodium and potassium. For example, the PPG sensor may detect sodium NACL concentration levels in the arterial blood flow to determine dehydration. In yet another aspect, the PPG sensor may be configured to help diagnose cancer by detecting proteins or abnormal cells or other elements or compounds associated with cancer. In another aspect, the PPG sensor may detect white blood cell counts.

## Embodiment - Biosensor Components

**[0013]** FIG. 1 illustrates a schematic block diagram of an exemplary embodiment of a biosensor 100. The biosensor 100 includes one or more processing circuits 102 communicatively coupled to a memory device 104. In one aspect, the memory device 104 may include one or more non-transitory processor readable memories that store instructions which when executed by the processing circuit 102, causes the processing circuit 102 to perform one or more functions described herein. The memory device 104 may also include an EEPROM to store a patient identification (ID) 172 that is associated with a patient being monitored by the biosensor 100. The memory device 104 may also store an electronic medical record (EMR) or portion of the EMR associated with the patient being monitored by the biosensor 100. The biosensor data obtained by the biosensor 100 may be stored in the EMR as well as the patient medical history. The processing circuit 102 may be co-located with one or more of the other circuits in the biosensor 100 in a same physical encasement or located separately in a different physical encasement or located remotely. In an embodiment, the biosensor 100 is battery operated and includes a battery 108, such as a lithium ion battery. The biosensor 100 may also include a display configured to display the biosensor data.

**[0014]** The biosensor 100 further includes a transceiver 106. The transceiver 106 may include a wireless or wired transceiver configured to communicate with one or more devices over a LAN, MAN and/or WAN. In one aspect, the wireless transceiver may include a Bluetooth enabled (BLE) transceiver or IEEE 802.11ah, Zigbee, IEEE 802.15-11 or WLAN (such as an IEEE 802.11 standard protocol) compliant transceiver. In another aspect, the wireless transceiver may operate using RFID, short range radio frequency, infrared link, or other short range wireless communication protocol. In another aspect, the wireless transceiver may also include or alternatively include an interface for communicating over a cellular network. In an embodiment, the wireless transceiver may include a thin foil for an antenna that is specially cut and includes a carbon pad contact to a main PCB of the biosensor 100. This type of antenna is inexpensive to manufacture and may be printed on the inside of an enclosure for the biosensor 100 situated away from the skin of the patient to minimize absorption. The transceiver 106 may also include a wired transceiver interface, e.g., a USB port or other type of wired connection, for communication with one or more other devices over a LAN, MAN and/or WAN.

**[0015]** The biosensor 100 includes one or more types of sensors, such as a PPG circuit 110, a temperature sensor 112 or an activity monitoring circuit 114. The temperature sensor 112 is configured to detect a temperature of a patient. For example, the temperature sensor 112 may include an array of sensors (e.g., 16x16 pixels) positioned on a side of the biosensor 100 such that the array of sensors are adjacent to the skin of the patient. The array of sensors then detects an indication of the temperature of the patient from the skin.

**[0016]** The activity monitoring circuit 114 is configured to monitor the activity level of the patient. For example, the

activity monitoring circuit 114 may include a multiple axes accelerometer that measures a position of the patient and motion of the patient. In one aspect, the activity monitoring circuit 114 determines periods of activity and rest. For example, the activity monitoring circuit 114 monitors and records periods of rest that meet a predetermined threshold of low motion or activity level, such as sitting, lying, sleeping, etc. The activity monitoring circuit 114 may also monitor and record periods of activity that meet a predetermined threshold of motion or activity level, such as walking, running, lifting, squatting, etc. The biosensor 100 is then configured to measure and store the patient vitals with an indicator of the activity level of the patient. For example, blood oxygen levels may vary greatly in patients with COPD during rest and activity. The vitals of the patient are tracked during periods of activity and rest and the level of activity at time of measuring the vitals is recorded. The biosensor 100 is thus configured to associate measurements of patient vitals with the activity level of the patient.

**[0017]** In another aspect, to help lower power consumption, in an embodiment, the biosensor 100 includes a rest mode. For example, the activity monitoring circuit 114 may signal a rest mode when a patient is asleep or meets a predetermined threshold of low activity level for a predetermined time period. In the rest mode, the biosensor 100 signals one or more modules to halt non-essential processing functions. When the activity monitoring circuit 114 detects a higher activity level exceeding another predetermined threshold for a predetermined time period, the the biosensor 100 signals one or more modules to exit rest mode and resume normal functions. This activity monitoring feature helps to save power and extend battery life of the biosensor 100.

**[0018]** In another aspect, the activity monitoring circuit is configured to include a fitness tracker application. The activity monitoring circuit 114 may monitor a number of steps of the patient, amount and length of periods of sleep, amount and length of periods of rest, amount and length of periods of activity, etc.

**[0019]** The biosensor 100 may also include an integrated drug delivery system 116 or be communicatively coupled to a drug delivery system 116. The biosensor 100 may be configured to control delivery of medicine to a patient based on biosensor data obtained by the biosensor 100 as described in more detail in U.S. Provisional Application No. 62/383,313 entitled, "System and Method for a Drug Delivery and Biosensor Patch," filed 09-02-2016.

**[0020]** The biosensor 100 may include a display 118. The biosensor 100 is configured to display a graphical user interface (GUI) that includes biosensor data.

**[0021]** The biosensor 100 also includes a PPG circuit 110. The PPG circuit 110 may be configured to detect oxygen saturation ( $\text{SaO}_2$  or  $\text{SpO}_2$ ) levels in blood flow, as well as heart rate and blood pressure. In addition, the PPG circuit 110 is configured to detect concentration levels or indicators of one or more substances in the blood flow of the patient as described in more detail herein.

### Embodiment - PPG Sensor

**[0022]** FIG. 2 illustrates a schematic block diagram illustrating an embodiment of the PPG circuit 110 in more detail. The PPG circuit 110 implements photoplethysmography (PPG) techniques for obtaining concentration levels or indicators of one or more substances in pulsating arterial blood flow. The PPG circuit 110 includes a light source 120 having a plurality of light sources, such as LEDs 122a-n, configured to emit light through at least one aperture 128a. The PPG circuit 110 is configured to direct the emitted light at an outer or epidermal layer of skin tissue of a patient. The plurality of light sources are configured to emit light in one or more spectrums, including infrared (IR) light, ultraviolet (UV) light, near IR light or visible light, in response to driver circuit 118. For example, the biosensor 100 may include a first LED 122a that emits visible light and a second LED 122b that emits infrared light and a third LED 122c that emits UV light, etc. In another embodiment, one or more of the light sources 122a-n may include tunable LEDs or lasers operable to emit light over one or more frequencies or ranges of frequencies or spectrums in response to driver circuit 118.

**[0023]** In an embodiment, the driver circuit 118 is configured to control the one or more LEDs 122a-n to generate light at one or more frequencies for predetermined periods of time. The driver circuit 118 may control the LEDs 122a-n to operate concurrently or progressively. The driver circuit 118 is configured to control a power level, emission period and frequency of emission of the LEDs 122a-n. The biosensor 100 is thus configured to emit one or more frequencies of light in one or more spectrums that is directed at the surface or epidermal layer of the skin tissue of a patient.

**[0024]** The PPG circuit 110 further includes one or more photodetector circuits 130a-n. For example, a first photodetector circuit 130 may be configured to detect visible light and the second photodetector circuit 130 may be configured to detect IR light. The first photodetector circuit 130 and the second photodetector circuit 130 may also include a first filter 160 and a second filter 162 configured to filter ambient light and/or scattered light. For example, in some embodiments, only light received at an approximately perpendicular angle to the skin surface of the patient is desired to pass through the filters. The first photodetector circuit 130 and the second photodetector circuit 132 are coupled to a first A/D circuit 138 and a second A/D circuit 140. Alternatively, a single A/D circuit may be coupled to each of the photodetector circuits 130a-n.

**[0025]** In another embodiment, a single photodetector circuit 130 may be implemented operable to detect light over multiple spectrums or frequency ranges. For example, the photodetector circuit 130 may include a Digital UV Index / IR

/ Visible Light Sensor such as Part No. Si1145 from Silicon Labs™.

**[0026]** The one or more photodetector circuits 130 include a spectrometer or other type of circuit configured to detect an intensity of light as a function of wavelength or frequency to obtain a spectral response. The one or more photodetector circuits 130 detects the intensity of light either transmitted through or reflected from tissue of a patient that enters one or more apertures 128b-n of the biosensor 100. For example, the light may be detected from transmissive absorption (e.g., through a fingertip or ear lobe) or from reflection (e.g., reflected from a forehead or stomach tissue). The photodetector circuits 130 then obtain a spectral response of the detected light by measuring the intensity of light either transmitted or reflected to the photodiodes.

**[0027]** FIG. 3 illustrates a schematic block diagram of another exemplary embodiment of the the PPG circuit 110. In this embodiment, the biosensor 100 is configured for emitting and detecting light through one or more optical fibers 152a-c. The PPG circuit 110 is optically coupled to a plurality of optical fibers 152a-c. In an embodiment, the plurality of optical fibers 152 includes a first optical fiber 152a optically coupled to the light source 120. An optical coupler (not shown) to spread the angle of light emitted from the optical fiber 152a may also be implemented. The optical fiber 152a may have a narrow viewing angle such that an insufficient area of skin surface is exposed to the light. An optical coupler may be used to widen the viewing angle to increase the area of skin surface exposed to the light.

**[0028]** A second optical fiber 152b is optically coupled to a first photodetector circuit 130 and a third optical fiber 152c is optically coupled to the second photodetector circuit 132. Other configurations and numbers of the plurality of optical fibers 152 may also be implemented.

**[0029]** In one aspect, the plurality of optical fibers 152 is situated within an outer ear canal to transmit and detect light in the ear canal. A light collimator 116, such as a prism, may be used to align a direction of the light emitted from the light source 120. One or more filters 160 may optionally be implemented to receive the reflected light 142 from the plurality of optical fibers 152b, 152c. However, the filters 160 may not be needed as the plurality of optical fibers 152b, 152c may be sufficient to filter ambient light and/or scattered light.

#### **Embodiment - PPG Measurement of Arterial Blood Flow**

**[0030]** One or more of the embodiments of the biosensor 100 described herein is configured to detect a concentration level or indicator of one or more substances within blood flow, such as analyte levels, nitric oxide levels, insulin resistance or insulin response after caloric intake and predict diabetic risk or diabetic precursors. The biosensor 100 may detect insulin response, vascular health, cardiovascular sensor, cytochrome P450 proteins (e.g. one or more liver enzymes or reactions), digestion phase 1 and 2 or caloric intake. The biosensor 100 may even be configured to detect proteins or other elements or compounds associated with cancer. The biosensor 100 may also detect various electrolytes and many common blood analytic levels, such as bilirubin amount and sodium and potassium. For example, the biosensor 100 may detect sodium NACL concentration levels in the arterial blood flow to determine dehydration. The biosensor 100 may also detect blood alcohol levels in vivo in the arterial blood flow. The biosensor 100 may also detect blood pressure, peripheral oxygen (SpO<sub>2</sub> or SaO<sub>2</sub>) saturation, heart rate, respiration rate or other patient vitals. Because blood flow to the skin can be modulated by multiple other physiological systems, the PPG sensor 110 may also be used to monitor breathing, hypovolemia, and other circulatory conditions.

**[0031]** In use, the biosensor 100 performs PPG techniques using the PPG circuit 110 to detect the concentration levels of substances in blood flow. In one aspect, the biosensor 100 analyzes reflected visible or IR light to obtain a spectrum response such as, the resonance absorption peaks of the reflected visible, UV or IR light. The spectrum response includes spectral lines that illustrate an intensity or power or energy at a frequency or wavelength in a spectral region of the detected light.

**[0032]** The ratio of the resonance absorption peaks from two different frequencies can be calculated and based on the Beer-Lambert law used to obtain various levels of substances in the blood flow. First, the spectral response of a substance or substances in the arterial blood flow is determined in a controlled environment, so that an absorption coefficient  $\alpha_{g1}$  can be obtained at a first light wavelength  $\lambda_1$  and at a second wavelength  $\lambda_2$ . According to the Beer-Lambert law, light intensity will decrease logarithmically with path length  $l$  (such as through an artery of length  $l$ ). Assuming then an initial intensity  $I_{in}$  of light is passed through a path length  $l$ , a concentration  $C_g$  of a substance may be determined using the following equations: At the first wavelength  $\lambda_1$ ,

$$I_1 = I_{in1} * 10^{-(\alpha_{g1} C_{gw} + \alpha_{w1} C_w) * l}$$

At the second wavelength

$$\lambda_2, I_2 = I_{in2} * 10^{-(\alpha_{g2} C_{gw} + \alpha_{w2} C_w) * l}$$

5 wherein:

$I_{in1}$  is the intensity of the initial light at  $\lambda_1$

$I_{in2}$  is the intensity of the initial light at  $\lambda_2$

$\alpha_{g1}$  is the absorption coefficient of the substance in arterial blood at  $\lambda_1$

10  $\alpha_{g2}$  is the absorption coefficient of the substance in arterial blood at  $\lambda_2$

$\alpha_{w1}$  is the absorption coefficient of arterial blood at  $\lambda_1$

$\alpha_{w2}$  is the absorption coefficient of arterial blood at  $\lambda_2$

$C_{gw}$  is the concentration of the substance and arterial blood

$C_w$  is the concentration of arterial blood

15

**[0033]** Then letting R equal:

20

$$R = \frac{\log_{10}(\frac{I_1}{I_{in1}})}{\log_{10}(\frac{I_2}{I_{in2}})}$$

**[0034]** The concentration of the substance  $C_g$  may then be equal to:

25

$$C_g = \frac{C_{gw}}{C_{gw} + C_w} = \frac{\alpha_{w2} R - \alpha_{w1}}{(\alpha_{w2} - \alpha_{gw2}) * R - (\alpha_{w1} - \alpha_{gw1})}$$

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**[0035]** The biosensor 100 may thus determine the concentration of various substances in arterial blood using spectroscopy at two different wavelengths using Beer-Lambert principles.

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**[0036]** FIG. 4 illustrates a logical flow diagram of an embodiment of a method 400 for determining concentration of one or more substances using Beer-Lambert principles. The biosensor 100 transmits light at least at a first predetermined wavelength in step 402 and at a second predetermined wavelength in step 404. The biosensor 100 detects the light (reflected from the skin or transmitted through the skin) and analyzes the spectral response at the first and second wavelengths to detect an indicator or concentration level of one or more substances in the arterial blood flow at 406. In general, the first predetermined wavelength is selected that has a high absorption coefficient for the targeted substance while the second predetermined wavelength is selected that has a low absorption coefficient for the targeted substance. Thus, it is generally desired that the spectral response for the first predetermined wavelength have a higher intensity level than the spectral response for the second predetermined wavelength.

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**[0037]** In another aspect, the biosensor 100 may transmit light at the first predetermined wavelength at 402 and in a range of approximately 1nm to 50nm around the first predetermined wavelength. Similarly at 404, the biosensor 100 may transmit light at the second predetermined wavelength and in a range of approximately 1nm to 50nm around the second predetermined wavelength. The range of wavelengths is determined based on the spectral response since a spectral response may extend over a range of frequencies, not a single frequency (i.e., it has a nonzero linewidth). The light that is reflected or transmitted light by the target substance may be spread over a range of wavelengths rather than just the single predetermined wavelength. In addition, the center of the spectral response may be shifted from its nominal central wavelength or the predetermined wavelength. The range of 1nm to 50nm is based on the bandwidth of the spectral response line and should include wavelengths with increased light intensity detected for the targeted substance around the predetermined wavelength.

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**[0038]** The first spectral response of the light over the first range of wavelengths including the first predetermined wavelength and the second spectral response of the light over the second range of wavelengths including the second predetermined wavelengths is then generated. The biosensor 100 analyzes the first and second spectral responses to detect an indicator or concentration level of one or more substances in the arterial blood flow at 406.

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**[0039]** FIG. 5A and FIG. 5B illustrate schematic block diagrams of an embodiment of a method for photoplethysmography (PPG) techniques. Photoplethysmography (PPG) is used to measure time-dependent volumetric properties of blood in blood vessels due to the cardiac cycle. For example, the heartbeat affects volume of arterial blood flow and the concentration of absorption levels being measured in the arterial blood flow. As shown in FIG. 5A, over a cardiac cycle 502, pulsating arterial blood 504 changes the volume of blood flow in an artery.



**[0040]** Incident light  $I_O$  512 is directed at a tissue site and a certain amount of light is reflected or transmitted 518 and a certain amount of light is absorbed 520. At a peak of arterial blood flow or arterial volume, the reflected/transmitted light  $I_L$  514 is at a minimum due to absorption by the venous blood 508, nonpulsating arterial blood 506, pulsating arterial blood 504, other tissue 510, etc. At a minimum of arterial blood flow or arterial volume during the cardiac cycle, the transmitted/reflected light  $I_H$  516 is at a maximum due to lack of absorption from the pulsating arterial blood 504.

**[0041]** The biosensor 100 is configured to filter the reflected/transmitted light  $I_L$  514 of the pulsating arterial blood 504 from the transmitted/reflected light  $I_H$  516. This filtering isolates the light due to reflection/transmission of substances in the pulsating arterial blood 504 from the light due to reflection/transmission from venous (or capillary) blood 508, other tissues 510, etc. The biosensor 100 may then measure the concentration levels of one or more substances from the reflected/transmitted light  $I_L$  514 in the pulsating arterial blood 504.

**[0042]** For example, as shown in FIG. 5B, incident light  $I_O$  512 is directed at a tissue site by an LED 122 at one or more wavelengths. The reflected/transmitted light  $I$  518 is detected by photodetector 130. At a peak of arterial blood flow or arterial volume, the reflected light  $I_L$  514 is at a minimum due to absorption by venous blood 508, non-pulsating arterial blood 506, pulsating arterial blood 504, other tissue 510, etc. At a minimum of arterial blood flow or arterial volume during the cardiac cycle, the Incident or reflected light  $I_H$  516 is at a maximum due to lack of absorption from the pulsating arterial blood 504. Since the light  $I$  518 is reflected or traverses through a different volume of blood at the two measurement times, the measurement provided by a PPG sensor is said to be a 'volumetric measurement' descriptive of the differential volumes of blood present at a certain location within the patient's arteriolar bed at different times. Though the above has been described with respect to arterial blood flow, the same principles described herein may be applied to venous blood flow.

**[0043]** In general, the relative magnitudes of the AC and DC contributions to the reflected/transmitted light signal  $I$  518 may be used to substantially determine the differences between the diastolic time and the systolic points. In this case, the difference between the reflected light  $I_L$  514 and reflected light  $I_H$  516 corresponds to the AC contribution of the reflected light 518 (e.g. due to the pulsating arterial blood flow). A difference function may thus be computed to determine the relative magnitudes of the AC and DC components of the reflected light  $I$  518 to determine the magnitude of the reflected light  $I_L$  514 due to the pulsating arterial blood 504. The described techniques herein for determining the relative magnitudes of the AC and DC contributions is not intended as limiting. It will be appreciated that other methods may be employed to isolate or otherwise determine the relative magnitude of the light  $I_L$  514 due to pulsating arterial blood flow.

**[0044]** FIG. 6 illustrates a schematic diagram of a graph of actual clinical data obtained using PPG techniques at a plurality of wavelengths. The biosensor 100 emits light having a plurality of wavelengths during a measurement period. The light at each wavelength (or range of wavelengths) may be transmitted concurrently or sequentially. The intensity of the reflected light at each of the wavelengths (or range of wavelengths) is detected and the spectral response is measured over the measurement period. The spectral response 606 for the plurality of wavelengths obtained using the biosensor in clinical trials is shown in FIG. 6. In this clinical trial, two biosensors 100 attached to two separate fingertips of a patient were used to obtain the spectral responses 606. The first biosensor 100 obtained the spectral response for a wavelength at 940nm 610, a wavelength at 660nm 612 and a wavelength at 390nm 614. The second biosensor 100 obtained the spectral response for a wavelength at 940nm 616, a wavelength at 592nm 618 and a wavelength at 468nm 620.

**[0045]** In one aspect, the spectral response of each wavelength may be aligned based on the systolic 602 and diastolic 604 points in their spectral responses. This alignment is useful to associate each spectral response with a particular stage or phase of the pulse-induced local pressure wave within the blood vessel (which may mimic the cardiac cycle 606 and thus include systolic and diastolic stages and sub-stages thereof). This temporal alignment helps to determine the absorption measurements acquired near a systolic point in time of the cardiac cycle and near the diastolic point in time of the cardiac cycle 606 associated with the local pressure wave within the patient's blood vessels. This measured local pulse timing information may be useful for properly interpreting the absorption measurements in order to determine the relative contributions of the AC and DC components measured by the biosensor 110. So for one or more wavelengths, the systolic points 602 and diastolic points 604 in the spectral response are determined. These systolic points 602 and diastolic points 604 for the one or more wavelengths may then be aligned as a method to discern concurrent responses across the one or more wavelengths.

**[0046]** In another embodiment, the the systolic points 602 and diastolic points 604 in the absorbance measurements are temporally correlated to the pulse-driven pressure wave within the arterial blood vessels - which may differ from the cardiac cycle. In another embodiment, the biosensor 100 may concurrently measure the intensity reflected at each the plurality of wavelengths. Since the measurements are concurrent, no alignment of the spectral responses of the plurality of wavelengths may be necessary. FIG. 6 illustrates the spectral response of the plurality of wavelengths with the systolic points 602 and diastolic points 604 aligned.

**[0047]** FIG. 7 illustrates a logical flow diagram of an embodiment of a method 700 of the biosensor 100. In one aspect, the biosensor 100 emits and detects light at a plurality of predetermined frequencies or wavelengths, such as approxi-

mately 940nm, 660nm, 390 nm, 592nm, and 468nm. The light is pulsed for a predetermined period of time (such as 100usec or 200Hz) sequentially at each predetermined wavelength. In another aspect, light may be pulsed in a wavelength range of 1nm to 50nm around each of the predetermined wavelengths. Then, the spectral responses are obtained for the plurality of wavelengths at 702. The spectral response may be measured over a predetermined period (such as 300usec.). This measurement process is repeated sequentially pulsing the light and obtaining spectral measurements over a desired measurement period, e.g. from 1-2 seconds to 1-2 minutes or 2-3 hours or continuously over days or weeks. Because the human pulse is typically on the order of magnitude of one 1 HZ, typically the time differences between the systolic and diastolic points are on the order of magnitude of milliseconds or tens of milliseconds or hundreds of milliseconds. Thus, spectral response measurements may be obtained at a frequency of around 10-100 Hz over the desired measurement period.

**[0048]** A low pass filter (such as a 5Hz low pass filter) is applied to the spectral response signal at 704. The relative contributions of the AC and DC components are obtained  $I_{AC+DC}$  and  $I_{AC}$ . A peak detection algorithm is applied to determine the systolic and diastolic points at 706. Beer Lambert equations are applied as described below at 708. For example, the  $L_{\lambda}$  values are then calculated for one or more of the wavelengths  $\lambda$ , wherein the  $L_{\lambda}$  values for a wavelength equals:

$$L_{\lambda} = \text{Log}10\left(\frac{I_{AC+DC}}{I_{DC}}\right)$$

wherein  $I_{AC+DC}$  is the intensity of the detected light with AC and DC components and  $I_{DC}$  is the intensity of the detected light with the AC filtered by the low pass filter. The value  $L_{\lambda}$  isolates the spectral response due to pulsating arterial blood flow, e.g. the AC component of the spectral response.

**[0049]** A ratio R of the  $L_{\lambda}$  values at two wavelengths may then be determined. For example,

$$\text{Ratio R} = \frac{L_{\lambda 1}}{L_{\lambda 2}}$$

**[0050]** The  $L_{\lambda}$  values and Ratio R may be determined for one or more of the predetermined measurement periods over a desired time period, e.g. from 1-2 seconds to 1-2 minutes or 2-3 hours or continuously over days or weeks to monitor the values.

#### Embodiment - Determination of Indicators or Concentration Levels of One or More Substances

**[0051]** In one aspect, based on unexpected results from clinical trials, it was determined that a ratio  $R_{390,940}$  obtained at approximately  $L_{\lambda 1} = 390\text{nm}$  and  $L_{\lambda 2} = 940$  is useful as a predictor or indicator of diabetic risk or diabetes. For example, during experimental clinical trials, spectral responses were obtained during predetermined measurement periods over a 1-2 minute time period at 390nm and 940nm. An  $R_{390,940}$  value was obtained based on the spectral responses measured during a plurality of the predetermined measurement periods over the 1-2 minute time period. From the unexpected results of the clinical trials, an average or mean  $R_{390,940}$  value of less than 1 (e.g., approximately .5) indicated that a person has diabetes or early onset of diabetes. An average or mean  $R_{390,940}$  value of 2 or above indicated that a person has a lower risk of a diabetes diagnosis. An average or mean  $R_{390,940}$  value in the 5-6 range indicated no current risk of diabetes. The  $R_{390,940}$  value determined using  $L_{\lambda 1} = 390\text{nm}$  and  $L_{\lambda 2} = 940$  was thus an indicator of diabetic risk and diabetes. Thus, based on the clinical trials, a non-invasive, quick 1-2 minute test produced an indicator of diabetes or diabetic risk in a person.

**[0052]** The  $R_{390,940}$  value with  $L_{\lambda 1} = 390\text{nm}$  and  $L_{\lambda 2} = 940$  may be non-invasively and quickly and easily obtained using the biosensor 100 in a physician's office or other clinical setting or at home. In one aspect, the  $R_{390,940}$  value may be used to determine whether further testing for diabetes needs to be performed. For example, upon detection of a low  $R_{390,940}$  value, a clinician may then determine to perform further testing and monitoring, e.g. using glucose ingestion tests over a longer period of time or using the biosensor 100 over a longer period of time or other type of testing.

**[0053]** In particular, in unexpected results, it is believed that nitrous oxide NO levels in the arterial blood flow is being measured at least in part by the biosensor 100 at  $\lambda 1 = 390\text{nm}$ . Since NO is partly in a gaseous form in blood vessels (prior to adhesion to hemoglobin), the total NO concentration levels of in vitro blood samples, e.g. from a finger prick, are not detected as the gas dissipates. Thus, the biosensor 100 measurements to determine the  $L_{390\text{nm}}$  values are the first time NO concentration levels in arterial blood flow have been measured directly in vivo. In clinical trials performed as described further herein, in unexpected results, it seems that the NO levels are an indication of insulin response in the blood as well as concentration levels of insulin and/or glucose levels in the blood. The  $L_{\lambda 1} = 390\text{nm}$  and R value obtained

from  $L_{\lambda 1=390\text{nm}}$  are thus an indicator of blood glucose levels, insulin response and diabetic risk as well as vascular health. These unexpected results have advantages in early detection of diabetic risk and easier, non-invasive monitoring of insulin resistance and glucose levels as well as vascular health and other conditions. These results are discussed in more detail herein with illustrative experimental data.

**[0054]** The biosensor 100 may also function as a pulse oximeter using similar principles under Beer-lambert law to determine pulse and oxygen saturation levels in pulsating arterial flow. For example, a first wavelength at approximately 940nm and a second wavelength at approximately 660nm may be used to determine oxygen saturation levels.

**[0055]** The biosensor 100 may also be used to determine alcohol levels in the blood using wavelengths at approximately 390nm and/or 468nm. In another embodiment, an  $R_{468,940}$  value for at least  $L_{468\text{nm}}/L_{940\text{nm}}$  may be used as a liver enzyme indicator, e.g. P450 enzyme indicator. In another embodiment, an  $R_{592,940}$  value for at least  $L_{592\text{nm}}/L_{940\text{nm}}$  may be used as a digestive indicator to measure digestive responses, such as phase 1 and phase 2 digestive stages. The biosensor 100 may also detect other types of electrolytes or analytes, such as sodium and potassium, using similar PPG techniques. In another aspect, the biosensor 100 may detect which blood cell counts or concentration levels in arterial blood flow using similar PPG techniques.

**[0056]** In another aspect, abnormal cells or proteins or compounds that are present or have higher concentrations in the blood with persons having cancer, may be detected using similar PPG techniques described herein at one or more other wavelengths. Thus, cancer risk may then be obtained through non-invasive testing by the biosensor 100. Since the biosensor 100 may operate in multiple frequencies, various health monitoring tests may be performed concurrently. These and other aspects of the biosensor 100 are described in more detail herein with clinical trial results.

**[0057]** FIG. 8 illustrates a logical flow diagram of an embodiment of a method 800 of determining concentration levels of one or more substances. The biosensor 100 transmits light at one or more predetermined wavelengths. In another aspect, the biosensor 100 may also transmit light at one or more ranges of approximately 1nm to 50nm wavelengths, each range including one or more predetermined wavelengths. For example, for the predetermined wavelength 390nm, the biosensor 100 may transmit light directed at skin tissue of the patient in a range of 360nm to 410nm including the predetermined wavelength 390nm. For the predetermined wavelength of 940nm, the biosensor 100 may transmit light directed at the skin tissue of the patient in a range of 920nm to 975 nm.

**[0058]** The biosensor 100 detects the reflected light at 804 from the skin tissue and analyzes a spectral response at the one or more predetermined wavelengths (or ranges including the predetermined wavelengths) at 806. The absorption levels are measured over one or more cardiac cycles and systolic and diastolic points of the spectral response are determined. Because the human pulse is typically on the order of magnitude of one 1 HZ, typically the time differences between the systolic and diastolic points are on the order of magnitude of milliseconds or tens of milliseconds or hundreds of milliseconds. Thus, spectral response measurements may need to be acquired at a frequency of around 10-100 Hz.

**[0059]** The systolic and diastolic points of the spectral response for a wavelength may also be aligned with systolic and diastolic points of another wavelength, an arterial pulse waveform or cardiac cycle at 808. The biosensor 100 is then configured to calculate  $L_{\lambda 1}$  and  $L_{\lambda 2}$  values at 810. The biosensor 100 may also calculate ratio  $R_{\lambda 1, \lambda 2}$  values at 810. Using the determined  $L_{\lambda 1}$  and  $L_{\lambda 2}$  values or ratio  $R_{\lambda 1, \lambda 2}$  value, concentration levels or indicators of one or more substances may be obtained in the pulsating arterial blood flow at 812. The biosensor 100 may thus be used to non-invasively detect concentration levels or indicators of one or more substances in pulsating arterial blood flow.

**[0060]** FIG. 9 illustrates a logical flow diagram of another embodiment of a method 900 of determining concentration levels of one or more substances. The biosensor 100 obtains a first spectral response signal including a first wavelength and a second response signal including a second wavelength at 902. In general, the first wavelength is selected that has a high absorption coefficient for the targeted substance while the second wavelength is selected that has a low absorption coefficient for the targeted substance. Thus, it is generally desired that the spectral response for the first predetermined wavelength have a higher intensity level than the spectral response for the second predetermined wavelength.

**[0061]** Each of the spectral response signals includes AC and DC components  $I_{AC+DC}$ . A low pass filter is applied to the spectral response signals  $I_{AC+DC}$  to isolate the DC component of the first and second spectral response signals  $I_{DC}$ . The AC fluctuation is due to the pulsatile expansion of the arteriolar bed due to the volume increase in arterial blood. In order to measure the AC fluctuation, measurements are taken at different times and a peak detection algorithm or other means is used to determine the diastolic point and the systolic point of the spectral response at 906. The systolic and diastolic measurements are compared in order to compute the aforementioned R ratio. For example, a logarithmic function may be applied to the ratio of  $I_{AC+DC}$  and  $I_{DC}$  to obtain an L value for the first wavelength  $L_{\lambda 1}$  at 908 and for the second wavelength  $L_{\lambda 2}$  at 910. The ratio R of the  $L_{\lambda}$  values may then be calculated at 912.

**[0062]** FIG. 10 illustrates a schematic block diagram of another embodiment of a biosensor 100 using a broad spectrum light source 1020. In one aspect, the biosensor 100 may include a broad spectrum light source 1020, such as a white light to infrared (IR) or near IR LED 1022, that emits light with wavelengths from e.g. 350nm to 2500nm. Broad spectrum light sources with different ranges may be implemented. In an aspect, a broad spectrum light source with a range across 100nm wavelengths to 2000nm range of wavelengths in the visible, IR and/or UV frequencies. For example, a broadband

tungsten light source for spectroscopy may be used. The spectral response of the reflected light is then measured across the wavelengths in the broad spectrum, e.g. from 350nm to 2500nm, concurrently. In an aspect, a charge coupled device (CCD) spectrometer 1030 may be configured to measure the spectral response of the detected light over the broad spectrum.

[0063] The spectral response of the reflected light is analyzed for a plurality of wavelengths, e.g. at 10nm to 15nm to 20nm, incremental wavelengths across the wavelengths from 10nm to 2500nm. For example, the processing described with respect to FIG. 9 is performed at the plurality of wavelengths. In one aspect, the L values are calculated at incremental wavelengths, such as at 1nm or 1.5nm or 2nm incremental wavelengths. This process may be used to determine one or more wavelengths or ranges of wavelengths useful in detection for one or more substances in the arterial blood flow. For example, a spectral response around a wavelength of 500 nm may have a higher intensity. Trials may then be conducted to determine the one or more substances in the blood that generates this spectral response. In another embodiment, a known substance may be present in the blood and the spectral response across the broad spectrum is then analyzed to determine a pattern or correlation of intensities of wavelengths in the spectral response to the known substance. For example, a pattern of intensities of wavelengths across a range of wavelengths may indicate the presence of a substance. The intensities of the wavelengths may then be analyzed to determine concentration levels of the substance as described in more detail herein.

[0064] In another embodiment, the spectral response is analyzed at a set of predetermined wavelengths (or a range of 1nm to 50nm including each predetermined wavelength). The L values are calculated for the set of predetermined wavelengths using the analyzed spectral responses. The concentration levels of one or more substances may then be determined based on absorption coefficients for the one or more substances at each of the predetermined wavelengths. The concentration levels of a plurality of substances may be determined using the spectral response of a plurality of frequencies. The biosensor 100 may thus be used to detect a plurality of substances based on data obtained during a single measurement period. The biosensor 100 may thus perform a blood panel analysis based on in vivo arterial blood flow in a relatively short measurement period of 1-5 minutes. The blood panel analysis may be performed in a physician's office to determine results of the test while the patient is in the office. The biosensor 100 may thus provide blood panel analysis results in a 1-5 minute measurement period without a need for blood samples and lab tests that may take hours or days or weeks to obtain.

[0065] FIG. 11A illustrates a graph of an embodiment of an output of a broad spectrum light source. The relative light intensity or power output of the broad spectrum light source is shown versus wavelength of the output light  $I_O$ . The light intensity or power of the output light extends from wavelengths of approximately 350nm to approximately 2500nm. The broad spectrum light source 1020 emits light with power across the wavelengths from 350nm to 2500nm. Broad spectrum light sources with different ranges may be implemented. In an aspect, a broad spectrum light source with a range across 100nm wavelengths to 2000nm range of wavelengths in the visible, IR and/or UV frequencies.

[0066] FIG. 11B illustrates a graph with an embodiment of an exemplary spectral response of detected light 1104 across a broad spectrum, e.g. from approximately 10nm to 2000nm. In one aspect, the spectral response of the detected light 1104 may be analyzed at a plurality of wavelengths, e.g. at a set of predetermined wavelengths or at incremental wavelengths. In another aspect, the spectral response of wavelengths with a detected intensity or power exceeding a predetermined threshold may be analyzed. For example, in the graph shown in FIG. 11B, the spectral response at wavelengths of 200nm, 680nm and 990nm (and ranges of +/-20 to 50 nm around these wavelengths) exceeding a relative intensity threshold of 20000 may be analyzed.

#### **Embodiment - Determination of Concentration Levels at a Plurality of Wavelengths**

[0067] FIG. 12 illustrates a logical flow diagram of an exemplary method 1200 to determine blood concentration levels of a plurality of substances using the spectral response for a plurality of wavelengths. The biosensor 100 transmits light directed at living tissue. The light may be across a broad spectrum or at a plurality of discrete frequencies or at a single frequency. For example, the light may be emitted using a broad spectrum light source or multiple LEDs transmitting at discrete wavelengths or a tunable laser transmitting at one or more frequencies. The spectral response of light (e.g. either transmitted through the living tissue or reflected by the living tissue) is detected at 1204. The spectral response is analyzed at a plurality of wavelengths (and ranges of +/- 20 to 50 nm around these wavelengths) at 1206. In one aspect, the systolic and diastolic points are determined at the plurality of wavelengths and the L values are calculated using the systolic and diastolic points. In one aspect, the L values are determined at incremental wavelengths, such as at 1 nm or 1.5nm or 2nm incremental wavelengths. In another aspect, the L values are calculated for a set of predetermined wavelengths. A ratio R value may also be determined using L values derived from a first spectral response obtained for a first wavelength (and in one aspect including a range of +/- 20 to 50 nm) and a spectral response obtained for a second wavelength (and in one aspect including a ranges of +/- 20 to 50 nm).

[0068] Using the absorption coefficients associated with the plurality of substances, the concentration levels of a plurality of substances may then be determined. For example, the intensity of light may be due to absorption by a plurality

of substances in the arterial blood flow. For example,

$$LN(I_{1-n}) = \mu_1 * C_1 + \mu_2 * C_2 + \mu_3 * C_3 \dots + \mu_n * C_n$$

wherein,

$I_{1-n}$  = intensity of light at wavelengths  $\lambda_{1-n}$

$\mu_n$  = absorption coefficient of substance 1, 2, ... n at wavelengths  $\lambda_{1-n}$

$C_n$  = Concentration level of substance 1, 2, ... n

**[0069]** When the absorption coefficients  $\mu_{1-n}$  are known at the wavelengths  $\lambda_{1-n}$ , then the concentration levels  $C_{1-n}$  of multiple substances may be determined.

**[0070]** FIG. 13 illustrates a logical flow diagram of an exemplary method 1300 to determine blood concentration levels of a single substance using the spectral response for a plurality of wavelengths. The intensity of light at a plurality of wavelengths may be due to absorption by a single substance in the arterial blood flow. For example, a single substance may absorb or reflect a plurality of different wavelengths of light. In this example then,

$$LN(I_{1-n}) = \mu_1 * C + \mu_2 * C + \mu_3 * C \dots + \mu_n * C$$

wherein,

$I_{1-n}$  = intensity of light at wavelengths  $\lambda_{1-n}$

$\mu_n$  = absorption coefficient of a substance at wavelengths  $\lambda_{1-n}$

$C$  = Concentration level of a substance

**[0071]** When the absorption coefficients  $\mu_{1-n}$  of the single substance are known at the wavelengths  $\lambda_{1-n}$ , then the concentration level  $C$  of the substance may be determined from the spectral response for each of the wavelengths (and in one aspect including a range of 1nm to 50 nm around each of the wavelengths). Using the spectral response at multiple frequencies provides a more robust determination of the concentration level of the substance.

**[0072]** In use, the biosensor 100 transmits light directed at living tissue at a plurality of discrete wavelengths or over a broad spectrum at 1302. The spectral response of light from the living tissue is detected at 1304, and the spectral response is analyzed for a plurality of wavelengths (and in one aspect including a range of +/- 20 to 50 nm around each of the wavelengths) at 1306. Then, the concentration level  $C$  of the substance may be determined from the spectral response for each of the plurality of wavelengths at 1308. An example for calculating the concentration of one or more substances over multiple wavelengths may be performed using a linear function, such as is illustrated herein below.

$$LN(I_{1-n}) = \sum_{i=0}^n \mu_i * C_i$$

wherein,

$I_{1-n}$  = intensity of light at wavelengths  $\lambda_{1-n}$

$\mu_n$  = absorption coefficient of substance 1, 2, ... n at wavelengths  $\lambda_{1-n}$

$C_n$  = Concentration level of substance 1, 2, ... n

**[0073]** FIG. 14 illustrates an exemplary graph 1400 of spectral responses of a plurality of wavelengths from clinical data using the biosensor 100. In this embodiment, the spectral response of a plurality of wavelengths was measured using the biosensor 100 over a measurement period of almost 600 seconds or approximately 10 minutes. The graph illustrates the spectral response for a first wavelength 1402 of approximately 940nm, the spectral response for a second wavelength 1404 of approximately 660nm and the spectral response for a third wavelength 1406 of approximately 390nm obtained from a first biosensor 100 measuring reflected light from a first fingertip of a patient. The graph further illustrates the spectral response for a fourth wavelength 1410 of approximately 592 nm and a fifth wavelength 1412 of approximately 468nm and the spectral response 1408 again at 940nm obtained from a second biosensor measuring reflected light from a second fingertip of a patient. The spectral responses are temporally aligned using the systolic and diastolic points. Though two biosensors were used to obtain the spectral responses in this clinical trial, a single biosensor 100 may also be configured to obtain the spectral responses of the plurality of wavelengths.

**[0074]** Various unexpected results were determined from clinical trials using the biosensor 100. In one aspect, based on the clinical trials, an R value obtained from the ratio  $L_{\lambda,1=390nm}/$  and  $L_{\lambda,2=940}$  was found to be a predictor or indicator of diabetic risk or diabetes as described in more detail herein. In another aspect, based on the clinical trials, the R value obtained from the ratio of  $L_{468nm}/L_{940nm}$ , was identified as an indicator of the liver enzyme marker, e.g. P450. In another aspect, based on the clinical trials, the R value obtained from the ratio of  $L_{592nm}/L_{940nm}$ , was identified as an indicator of digestion phases, such as phase 1 and phase 2, in the arterial blood flow. In another aspect, the R value from the ratio of  $L_{660nm}/L_{940nm}$ , was found to be an indicator of oxygen saturation levels  $SpO_2$  in the arterial blood flow. In another aspect, it was determined that the biosensor 100 may determine alcohol levels in the blood using spectral responses for wavelengths at 390 and/or 468nm. In general, the second wavelength of 940 nm is selected because it has a low absorption coefficient for the targeted substances described herein. Thus, another wavelength other than 940nm with a low absorption coefficient for the targeted substances (e.g. at least less than 25% of the absorption coefficient of the targeted substance for the first wavelength) may be used instead. For example, the second wavelength of 940nm may be replaced with 860nm that has a low absorption coefficient for the targeted substances. In another aspect, the second wavelength of 940nm may be replaced with other wavelengths, e.g. in the IR range, that have a low absorption coefficient for the targeted substances. In general, it is desired that the spectral response for the first predetermined wavelength have a higher intensity level than the spectral response for the second predetermined wavelength.

**[0075]** In another aspect, it was determined that other proteins or compounds, such as those present or with higher concentrations in the blood with persons having cancer, may be detected using similar PPG techniques described herein with biosensor 100 at one or more other wavelengths. Cancer risk may then be determined using non-invasive testing over a short measurement period of 1-10 minutes. Since the biosensor may operate in multiple frequencies, various health monitoring tests may be performed concurrently. For example, the biosensor 100 may measure for diabetic risk, liver enzymes, alcohol levels, cancer risk or presence of other analytes within a same measurement period using PPG techniques.

**[0076]** FIG. 15 illustrates a logical flow diagram of an exemplary method 1500 to determine an absorption coefficients  $\mu_a$  of a substance at a wavelength  $\lambda$ . The concentration level of a substance in arterial blood is obtained using a known method at 1502. For example, blood may be extracted at predetermined intervals during a time period and a blood gas analyzer may be used to measure a concentration level of a substance. The biosensor 100 emits light at a wavelength (and in one aspect for a range of 1nm-50nm around the wavelength) and detects a spectral response for the wavelength (and in one aspect for a range of 1nm-50nm around the wavelength). The spectral response for the predetermined wavelength is analyzed at 1506. The intensity of the detected light is determined. The intensity of the detected light is compared to the known concentration level of the substance at 1508. The absorption coefficient for the substance may then be determined using the Beer-Lambert equations described herein at 1510.

**[0077]** The above process may be repeated at one or more other frequencies at 1512. For example, as described herein, the spectral analysis over a range or at multiple frequencies may be analyzed to determine one or more frequencies with a higher intensity or power level in response to a concentration level or presence of the substance. Thus, one or more frequencies may be analyzed and identified for detection of the substance, and the absorption coefficient for the substance determined at the one or more frequencies.

**[0078]** In another embodiment, the concentration level of a substance may be obtained from predetermined values obtained through experimentation. For example, in a calibration phase, a correlation table may be compiled through experimentation that includes light intensity values  $I_{1-n}$  at one or more wavelengths  $\lambda_{1-n}$  and a corresponding known concentration level for the substance for the light intensity values. In use, the biosensor 100 detects a spectral response and determines the light intensity values  $I_{1-n}$  at one or more wavelengths  $\lambda_{1-n}$ . The biosensor 100 then looks up the detected light intensity values  $I_{1-n}$  in the correlation table to determine the concentration level of the substance.

**[0079]** FIG. 16 illustrates a schematic block diagram of a spatial distribution of light intensity amplitude for different forces of contact between the biosensor 100 and a skin surface. Spatial distribution of the PPG amplitude for different forces of contact was measured between a glass table and skin of one of the subjects during steps a, b and c. The results of the experiment are illustrated in FIG. 16 wherein the spatial distributions of the PPG-amplitude obtained during the steps a, b, and c are presented respectively. The mechanical contact of the glass with the subject's skin substantially increases the amplitude of the observed PPG signal. Moreover, by increasing the force of the contact, the amplitude of the PPG signal and the area with elevated PPG amplitude is increased. As such, compression enhances the PPG signal. So compression of the biosensor 100 against the skin of a patient may be implemented during use of biosensor 100 in its one or more form factors. The article by Kamshilin AA, Nippolainen E, Sidorov IS, et al. entitled "A new look at the essence of the imaging photoplethysmography" in Scientific Reports, May 21, 2015, 5:10494 and doi:10.1038/srep10494 includes further details on spatial distribution of PPG intensity amplitude for different forces of contact.

#### Embodiment - Biosensor Form Factors

**[0080]** FIG. 17A illustrates an exemplary embodiment of a form factor of the biosensor 100. In an embodiment, the

biosensor 100 is implemented on a wearable patch 1700. The wearable patch 1700 may include an adhesive backing to attach to a skin surface of a patient, such as on a hand, arm, wrist, forehead, chest, abdominal area, or other area of the skin or body or living tissue. Alternatively, the wearable patch 1700 may be attached to the skin surface using adhesive tape. A flexible cable 1702 may be used to attach an optical head 1704 of the wearable patch 1700 to the other components of the biosensor 100, such as the wireless transceiver 106 and battery 108. Thus, during a magnetic resonance imaging (MRI) test when metal needs to be minimal, the battery 108 and transceiver 106 may be temporarily removed. In addition, the flexible cable 1702 may be used to open the biosensor 100 to replace the battery 108.

**[0081]** FIG. 17B illustrates an exemplary embodiment of another form factor of the biosensor 100. In this embodiment, the biosensor 100 is implemented on an arm band 1710. The arm band 1710 may be configured with an adjustable band for placement on an arm, wrist, on one or more fingers, around a leg, etc. In general, the arm band 1710 should be secured such that the PPG circuit 110 is positioned to direct light towards the skin surface.

**[0082]** FIG. 18A illustrates an exemplary embodiment of another form factor of the biosensor 100. In this embodiment, the biosensor 100 may be coupled to an attachable bandaid 1800. The attachable bandaid 1800 may be attached via adhesive or adhesive tape to a skin surface of the patient, e.g. finger, forehead, arm, stomach, leg, wrist, etc.

**[0083]** FIG. 18B illustrates an exemplary embodiment of another form factor of the biosensor 100. In this embodiment, the biosensor 100 is configured in an earpiece 1810. The earpiece 1810 includes an earbud 1812. The biosensor 100 is configured to transmit light into the ear canal from one or more optical fibers in the ear bud 1812 and detect light from the ear canal using one or more optical fibers.

**[0084]** FIG. 19A illustrates an exemplary embodiment of another form factor of the biosensor 100. In this embodiment, the biosensor 100 is configured to attach to a finger or fingertip using finger attachment 1902. The finger attachment 1902 is configured to securely hold a finger that is inserted into the finger attachment 1902. A display 1900 is implemented on the biosensor 100 with a graphical user interface (GUI) that displays biosensor data. For example, in use, the biosensor 100 measures blood glucose levels using the PPG circuit 110. The blood glucose levels are then displayed using the GUI on the display 1900. The PPG circuit may also measure other patient vitals that are displayed on the display 1900, such as oxygen saturation levels, temperature, blood alcohol levels, digestive response, calorie intake, white blood cell count, electrolyte or other blood analyte concentrations, liver enzymes, etc. The biosensor 100 may thus provide biosensor data non-invasively without a blood sample.

**[0085]** FIG. 19B illustrates an exemplary embodiment of another form factor of the biosensor 100. In this embodiment, the biosensor 100 is configured to attach to a finger or fingertip using finger attachment 1906. The finger attachment 1906 includes the PPG circuit 110 and is configured to securely hold a finger that is inserted into the finger attachment 1906. The finger attachment 1906 may be implemented within the same encasement as the other components of the biosensor 100 or be communicatively coupled either through a wired or wireless interface to the other components of the biosensor 100. A display 1908 is implemented for the biosensor 100 with a graphical user interface (GUI) that displays biosensor data including blood glucose levels.

**[0086]** The biosensor 100 may be configured to be attached to an ear lobe or other body parts in other form factors. In addition, one or more biosensors 100 in one or more form factors may be used in combination to determine biosensor data at one or more areas of the body.

**[0087]** In these or other form factors, the biosensor 100 may store a unique patient identification 172 that is generally included as a barcode on current armbands. The biosensor 100 may also store patient health data measured by the biosensor 100 or EMR 170 of the patient that may be used in one or more applications or systems in the health care chain of a patient. For example, the biosensor 100 is programmed with a unique patient identification 172 that is assigned to a patient during admission to a hospital and is used for tracking of the patient through the transceiver 106 of the biosensor 100. As such, a separate scanner is not needed to track a patient or scan an arm band. The biosensor 100 monitors the patients vitals as part of the care management of the patient. The patients vitals are used in data analytics for diagnosis, treatment options, monitoring, etc. The patient vitals may be included in the patient EMR 170 and otherwise used for patient health. The biosensor 100 may also communicate with inventory management. For example, when a medicine is provided to a patient, this information of the medicine and dosage may be provided to the inventory management system. The inventory management system is then able to adjust the inventory of the medicine. The biosensor 100 may thus have these and/or additional applications.

## Embodiment - EMR Network

**[0088]** FIG. 20 illustrates a schematic block diagram of an embodiment of an exemplary network 2000 in which the biosensor 100 described herein may operate. The exemplary network 2000 may include a combination of one or more networks that are communicatively coupled, e.g., such as a wide area network (WAN) 2002, a wired local area network (LAN) 2004, a wireless local area network (WLAN) 2006, or a wireless wide area network (WAN) 2008. The wireless WAN 1228 may include, for example, a 3G or 4G cellular network, a GSM network, a WIMAX network, an EDGE network, a GERAN network, etc. or a satellite network or a combination thereof. The WAN 1222 includes the

Internet, service provider network, other type of WAN, or a combination of one or more thereof. The LAN 2004 and the WLANs 20066 may operate inside a home 2016 or enterprise environment, such as a physician's office 2018, pharmacy 2020 or hospital 2022 or other caregiver.

[0089] The biosensor 100 may communicate to one or more user devices 2010, such as a smart phone, laptop, desktop, smart tablet, smart watch, or any other electronic device that includes a display for illustrating the patient's vitals. In one aspect, the user device 2010 or biosensor 100 may communicate the patient's vitals to a local or remote monitoring station 2012 of a caregiver or physician.

[0090] One or more biosensor 100s are communicatively coupled to an EMR application server 2030 through one or more of user devices and/or the exemplary networks in the EMR network 2000. The EMR server 2030 includes a network interface card (NIC) 2032, a server processing circuit 2034, a server memory device 2036 and EMR server application 2038. The network interface circuit (NIC) 1202 includes an interface for wireless and/or wired network communications with one or more of the exemplary networks in the EMR network 1220. The network interface circuit 1202 may also include authentication capability that provides authentication prior to allowing access to some or all of the resources of the EMR application server 1200. The network interface circuit 1202 may also include firewall, gateway and proxy server functions.

[0091] One or more of the biosensors 100 are communicatively coupled to an EMR application server 1200 through one or more of the exemplary networks in the EMR network 1220. The EMR application server 1200 includes a network interface circuit 1202 and a server processing circuit 1204. The network interface circuit (NIC) 1202 includes an interface for wireless and/or wired network communications with one or more of the exemplary networks in the EMR network 1220. The network interface circuit 1202 may also include authentication capability that provides authentication prior to allowing access to some or all of the resources of the EMR application server 1200. The network interface circuit 1202 may also include firewall, gateway and proxy server functions.

[0092] The EMR application server 1200 also includes a server processing circuit 2034 and a memory device 2036. For example, the memory device 2036 is a non-transitory, processor readable medium that stores instructions which when executed by the server processing circuit 2034, causes the server processing circuit 2034 to perform one or more functions described herein. In an embodiment, the memory device 2036 stores a patient EMR 170 that includes biosensor data and historical data of a patient associated with the patient ID 172.

[0093] The EMR application server 1200 includes an EMR server application 2038. The EMR server application 2038 is operable to communicate with the biosensors 100 and/or user devices 2010 and monitoring stations 2012. The EMR server application 2038 may be a web-based application supported by the EMR application server 2030. For example, the EMR application server 2030 may be a web server and support the EMR server application 2038 via a website. In another embodiment, the EMR server application 2038 is a stand-alone application that is downloaded to the user devices 2010 by the EMR application server 2030 and is operable on the user devices 2010 without access to the EMR application server 2030 or only needs to access the EMR application server 2030 for additional information and updates.

[0094] In use, the biosensors 100 may communicate patient's biosensor data to the EMR application server 2030. A biosensor 100 may be programmed with a patient identification 172 that is associated with a patient's EMR 170. The biosensor 100 measures the patient's vitals, such as heart rate, pulse, blood oxygen levels, blood glucose levels, etc. and may also control an integrated or separate drug delivery system to administer medications to the patient. The biosensor 100 is configured to transmit the patient vitals to the EMR application server 2030. The EMR server application 2038 updates an EMR 170 associated with the patient identification 172 with the patient vitals.

[0095] The EMR application server 2030 may also be operable to communicate with a physician's office 2018 or pharmacy 2016 or other third party health care provider over the EMR network 2000 to provide biosensor data and receive instructions on dosages of medication. For example, the EMR server application 2038 may transmit glucose level information, heart rate information or pulse rate information or medication dosages or blood concentration levels of one or more relevant substances to a physician's office 2018. The EMR server application 2038 may also be configured to provide medical alerts to notify a user, physician or other caregiver when vitals are critical or reach a certain predetermined threshold.

[0096] The EMR server application 1408 may also receive instructions from a doctor's office, pharmacy 2016 or hospital 2022 or other caregiver regarding a prescription or administration of a dosage of medication. The EMR server application 2038 may then transmit the instructions to the biosensor 100. The instructions may include a dosage amount, rate of administration or frequency of dosages of a medication. The biosensor 100 may then control a drug delivery system to administer the medication automatically as per the transmitted instructions.

#### Embodiment - Interoperability of Biosensors and Other Devices

[0097] FIG. 21A illustrates a schematic block diagram of an embodiment of a network illustrating interoperability of a plurality of biosensors 100. A plurality of biosensors 100 may interface with a patient and communicate with one or more of the other biosensor 100s. The biosensors 100 may communicate directly or communicate indirectly through a WLAN



or other type of network as illustrated in the Network 2000 of FIG. 20. For example, a first biosensor 100a may include a PPG circuit 110 configured to detect a blood glucose level. For better detection, the biosensor 100a is positioned on a wrist. A second biosensor 100b may include a drug delivery system 116 configured to administer insulin to the patient 2100 and is positioned on an abdominal area of the patient 2100. In use, the first biosensor 100a continuously monitors blood glucose levels and then communicates either directly or indirectly the detected levels to the second biosensor 100b. The second biosensor 100b then administers a dosage of insulin at an administration rate and/or frequency rate in response to the detected blood glucose levels.

**[0098]** In another example, one or more biosensor 100s may communicate directly or indirectly with one or more other types of medical devices 2102 interfacing with a same patient, such as a first medical device 2100a and a second medical device 2100b. The first medical device 2102a may include an insulin pump, e.g. on body insulin pump or catheter tethered drip system. In use, the biosensor 100a monitors glucose and/or insulin indicators or concentration levels in the patient using the PPG circuit 110. In response to the detected glucose and/or insulin concentration/indicators, the biosensor 100a communicates either directly or indirectly administration instructions to the first medical device 2102a. The administration instructions may include dosage amount, administration rate and/or frequency rate. In response to the administration instructions, the first medical device 2102a administers an insulin infusion to the patient. The first biosensor 100a may continuously monitor glucose/insulin indicators or concentration levels and provide automatic instructions to the first medical device 2102a for the administration of insulin.

**[0099]** In another example, a plurality of biosensors 100, such as the first biosensor 100a and the second biosensor 100b, may be positioned on a patient to monitor an ECG of the patient. The biosensors 100 may communicate the ECG measurements directly or indirectly to each other to generate an electrocardiogram. The electrocardiogram is transmitted to an EMR application server 2030 or monitoring station 2012 or to a user device 2010. Based on the electrocardiogram, a doctor or user may provide instructions to the second medical device 2102b. For example, the second medical device 2102b may include a Pacemaker or drug delivery system.

**[0100]** In another example, the biosensor 100a may include a PPG circuit 110 configured to detect alcohol levels in arterial blood flow. The user device 2010 may include a locking system installed in an ignition system of a vehicle. In order to start the vehicle, the the biosensor 100a detects the blood alcohol concentration (BAC) of the patient. Then the biosensor 100a determines whether the blood alcohol concentration (BAC) is above or below a preset legal limit. If it is below this limit, the biosensor 100a communicates an instruction to the user device 2010 to unlock the ignition to allow starting of the vehicle. If it is above the limit, the biosensor 100a instructs the user device 2010 to lock the ignition to prevent starting of the vehicle. Since the biosensor 100a is directly testing the blood alcohol levels, the biosensor 100a may be more accurate and convenient than current breathe analyzers.

#### **Embodiment - Adjustments in response to Positioning of the Biosensor**

**[0101]** FIG. 21B illustrates a logical flow diagram of an embodiment of a method 2110 for adjusting operation of the biosensor 100 in response to a position of the biosensor 100. The biosensor 100 may be positioned on different parts of a patient that exhibit different characteristics. For example, the biosensor 100 may be positioned on or attached to various areas of the body, e.g. a hand, a wrist, an arm, forehead, chest, abdominal area, ear lobe, fingertip or other area of the skin or body or living tissue. The characteristics of underlying tissue vary depending on the area of the body, e.g. the underlying tissue of an abdominal area has different characteristics than the underlying tissue at a wrist. The operation of the biosensor 100 may need to be adjusted in response to its positioning due to such varying characteristics of underlying tissue.

**[0102]** The biosensor 100 is configured to obtain position information on a patient at 2112. The position information may be input from a user interface. In another aspect, the biosensor 100 may determine its positioning, e.g. using the activity monitoring circuit 114 and/or PPG circuit 110. For example, the PPG circuit 110 may be configured to detect characteristics of underlying tissue. The biosensor 100 then correlates the detected characteristics of the underlying tissue with known or predetermined characteristics of underlying tissue (e.g. measured from an abdominal area, wrist, forearm, leg, etc.) to determine its positioning. Information of amount and types of movement from the activity monitoring circuit 114 may be used as well in the determination of position.

**[0103]** In response to the determined position and/or detected characteristics of the underlying tissue, the operation of the biosensor 100 is adjusted at 2114. For example, the biosensor 100 may adjust operation of the PPG circuit 110. The article, "Optical Properties of Biological Tissues: A Review," by Steven L. Jacques, Phys. Med. Biol. 58 (2013), describes wavelength-dependent behavior of scattering and absorption of different tissues. The PPG circuit 110 may adjust a frequency or wavelength in detection of a concentration level of a substance based on the underlying tissue. The PPG circuit 110 may adjust an absorption coefficient when determining a concentration level of a substance based on Beer-Lambert principles due to the characteristics of the underlying tissue. Other adjustments may also be implemented depending on predetermined or measured characteristics of the underlying tissue.

**[0104]** Adjustments to the activity monitoring circuit 114 may need to be made depending on positioning as well. For

example, the type and level of movement detected when positioned on a wrist of a patient may vary from the type and level of movement when positioned on an abdominal area of the patient. In another aspect, the biosensor 100 may adjust measurements from the temperature sensor 112 depending on placement of the patient, e.g. the sensor array measurements may vary from a wrist or forehead.

**[0105]** The biosensor 100 is thus configured to obtain position information and perform adjustments to its operation in response to the position information.

#### Embodiment - Diabetic Parameter Measurements

**[0106]** Clinical data obtained using the biosensor 100 is now described herein. The biosensor 100 was used to monitor concentration levels or indicators of one or more substances in the blood flow of the patient in the clinical trials over a measurement time period. For example, the biosensor 100 was used in the clinical trials to non-invasively detect diabetic parameters, such as insulin response over time, nitric oxide (NO) levels, glucose levels, and predict diabetic risk or diabetic precursors, in pulsatile arterial blood flow. The biosensor 100 was also used to detect blood alcohol levels in pulsatile arterial blood flow. The biosensor 100 was also used to detect digestive parameters, such as digestion phase 1 and 2 responses. The biosensor 100 also detected heart rate and blood oxygen saturation levels in the clinical trials.

**[0107]** FIG. 22 illustrates a schematic drawing of an exemplary embodiment of results of clinical data 2200 obtained using the biosensor 100 from a first patient. This first patient is a 42 year old female with no known diagnosis of diabetes. A biosensor 100 is placed on at least one finger of the first patient and the spectral response is measured over the least three wavelengths at 390nm, 660nm and 940nm (and also in range of 1nm to 50nm). The graph 2006 illustrates the spectral response or frequency spectrum data obtained for the three wavelengths. The spectral response in graph 2206 shows the frequency versus the relative intensity measured by the biosensor 100. The graph 2202 illustrates the L value obtained from the spectral responses for each of the three wavelengths obtained, e.g., from the spectral response data shown in graph 2206. The L value obtained for the three wavelengths is a measured response from the pulsating arterial blood flow in the patient.

**[0108]** The graph 2208 illustrates the calculated Ratio R for  $R_1 = L_{390nm}/L_{940nm}$  and  $R_2 = L_{390nm}/L_{660nm}$ . In one aspect, based on unexpected results from clinical trials, it was determined that a ratio R value obtained at approximately  $L_{\lambda 1} = 390nm$  and  $L_{\lambda 2} = 940nm$  is useful as a predictor or indicator of diabetic risk or diabetes. For example, during experimental clinical trials, spectral responses were obtained during a measurement period over a 1-2 minute time period for wavelengths of 390nm and 940nm (and also in ranges of 1nm to 50nm including these wavelengths). An R value was obtained based on the spectral responses. From the unexpected results of the clinical trials, an R value obtained during a period of fasting, e.g. prior to ingestion of food or liquids, of less than 1 (e.g., approximately .5) indicated that a person has diabetes or early onset of diabetes. An R value of 2 or above indicated that a person has a lower risk of a diabetes diagnosis. An R value in the 5-6 range indicated no current risk of diabetes. For example, as shown in graph 2208, the R value obtained for  $L_{\lambda 1} = 390nm$  and  $L_{\lambda 2} = 940nm$  has an average value greater than 5 in this first patient without a diabetes diagnosis.

**[0109]** FIG. 23 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2300 obtained using the biosensor 100 from the first patient. The graph 2302 illustrates the heart rate obtained over a measurement period of 900 seconds. The graph 2304 illustrates the oxygen saturation level  $SpO_2$  obtained over the measurement period of 900 seconds.

**[0110]** The graph 2306 illustrates an insulin response measured in the arterial blood flow of the patient over a measurement period of 900 seconds. The graph illustrates the Ratio R for approximately  $L_{390nm}/L_{940nm}$ , for approximately  $L_{660nm}/L_{940nm}$ , for approximately  $L_{466nm}/L_{940nm}$ , and for approximately  $L_{582nm}/L_{940nm}$ . In unexpected results, the Ratio R value for  $L_{390nm}/L_{940nm}$  2310 between 0 and 200 seconds is seen to correlate with the base insulin resistance factor, e.g. the base insulin concentration levels after fasting for 2-8 hours. At approximately, 200 seconds, the patient consumed a high sugar substance, e.g. a candy bar. In unexpected results, the insulin response 2308 of the patient is obtained from the biosensor data. In particular, the Ratio R for approximately  $L_{390nm}/L_{940nm}$  shows the increase in insulin response 2308 from the base insulin resistance factor 2310 in the pulsating arterial blood flow starting at approximately 600 seconds in response to the consummation of the high sugar substance. The Ratio R for approximately  $L_{390nm}/L_{940nm}$  has a value between 4 and 6 in the healthy patient without a diagnosis of diabetes in response to the ingestion of the high sugar substance.

**[0111]** Graph 2312 illustrates the L values obtained from the spectral responses for the four wavelengths,  $L_{940nm}$ ,  $L_{660nm}$ ,  $L_{390nm}$ ,  $L_{582nm}$ , and  $L_{463nm}$  over the measurement period of 900 seconds. The glucose response from the consummation of the high sugar substance is starting at approximately 600 seconds. In particular, in unexpected results, it is believed that nitrous oxide NO levels in the arterial blood flow is being measured at least in part by the biosensor 100 using the spectral response for the wavelength 390nm (and 1nm-50nm range around 390nm). The spectral response is responsive to nitrous oxide (NO) concentration levels in the blood. As such, the  $L_{390nm}$  values may be used to determine nitrous oxide (NO) concentration levels in the pulsating blood flow.

**[0112]** In addition, insulin in the blood generates NO as it penetrates blood vessel walls. The NO is released as a gas before attaching to one or more hemoglobin type molecules. Since at least part of the NO gas concentration is in a gaseous form in the arterial blood flow, the NO in the gaseous form will dissipate prior to measurement from in vitro blood samples. As such, the complete NO concentration levels may not be measured using in vitro blood samples, e.g. from a finger prick. Thus, the biosensor 100 measurements, e.g. using the spectral response and calculated L values at 390nm, are the first time NO levels in arterial blood flow have been measured in vivo. These unexpected results of measuring nitric oxide NO concentration levels in pulsating arterial blood flow are obtained non-invasively and continuously over a measurement period using the biosensor 100.

**[0113]** From the clinical trials performed, it has been determined that the measured NO levels are an indication of insulin response and blood glucose concentration levels in the blood. The R value derived from  $L_{390nm}/L_{940nm}$  may thus be used as an indicator of insulin response and diabetic risk as well as vascular health. These unexpected results have advantages in early detection of diabetic risk and easier, non-invasive monitoring of insulin resistance and blood glucose levels. The biosensor 100 may display the R value or an analysis of the diabetic risk based on the R value. In one aspect, the biosensor 100 may display, no diabetic risk based on R values of 5 or greater. In another aspect, the biosensor 100 may display, low diabetic risk based on R values of 2-5. In another aspect, the biosensor 100 may display, high diabetic risk based on an R values of 1-2. In another aspect, the biosensor 100 may display, diabetic condition detected based on an R value less than one.

**[0114]** FIG. 24 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2400 obtained using the biosensor 100 from a second patient. The second patient was a 65 year old male with a known diagnosis of type 1 diabetes. The graph 2402 illustrates the heart rate obtained over a measurement period of approximately 135 minutes. The graph 2404 illustrates the oxygen saturation level  $SpO_2$  obtained over the measurement period of 135 minutes.

**[0115]** The graph 2406 illustrates an insulin response 2410 measured in the arterial blood flow of the patient over a measurement period of 135 minutes. The graph illustrates the Ratio R for approximately  $L_{390nm}/L_{940nm}$ , for approximately  $L_{660nm}/L_{940nm}$ , for approximately  $L_{466nm}/L_{940nm}$ , and for approximately  $L_{582nm}/L_{940nm}$ . In unexpected results, the Ratio R for approximately  $L_{390nm}/L_{940nm}$  correlates with a base insulin resistance factor shown prior to approximately 200 seconds. At approximately, 200 seconds, the patient consumed a high sugar substance, e.g. a glucose drink. In unexpected results, the insulin response 2410 of the patient is obtained from the biosensor data. In particular, the Ratio R for approximately  $L_{390nm}/L_{940nm}$  shows the minimal insulin response 2410 in the patient with diabetes after the consumption of the glucose drink. The R value for  $L_{390nm}/L_{940nm}$  remains below a value of 1 even after the consummation of the glucose drink indicating the lack of generation of natural insulin by the patient. At approximately 4500 seconds or 75 minutes, insulin is administered to the patient through two injections. The graph 2406 illustrates the increase in the R value due to the increase in insulin response 2410 from the injections after 4500 seconds. The Ratio R for approximately  $L_{390nm}/L_{940nm}$  still remains low with a value between 2 and 4 even after the insulin injections in the patient with diabetes.

**[0116]** Graph 2412 illustrates the L values for the four wavelengths,  $L_{940nm}$ ,  $L_{660nm}$ ,  $L_{390nm}$ ,  $L_{582nm}$ , and  $L_{463nm}$  over the measurement period of 1000 seconds. The graph of  $L_{390nm}$  2408 shows no increase in insulin levels until after the insulin injections at 75 minutes. In specific, the  $L_{390nm}$  shows particularly sensitivity in the measurement of the base insulin resistance factor measured after fasting and the insulin response measured after caloric intake.

**[0117]** FIG. 25 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2500 obtained using the biosensor 100 from the second patient. At predetermined time periods of about 15 minutes, blood glucose level (BGL) was measured using a known method and the BGL measurements plotted. The plotted measurements were interpolated to generate a polynomial showing the approximate BGLs 2504 in mg/dl units. The biosensor 100 obtained measurements over the same time period to derive the Ratio R for approximately  $L_{390nm}/L_{940nm}$  2502, as shown on the graph as well.

**[0118]** In this clinical trial, the R value for  $L_{390nm}/L_{940nm}$  has a low base insulin resistance factor 2504 of less than 1 (in an R value range from 0-8) indicating a diabetic condition in the patient. After consumption of a high sugar substance at around 200 seconds, an insulin response 2510 is seen at approximately 232 seconds. It seems that the  $L_{390nm}$  is measuring NO levels in the arterial blood flow. As insulin is generated in the body, it reacts with blood vessels to generate NO gas. The NO gas bonds to hemoglobin and is transported in the blood stream. The NO is thus a good indicator of a base insulin resistance factor after fasting and an insulin response after caloric intake.

**[0119]** The ratio R values may also be correlated with blood glucose levels (BGL) using the graph or using a similar table or other correlation method. For example, the ratio R for  $L_{390nm}/L_{940nm}$  with a value of 1.75 is correlated to a BGL of about 150 mg/DL using the graph. The R value for  $L_{390nm}/L_{940nm}$  may thus be used to show a base insulin resistance factor 2508 insulin response 2510 as well as obtain blood glucose levels for the patient.

**[0120]** In addition, nitric oxide NO generation helps hemoglobin in the uptake of oxygen. Thus, the NO measurements, such as the R value for  $L_{390nm}/L_{940nm}$ , are also a good indicator of vascular health.

**[0121]** FIG. 26 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2600 obtained using the biosensor 100 from a third patient. The third patient is a 37 year old female with a known diagnosis

of Type 1 diabetes. At predetermined time periods of about 15 minutes, blood glucose levels (BGL) were measured using a known method and the BGL measurements plotted. The plotted measurements were interpolated to generate a polynomial showing the approximate BGL 2604 in mg/dl units. The biosensor 100 obtained measurements over the same time period to derive the Ratio R for approximately  $L_{390nm}/L_{940nm}$  2602, as shown on the graph as well.

**[0122]** In this clinical trial, the insulin resistance level or R value for  $L_{390nm}/L_{940nm}$  measured prior to eating has a low baseline value of less than 1 indicating a diabetic condition. In unexpected results, the base insulin resistance factor 2606 for the R value at  $L_{390nm}/L_{940nm}$  is seen as less than .8. Thus, from unexpected clinical results, it is determined that a base insulin resistance factor or R value for  $L_{390nm}/L_{940nm}$  of less than 1 from an R value range of 0-8 indicates a diabetic condition. After consumption of a high sugar substance, insulin response is seen from 1-191 seconds.

**[0123]** From the clinical trials, it seems that the  $L_{390nm}$  is measuring NO levels in the arterial blood flow. As insulin is generated in the body, it reacts with blood vessels to generate NO gas. The NO gas bonds to hemoglobin and is transported in the blood stream. The R value for  $L_{390nm}/L_{940nm}$  measures the NO levels in the pulsating arterial blood flow and thus provides a good indicator of BGLs, base insulin resistance factor and insulin response after caloric intake. The BGLs may be obtained from the R values using the graph 2600 or a similar table that correlates the R value with known BGL measurements for the patient.

**[0124]** FIG. 27 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2700 obtained using the biosensor 100 from a fourth patient. The fourth patient is a 59 year old male with a known diagnosis of Type 2 diabetes. At predetermined time periods of about 15 minutes, blood glucose level (BGL) was measured using a known method of a blood glucose meter (BGM) using blood from finger pricks. The BGM glucose measurements 2704 are plotted. The plotted measurements were interpolated to generate a polynomial 2706 showing the approximate BGM glucose measurements over time in mg/DL units. The biosensor 100 obtained measurements over the same time period to derive the Ratio R for approximately  $L_{390nm}/L_{940nm}$  2702, as shown on the graph as well.

**[0125]** In this clinical trial, the base insulin resistance factor 2708 measured prior to eating has a low baseline value of about .5 indicating a diabetic condition. In unexpected results, the base insulin resistance factor or R value for  $L_{390nm}/L_{940nm}$  of less than 1 (in an R value range of 0-8) thus seems to indicate a diabetic condition from the clinical trial results. After consumption of a high sugar substance, insulin response 2710 is seen after about 7 minutes. The blood glucose levels may be obtained from the R values using the graph 2700 or a similar calibration table that correlates the R value with known BGL measurements for the patient. The calibration table may be generated for a specific patient or may be generated from a sample of a general population. It is determined that the R values should correlate to similar BGL measurements across a general population. Thus, the calibration table may be generated from testing of a sample of a general population.

**[0126]** From the unexpected results of the clinical trials, an R value of less than 1 (in an R value range of 0-8) indicated that a person has diabetes or early onset of diabetes. An R value of 5 (in an R value range of 0-8) or above indicated that a person has no diabetic condition. For example, as shown in graph 2208, the base insulin resistance factor measured using an R value of approximately  $L_{390nm}/L_{940nm}$  has generally an average value greater than 5 in the first patient without a diabetes diagnosis. The base insulin resistance factor measured using an R value of approximately  $L_{390nm}/L_{940nm}$  was generally an average value less than 1 (in an R value range from 0-8) in the other patients with a diabetes diagnosis of either Type 1 or Type II. The base insulin resistance factor measured using an R value in the 1-2 (in an R value range from 0-8) range indicated a high risk of diabetes and need for further testing.

**[0127]** It seems that the  $L_{390nm}$  is measuring NO levels in the arterial blood flow. As insulin is generated in the body, it reacts with blood vessels to generate NO gas. The NO gas bonds to hemoglobin and is transported in the blood stream. The NO is thus a good indicator of a base insulin resistance factor after fasting and an insulin response after caloric intake.

**[0128]** From the clinical trials, it seems that the NO levels are reflected in the R values obtained from  $L_{390nm}/L_{940nm}$ . Based on the clinical trials and R values obtained in the clinical trials, it is determined that a base insulin resistance factor of less than 1 corresponds to an NO concentration level of at least less than 25% of average NO levels. For example, average NO levels are determined by sampling a general population of persons without diabetes or other health conditions affecting NO levels. From the clinical trials, an R value correlating to a base insulin factor of less than 1 indicates that the NO levels are in a range of 25% to 50% less than average NO levels. After fasting, a person with a diabetic condition will have low NO concentration levels that are at least 25% less than average NO levels due to the low level of insulin in the blood. Thus, an NO concentration level of at least less than 25% of normal ranges of NO concentration levels indicates a diabetic condition (e.g., the NO levels corresponding to R value less than 1 in this clinical trial). Thus, a base insulin resistance factor of less than 1 correlates to at least less than 25% of average NO levels of a sample population and indicates a diabetic condition.

**[0129]** Based on the clinical trials and R values obtained in the clinical trials, it is determined that a base insulin resistance factor in the range of 2-8 corresponds to average NO concentration levels. Thus, a base insulin resistance factor (e.g. in the range of 2-8) correlates to an average NO level of a sample population and little to no diabetic risk.

**[0130]** Based on these unexpected results, in one aspect, the biosensor 100 may display or transmit, e.g. to a user device or monitoring station, or otherwise output an indicator of the diabetic risk of a patient based on the R value. For

example, the biosensor 100 may output no diabetic risk based on an obtained R value for a patient of 5 or greater. In another aspect, the biosensor 100 may output low diabetic risk based on an obtained R value of 2-5. In another aspect, the biosensor 100 may output high diabetic risk based on an obtained R values of 1-2. In another aspect, the biosensor 100 may output diabetic condition detected based on an R value less than one. In the clinical trials herein, the R value was in a range of 0-8. Other ranges, weights or functions derived using the R value described herein may be implemented that changes the numerical value of the R values described herein or the range of the R values described herein. In general, from the results obtained herein, an R value corresponding to at least the lower 10% of the R value range indicates a diabetic condition, an R value in the lower 10% to 25% of the R value range indicates a high risk of diabetes, an R value in the 25% to 60% range indicates a low risk of diabetes, and an R value greater than 60% indicates no diabetic condition.

[0131] The R value of  $L_{390nm}/L_{940nm}$  may be non-invasively and quickly and easily obtained using the biosensor 100 in a physician's office or other clinical setting or at home. In one aspect, the R value may be used to determine whether further testing for diabetes needs to be performed. For example, upon detection of a low R value of less than 1, a clinician may then determine to perform further testing and monitoring, e.g. using glucose ingestion tests over a longer period of time or using the biosensor 100 over a longer period of time or other type of testing.

#### Embodiment - Blood Alcohol Level Measurements

[0132] FIG. 28 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2800 obtained using the biosensor 100 from a fifth patient. In this trial, the fifth patient was a 55 year old male that ingested a shot of whiskey at approximately 7 seconds. The biosensor 100 was used to measure an indicator of blood alcohol levels over a measurement period of approximately 271 seconds using a wavelength of approximately 468nm. The graph illustrates the values obtained for ratio  $R=L_{468nm}/L_{940nm}$  2802 over the measurement period. The biosensor 100 was able to detect the increase in the blood alcohol levels over the measurement period. The ratio R values 2802 may be correlated with blood alcohol levels using a table or graph that associates the R values 2802 with blood alcohol levels. For example, the table or graph may be obtained through blood alcohol levels measured from blood drawn at preset intervals (such as every 1-5 minutes) during a measurement period (such as 1-5 hours) and interpolating the resulting measurements. The interpolated measurements are then associated with the measured ratio R values 2802 over the same measurement period. In general, the ratio R values 2802 are consistent with an approximate measured blood alcohol level in subsequent clinical trials for a patient. The calibration of measured blood alcohol levels to ratio R values 2802 may thus only be performed once for a patient. In another aspect, the calibration table may be generated using testing of a sample of a general population. It is determined that the R values should correlate to similar BAL measurements across a general population. Thus, the calibration table may be generated from testing of a sample of a general population.

#### Embodiment - Digestive Stage and Caloric Intake Measurements

[0133] FIG. 29 illustrates a schematic drawing of another exemplary embodiment of results of clinical data 2900 obtained using the biosensor 100 from the fifth patient. In this trial, the fifth patient ingested whiskey at approximately 13 seconds. The biosensor 100 was used to measure the digestive stages over a measurement period of approximately 37 minutes using a wavelength of approximately 390nm to track the blood glucose levels. The graph illustrates the values for  $L_{390nm}$  2902 obtained over the measurement period. The biosensor 100 was able to detect the digestive stage 1 2904 and digestive stage 2 2906 based on the obtained values for  $L_{390nm}$ . The first digestive stage 1 2904 is indicated by an initial spike around 20 seconds as blood rushes to the stomach to aid in digestion. The second digestive stage 2 is indicated by a later, more prolonged increase in blood glucose levels between 60 and 180 seconds.

[0134] Based on the insulin response and BGL measurements, a calibration of caloric intake may be performed for a patient. For example, known caloric intakes may be correlated with insulin response in phase 1 and phase 2 digestions measured using values for  $L_{390nm}$  2902. In another aspect, the calibration table may be generated using testing of a sample of a general population. It is determined that the R values using  $L_{390nm}$  2902 should correlate to similar caloric intake measurements across a general population. Thus, the calibration table may be generated from testing of a sample of a general population.

#### Embodiment - Liver Enzyme Measurements

[0135] FIG. 30 illustrates a schematic drawing of an exemplary embodiment of using the biosensor 100 for measurements of a liver enzyme. In unexpected results, concentration levels of a liver enzyme called cytochrome P450 Oxidase (P450) 2900 was measured by the biosensor 100. In one aspect, spectral response around a wavelength at approximately 468nm was used by the biosensor 100 to obtain L values that tracked the concentration levels of the liver enzyme P450 2900. The liver enzyme is generated to react with various substances 2902 and may be generated in response to alcohol

levels. Thus, the measurement of the spectral response for the wavelength at approximately 468nm may indicate blood alcohol levels and/or concentration levels of P450 2900.

#### Embodiment - Measurements of other Substances

**[0136]** Using similar principles described herein, the biosensor 100 may measure concentration levels or indicators of other substances in pulsating blood flow. For example, using the process 1500 described with respect to FIG. 15, absorption coefficients for one or more frequencies that have an intensity level responsive to concentration level of substance may be determined. The biosensor 100 may then detect the substance at the determined one or more frequencies as described herein and determine the concentration levels using the Beer-Lambert principles and the absorption coefficients. The L values and R values may be calculated based on the obtained spectral response. In one aspect, the biosensor 100 may detect various electrolyte concentration levels or blood analyte levels, such as bilirubin and sodium and potassium. In another aspect, the biosensor 100 may detect sodium NACL concentration levels in the arterial blood flow to determine dehydration. In yet another aspect, the biosensor 100 may be configured to detect proteins or abnormal cells or other elements or compounds associated with cancer. In another aspect, the PPG sensor may detect white blood cell counts.

**[0137]** FIG. 31 illustrates a schematic block diagram of an embodiment of a method 3100 for determining concentration levels or indicators of substances in pulsating blood flow in more detail. The biosensor 100 obtains a spectral response signal at a first wavelength and at a second wavelength at 3102. The spectral response signal includes AC and DC components IAC+DC. A low pass filter is applied to the spectral response signal IAC+DC to isolate the DC component 3106 of the spectral response signal at each wavelength at 3104. The AC fluctuation is due to the pulsatile expansion of the arteriolar bed due to the volume increase in arterial blood. In order to measure the AC fluctuation, measurements are taken at different times and a peak detection algorithm or other means is used to determine the diastolic point and the systolic point of the spectral response at 3108. The systolic and diastolic measurements are compared in order to compute the L values using Beer-Lambert equations at 3110. For example, a logarithmic function may be applied to the ratio of  $I_{AC+DC}$  and  $I_{DC}$  to obtain an L value for the first wavelength  $L_{\lambda 1}$  and for the second wavelength  $L_{\lambda 2}$ . The ratio R of the first wavelength  $L_{\lambda 1}$  and for the second wavelength  $L_{\lambda 2}$  may then be calculated at 3112. When multiple frequencies are used to determine a concentration level of one or more substances, the the linear function described herein are applied at 3116, and the one or more concentration levels of the substances or analytes are determined at 3118.

**[0138]** In an embodiment, a substances or analyte may be attached in the blood stream to one or more hemoglobin compounds. The concentration level of the hemoglobin compounds may then need to be subtracted from the concentration level of the substance determined at 3118 to isolate the concentration level of the substance at 3120 from the hemoglobin compounds. For example, nitric oxide (NO) is found in the blood stream in a gaseous form and also attached to hemoglobin compounds. Thus, the measurements at  $L_{390nm}$  to detect nitric oxide may include a concentration level of the hemoglobin compounds as well as nitric oxide. The hemoglobin compound concentration levels may then be determined and subtracted to isolate the nitric oxide concentration levels. This process is discussed in more detail with respect to FIG. 32 below.

**[0139]** FIG. 32 illustrates a schematic block diagram of an exemplary embodiment of a graph 3200 illustrating the extinction coefficients over a range of frequencies for a plurality of hemoglobin compounds. The hemoglobin compounds include, e.g., Oxyhemoglobin [HbO<sub>2</sub>] 3202, Carboxyhemoglobin [HbCO] 3204, Methemoglobin [HbMet] 3206, and reduced hemoglobin fractions [RHb] 3208. As seen in FIG. 32, the biosensor 100 may control the PPG circuit 110 to detect the total concentration of the hemoglobin compounds using a center frequency of 660nm and a range of 1nm to 50nm. A method for determining the relative concentration or composition of different kinds of hemoglobin contained in blood is described in more detail in U.S. Patent No. 6,104,938 issued on August 15, 2000.

**[0140]** Though the above description includes details with respect to pulsating arterial blood flow, the biosensor 100 may use similar techniques described herein for pulsating venous blood flow. The biosensor 100 is positioned on skin tissue over veins, such as on the wrist, and spectral responses obtained from light reflected by or transmitted through the pulsating venous blood flow.

**[0141]** One or more embodiments have been described herein for the non-invasive and continuous biosensor 100. Due to its compact form factor, the biosensor 100 may be configured for measurements on various skin surfaces of a patient, including on a forehead, arm, wrist, abdominal area, chest, leg, ear lobe, finger, toe, ear canal, etc. The biosensor includes one or more sensors for detecting biosensor data, such as a patient's vitals, activity levels, or concentrations of substances in the blood flow of the patient. In particular, the PPG sensor is configured to monitor concentration levels or indicators of one or more substances in the blood flow of the patient. In one aspect, the PPG sensor may non-invasively and continuously detect diabetic parameters, such as insulin resistance, insulin response over time, nitric oxide (NO) levels, glucose levels, and predict diabetic risk or diabetic precursors, in pulsatile arterial blood flow. In another aspect, the PPG sensor may measure vascular health using NO concentration levels. In another aspect, the PPG sensor may detect blood alcohol levels in pulsatile arterial blood flow. In another aspect, the PPG sensor may detect cytochrome

P450 proteins or one or more other liver enzymes or proteins. In another aspect, the PPG sensor may detect digestive parameters, such as digestion phase 1 and 2 responses. The PPG sensor may detect various electrolyte concentration levels or blood analyte levels, such as bilirubin and sodium and potassium. For example, the PPG sensor may detect sodium NACL concentration levels in the arterial blood flow to determine dehydration. In yet another aspect, the PPG sensor may be configured to help diagnose cancer by detecting proteins or abnormal cells or other elements or compounds associated with cancer. In another aspect, the PPG sensor may detect white blood cell counts.

**[0142]** In one or more aspects herein, a processing module or circuit includes at least one processing device, such as a microprocessor, micro-controller, digital signal processor, microcomputer, central processing unit, field programmable gate array, programmable logic device, state machine, logic circuitry, analog circuitry, digital circuitry, and/or any device that manipulates signals (analog and/or digital) based on hard coding of the circuitry and/or operational instructions. A memory is a non-transitory memory device and may be an internal memory or an external memory, and the memory may be a single memory device or a plurality of memory devices. The memory may be a read-only memory, random access memory, volatile memory, non-volatile memory, static memory, dynamic memory, flash memory, cache memory, and/or any non-transitory memory device that stores digital information.

**[0143]** As may be used herein, the term "operable to" or "configurable to" indicates that an element includes one or more of circuits, instructions, modules, data, input(s), output(s), etc., to perform one or more of the described or necessary corresponding functions and may further include inferred coupling to one or more other items to perform the described or necessary corresponding functions. As may also be used herein, the term(s) "coupled", "coupled to", "connected to" and/or "connecting" or "interconnecting" includes direct connection or link between nodes/devices and/or indirect connection between nodes/devices via an intervening item (e.g., an item includes, but is not limited to, a component, an element, a circuit, a module, a node, device, network element, etc.). As may further be used herein, inferred connections (i.e., where one element is connected to another element by inference) includes direct and indirect connection between two items in the same manner as "connected to".

**[0144]** As may be used herein, the terms "substantially" and "approximately" provides an industry-accepted tolerance for its corresponding term and/or relativity between items. Such an industry-accepted tolerance ranges from less than one percent to fifty percent and corresponds to, but is not limited to, frequencies, wavelengths, component values, integrated circuit process variations, temperature variations, rise and fall times, and/or thermal noise. Such relativity between items ranges from a difference of a few percent to magnitude differences.

**[0145]** Note that the aspects of the present disclosure may be described herein as a process that is depicted as a schematic, a flowchart, a flow diagram, a structure diagram, or a block diagram. Although a flowchart may describe the operations as a sequential process, many of the operations can be performed in parallel or concurrently. In addition, the order of the operations may be re-arranged. A process is terminated when its operations are completed. A process may correspond to a method, a function, a procedure, a subroutine, a subprogram, etc. When a process corresponds to a function, its termination corresponds to a return of the function to the calling function or the main function.

**[0146]** The various features of the disclosure described herein can be implemented in different systems and devices without departing from the disclosure. It should be noted that the foregoing aspects of the disclosure are merely examples and are not to be construed as limiting the disclosure. The description of the aspects of the present disclosure is intended to be illustrative, and not to limit the scope of the claims. As such, the present teachings can be readily applied to other types of apparatuses and many alternatives, modifications, and variations will be apparent to those skilled in the art.

**[0147]** In the foregoing specification, certain representative aspects of the invention have been described with reference to specific examples. Accordingly, the scope of the invention should be determined by the claims rather than by merely the examples described.

**[0148]** Furthermore, certain benefits, other advantages and solutions to problems have been described above with regard to particular embodiments; however, any benefit, advantage, solution to a problem, or any element that may cause any particular benefit, advantage, or solution to occur or to become more pronounced are not to be construed as critical, required, or essential features or components of any or all the claims.

**[0149]** As used herein, the terms "comprise," "comprises," "comprising," "having," "including," "includes" or any variation thereof, are intended to reference a nonexclusive inclusion, such that a process, method, article, composition or apparatus that comprises a list of elements does not include only those elements recited, but may also include other elements not expressly listed or inherent to such process, method, article, composition, or apparatus. Other combinations and/or modifications of the above-described structures, arrangements, applications, proportions, elements, materials, or components used in the practice of the present invention, in addition to those not specifically recited, may be varied or otherwise particularly adapted to specific environments, manufacturing specifications, design parameters, or other operating requirements without departing from the general principles of the same.

**[0150]** Moreover, reference to an element in the singular is not intended to mean "one and only one" unless specifically so stated, but rather "one or more." Unless specifically stated otherwise, the term "some" refers to one or more. All structural and functional equivalents to the elements of the various aspects described throughout this disclosure that are known or later come to be known to those of ordinary skill in the art are expressly incorporated herein by reference

and are intended to be encompassed by the claims. Moreover, nothing disclosed herein is intended to be dedicated to the public regardless of whether such disclosure is explicitly recited in the claims.

## Claims

### 1. A biosensor (100), comprising:

a PPG circuit (110) configured to:

emit light (126) having at least a first wavelength and a second wavelength directed at outer epidermal layer of skin tissue of a patient;  
generate a first spectral response for light detected around the first wavelength from the outer epidermal layer of the skin tissue of the patient;  
generate a second spectral response for light detected around the second frequency from the outer epidermal layer of the skin tissue of the patient;

a processing circuit (102) configured to:

isolate a systolic point and a diastolic point in the first spectral response and obtain a value  $L_{\lambda 1}$  using a ratio of the systolic point and the diastolic point in the first spectral response;  
isolate a systolic point and a diastolic point in the second spectral response and obtain a value  $L_{\lambda 2}$  using a ratio of the systolic point and diastolic point in the second spectral response;  
obtain a value  $R_{\lambda 1, \lambda 2}$  from a ratio of the value  $L_{\lambda 1}$  and the value  $L_{\lambda 2}$ ;  
obtain a blood glucose concentration level from a calibration table using the value  $R_{\lambda 1, \lambda 2}$ ; and  
transmit the blood glucose concentration level for display.

2. The biosensor (100) of claim 1, wherein the first spectral response generated for light detected around the first wavelength is responsive to nitric oxide (NO) levels generated during an insulin response after caloric intake in pulsating blood flow.

3. The biosensor (100) of claim 1, wherein the value  $R_{\lambda 1, \lambda 2}$  obtained from the ratio of the value  $L_{\lambda 1}$  and the value  $L_{\lambda 2}$  is responsive to a base insulin resistance factor measured after a period of fasting and correlates to an indicator of diabetic risk of the patient.

4. The biosensor (100) of claim 3, wherein the processing circuit (102) is further configured to output the indicator of the diabetic risk of the patient obtained using the base insulin resistance factor.

5. The biosensor (100) of claim 4, wherein the processing circuit (102) is further configured to output an indicator of no diabetic risk in response to determining a base insulin resistance factor that correlates to average NO levels of a sample population.

6. The biosensor (100) of claim 5, wherein the processing circuit (102) is further configured to output an indicator of a diabetic condition in response to determining a base insulin resistance factor that correlates to NO levels of at least less than 25% of average NO levels of a sample population.

7. The biosensor (100) of claim 6, wherein the first frequency is approximately 390nm and wherein the second frequency has a low absorption coefficient for NO.

8. The biosensor (100) of claim 5, wherein the PPG circuit (110) is configured to generate the first spectral response for light detected at the wavelength of 390nm and for wavelengths in a range of 1nm to 50 nm around 390nm.

9. The biosensor (100) of claim 8, wherein the calibration table includes a range of  $R_{\lambda 1, \lambda 2}$  values and correlated blood glucose levels, wherein the calibration table is generated using blood glucose level measurements obtained from a sample population during a same measurement period as the range of  $R_{\lambda 1, \lambda 2}$  values is obtained by the biosensor (100) for the sample population.



## Patentansprüche

### 1. Biosensor (100), umfassend

einen PPG-Schaltkreis, der dazu bestimmt ist:

Licht mit mindestens einer ersten Wellenlänge und einer zweiten Wellenlänge zu emittieren, die auf die äußere Epidermisschicht des Hautgewebes eines Patienten gerichtet sind;  
eine erste Spektralempfindlichkeit für Licht zu erzeugen, das um die erste Wellenlänge herum von der äußeren Epidermisschicht des Hautgewebes eines Patienten detektiert wird;  
eine zweite Spektralempfindlichkeit für Licht zu erzeugen, das um die zweite Frequenz herum von der äußeren Epidermisschicht des Hautgewebes eines Patienten detektiert wird;

eine Verarbeitungseinheit (102), die dazu bestimmt ist:

einen systolischen Punkt und einen diastolischen Punkt in der ersten Spektralempfindlichkeit zu isolieren und anhand eines Verhältnisses des systolischen Punkts und des diastolischen Punkts in der ersten Spektralempfindlichkeit einen Wert  $L_{\lambda 1}$  zu ermitteln;  
einen systolischen Punkt und einen diastolischen Punkt in der zweiten Spektralempfindlichkeit zu isolieren und anhand eines Verhältnisses des systolischen Punkts und des diastolischen Punkts in der zweiten Spektralempfindlichkeit einen Wert  $L_{\lambda 2}$  zu ermitteln;  
anhand eines Verhältnisses des Wertes  $L_{\lambda 1}$  und des Wertes  $L_{\lambda 2}$  einen Wert  $R_{\lambda 1, \lambda 2}$  zu ermitteln;  
aus einer Kalibrierungstabelle mittels des Wertes  $R_{\lambda 1, \lambda 2}$  einen Blutzuckerspiegel zu ermitteln; und  
den Blutzuckerspiegel zur Anzeige zu übermitteln.

2. Biosensor (100) nach Anspruch 1, wobei die erste Spektralempfindlichkeit, die für Licht erzeugt wird, das um die erste Wellenlänge herum detektiert wird, für Stickoxid-(NO)-Werte empfindlich ist, die nach einer Kalorienzufuhr während einer Insulinausschüttung in der pulsierenden Blutströmung erzeugt werden.

3. Biosensor (100) nach Anspruch 1, wobei der anhand des Verhältnisses des Wertes  $L_{\lambda 1}$  und des Wertes  $L_{\lambda 2}$  ermittelte Wert  $R_{\lambda 1, \lambda 2}$  für einen Basisinsulinresistenzfaktor empfindlich ist, der nach einem Fastenzeitraum gemessen wird und mit einem Indikator für das Diabetesrisiko des Patienten korreliert.

4. Biosensor (100) nach Anspruch 3, wobei die Verarbeitungseinheit (102) weiterhin dazu bestimmt ist, den Indikator für das Diabetesrisiko des Patienten auszugeben, der anhand des Basisinsulinresistenzfaktors ermittelt worden ist.

5. Biosensor (100) nach Anspruch 4, wobei die Verarbeitungseinheit (102) weiterhin dazu bestimmt ist, als Antwort auf das Ermitteln eines Basisinsulinresistenzfaktors, der mit durchschnittlichen NO-Werten einer Stichprobenpopulation korreliert, einen Indikator für kein Diabetesrisiko auszugeben.

6. Biosensor (100) nach Anspruch 5, wobei die Verarbeitungseinheit (102) weiterhin dazu bestimmt ist, als Antwort auf das Ermitteln eines Basisinsulinresistenzfaktors, der mit NO-Werten von mindestens weniger als 25% der durchschnittlichen NO-Werte einer Stichprobenpopulation korreliert, einen Indikator für einen diabetischen Zustand auszugeben.

7. Biosensor (100) nach Anspruch 6, wobei die erste Frequenz etwa 390nm beträgt und die zweite Frequenz einen niedrigeren Absorptionskoeffizienten für NO aufweist.

8. Biosensor (100) nach Anspruch 5, wobei der PPG-Schaltkreis (110) dazu bestimmt ist, die erste Spektralempfindlichkeit für Licht zu erzeugen, das bei der Wellenlänge von 390nm detektiert wird, und für Wellenlängen im Bereich von 1nm bis 50nm um 390nm herum.

9. Biosensor (100) nach Anspruch 8, wobei die Kalibrierungstabelle einen Bereich von  $R_{\lambda 1, \lambda 2}$ -Werten und korrelierten Blutzuckerspiegelwerten enthält, wobei die Kalibrierungstabelle anhand von Blutzuckermesswerten erzeugt wird, die von einer Stichprobenpopulation während desselben Messzeitraumes ermittelt werden, in dem die  $R_{\lambda 1, \lambda 2}$ -Werte von dem Biosensor (100) für die Stichprobenpopulation ermittelt werden.

## Revendications

### 1. Un biocapteur (100), comprenant:

un circuit PPG (110) configuré pour:

émettre une lumière (126) ayant au moins une première longueur d'onde et une deuxième longueur d'onde dirigée vers la couche épidermique externe du tissu cutané d'un patient;  
généraliser une première réponse spectrale pour la lumière détectée autour de la première longueur d'onde de la couche épidermique externe du tissu cutané du patient;  
généraliser une deuxième réponse spectrale pour la lumière détectée autour de la deuxième fréquence provenant de la couche épidermique externe du tissu cutané du patient;

un circuit de traitement (102) configuré pour:

isoler un point systolique et un point diastolique dans la première réponse spectrale et obtenir une valeur  $L_{\lambda 1}$  en utilisant un rapport entre le point systolique et le point diastolique dans la première réponse spectrale;  
isoler un point systolique et un point diastolique dans la deuxième réponse spectrale et obtenir une valeur  $L_{\lambda 2}$  en utilisant un rapport entre le point systolique et le point diastolique dans la deuxième réponse spectrale;  
obtenir une valeur  $R_{\lambda 1, \lambda 2}$  à partir d'un rapport entre la valeur  $L_{\lambda 1}$  et la valeur  $L_{\lambda 2}$ ;  
obtenir un niveau de concentration de glucose dans le sang à partir d'un tableau d'étalonnage utilisant la valeur  $R_{\lambda 1, \lambda 2}$ ; et  
transmettre le niveau de concentration de glucose dans le sang pour affichage.

2. Biocapteur (100) selon la revendication 1, dans lequel la première réponse spectrale générée pour la lumière détectée autour de la première longueur d'onde est sensible aux niveaux d'oxyde nitrique (NO) générés pendant une réponse insulinaire après l'apport calorique dans un flux sanguin pulsé.

3. Biocapteur (100) selon la revendication 1, dans lequel la valeur  $R_{\lambda 1, \lambda 2}$  obtenue à partir du rapport de la valeur  $L_{\lambda 1}$  et de la valeur  $L_{\lambda 2}$  est sensible à un facteur de résistance à l'insuline de base mesuré après une période de jeûne et est corrélée à un indicateur du risque diabétique du patient.

4. Biocapteur (100) selon la revendication 3, dans lequel le circuit de traitement (102) est en outre configuré pour produire l'indicateur du risque diabétique du patient obtenu en utilisant le facteur de résistance à l'insuline de base.

5. Biocapteur (100) selon la revendication 4, dans lequel le circuit de traitement (102) est en outre configuré pour produire un indicateur d'absence de risque diabétique en réponse à la détermination d'un facteur de résistance à l'insuline de base qui est corrélé aux niveaux moyens de NO d'une population échantillon.

6. Biocapteur (100) selon la revendication 5, dans lequel le circuit de traitement (102) est en outre configuré pour produire un indicateur d'absence de condition diabétique en réponse à la détermination d'un facteur de résistance à l'insuline de base qui est corrélé aux niveaux moyens de NO au moins inférieurs à 25 % des niveaux moyens de NO d'une population échantillon.

7. Biocapteur (100) selon la revendication 6, dans lequel la première fréquence est d'environ 390 nm et dans lequel la deuxième fréquence a un faible coefficient d'absorption pour le NO.

8. Biocapteur (100) selon la revendication 5, dans lequel le circuit PPG (110) est configuré pour généraliser la première réponse spectrale pour la lumière détectée à la longueur d'onde de 390 nm et pour les longueurs d'onde dans une gamme de 1 nm à 50 nm autour de 390 nm.

9. Biocapteur (100) selon la revendication 8, dans lequel le tableau d'étalonnage comprend une plage de  $R_{\lambda 1, \lambda 2}$  valeurs et des niveaux de glucose sanguin corrélés, dans lequel le tableau d'étalonnage est généré en utilisant des mesures de niveau de glucose sanguin obtenues à partir d'une population échantillon pendant une même période de mesure que la plage de  $R_{\lambda 1, \lambda 2}$  valeurs est obtenue par le biocapteur (100) pour la population échantillon.

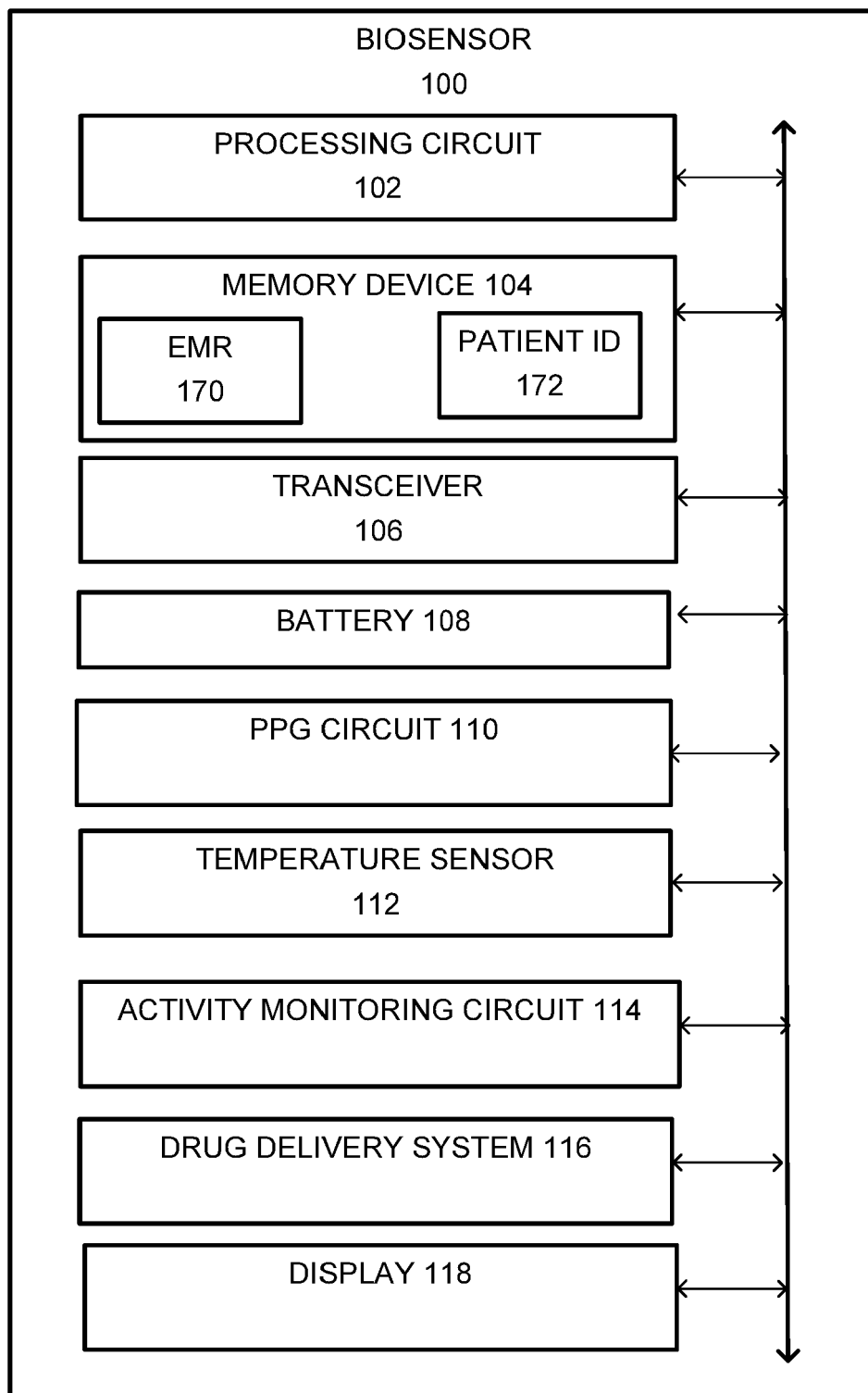


FIG. 1

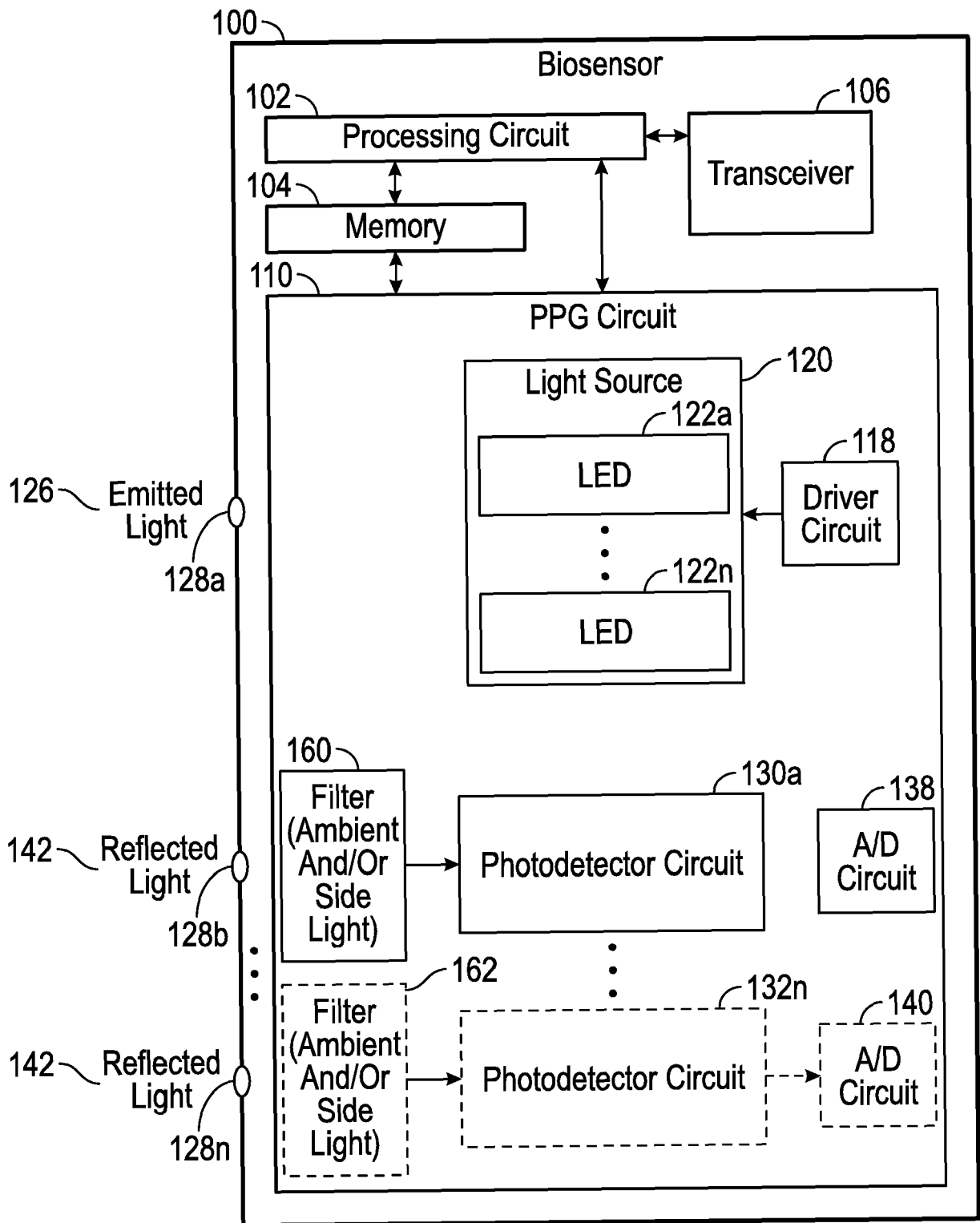


FIG. 2

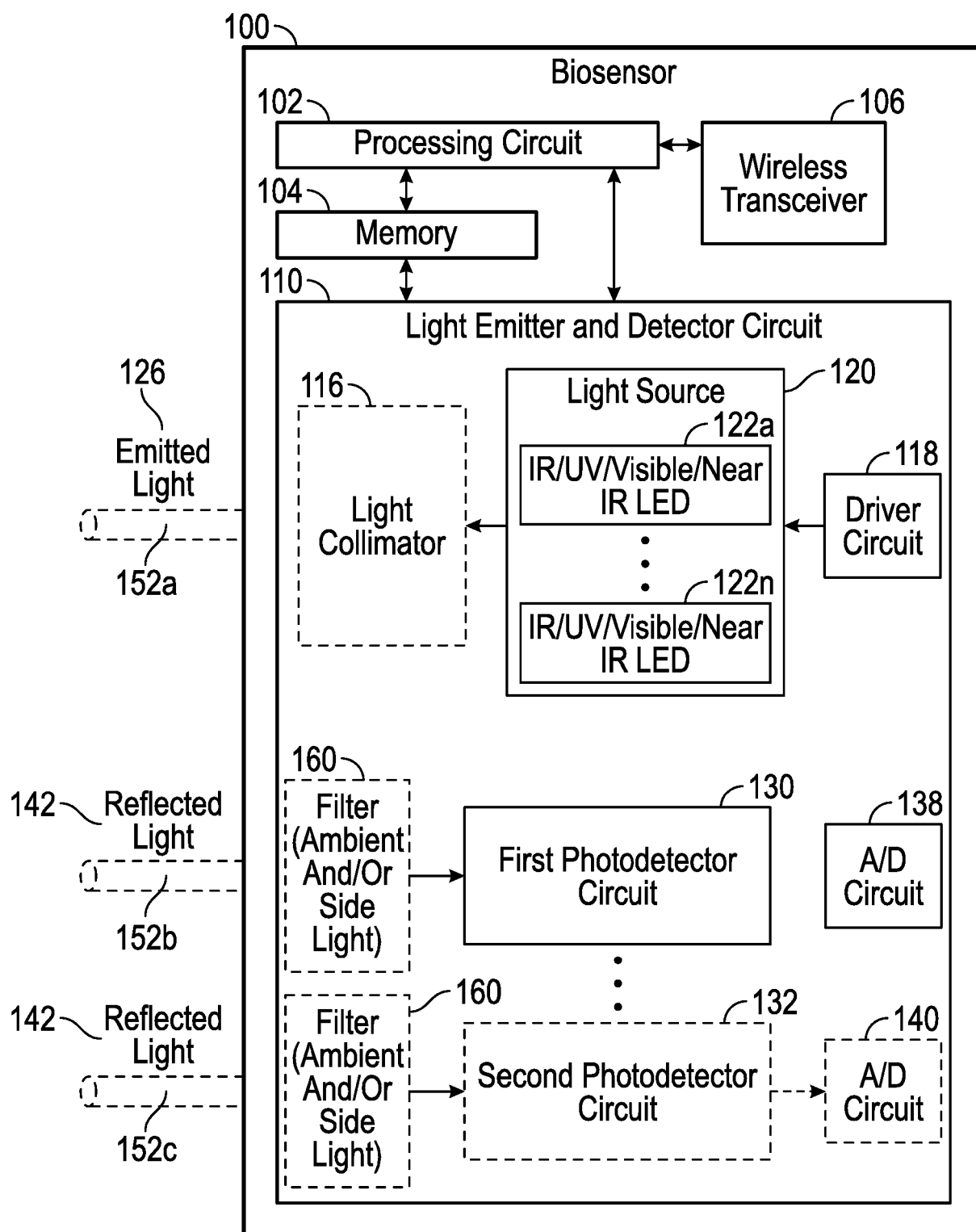
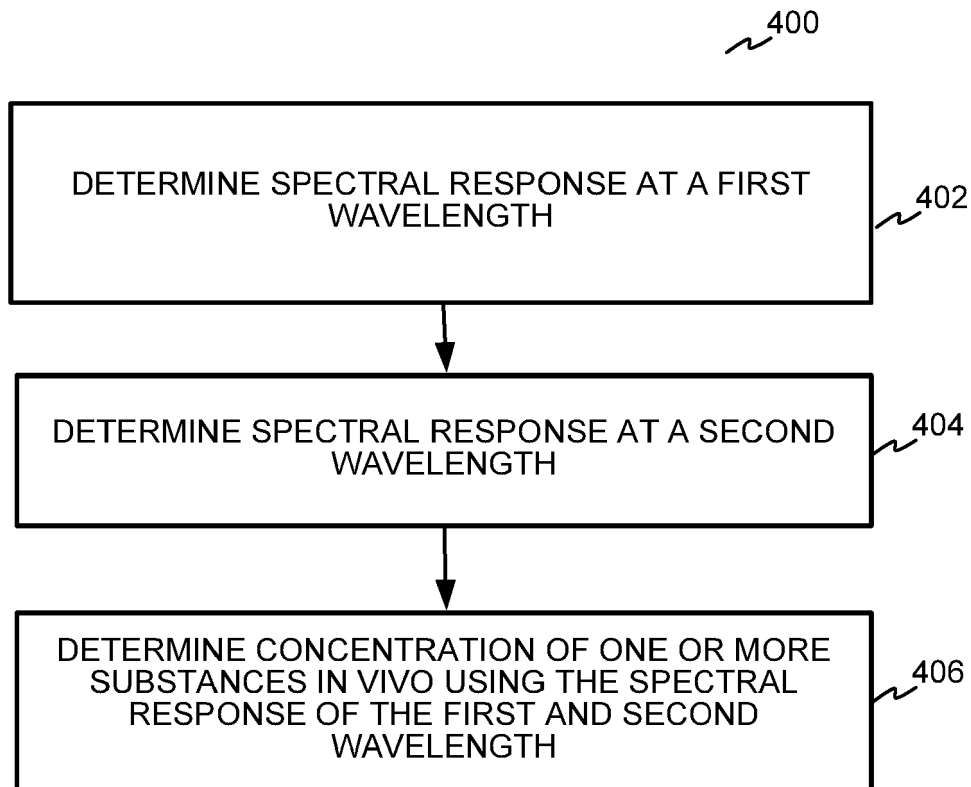


FIG. 3



**FIG. 4**

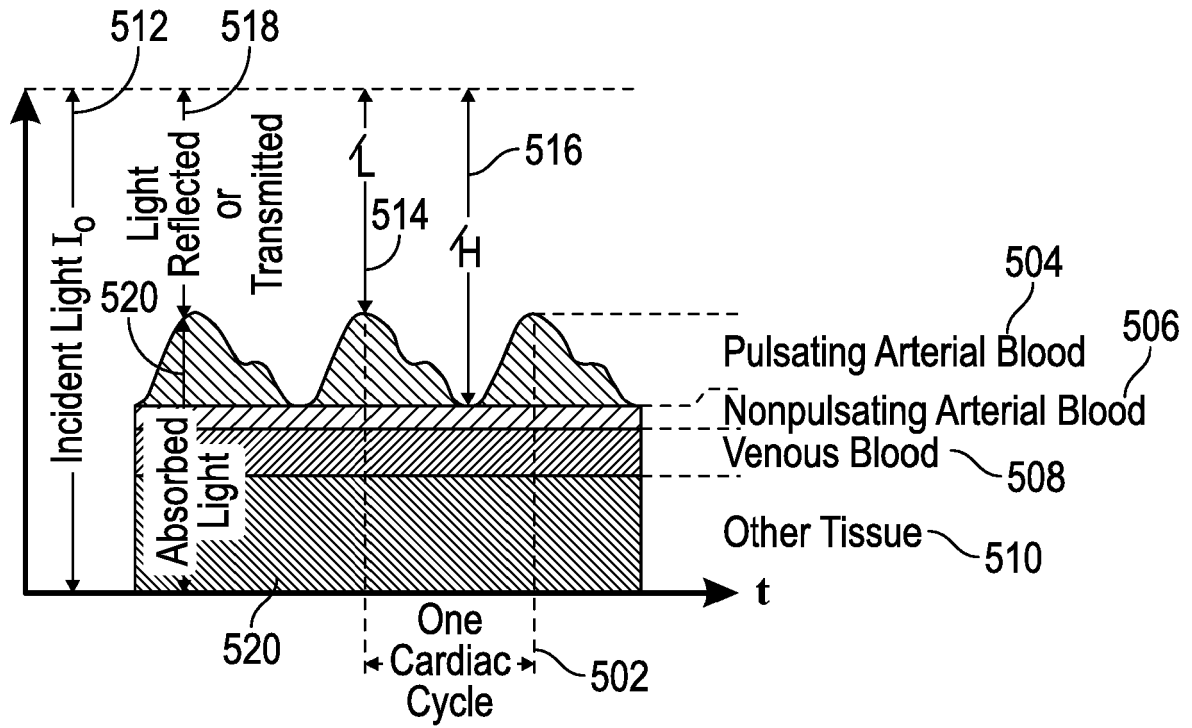


FIG. 5A

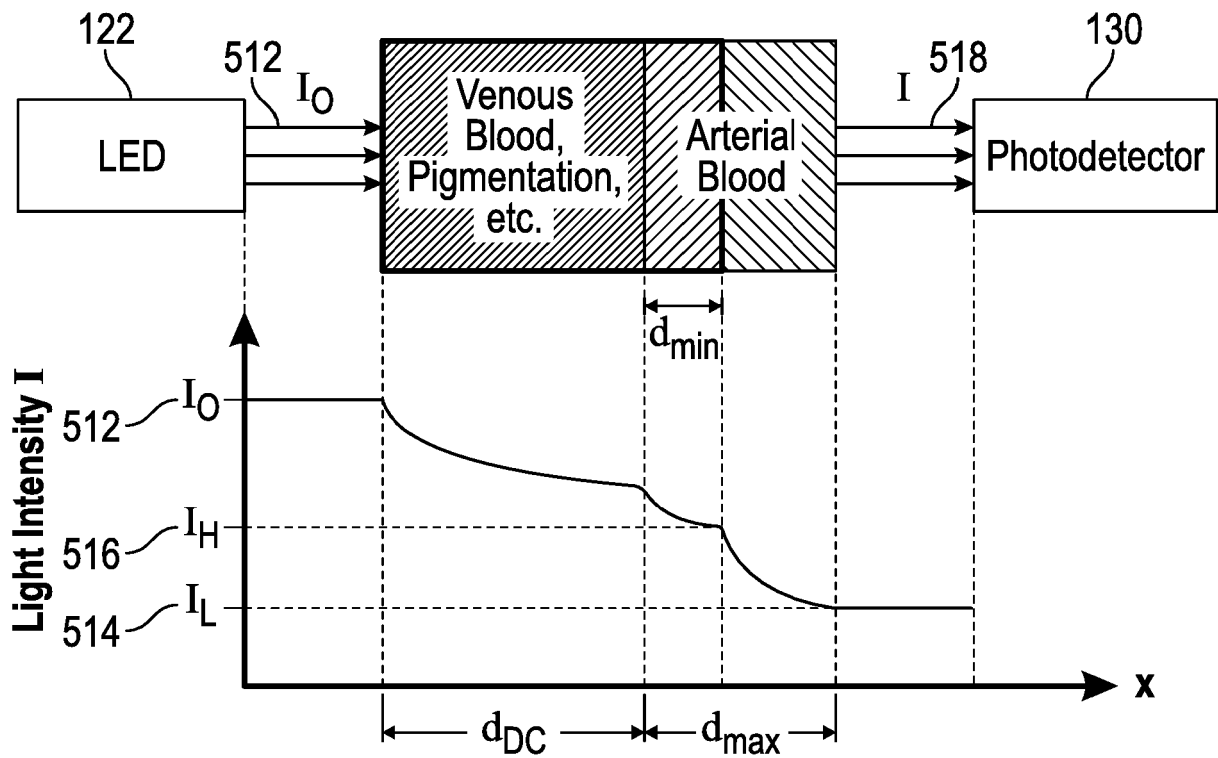
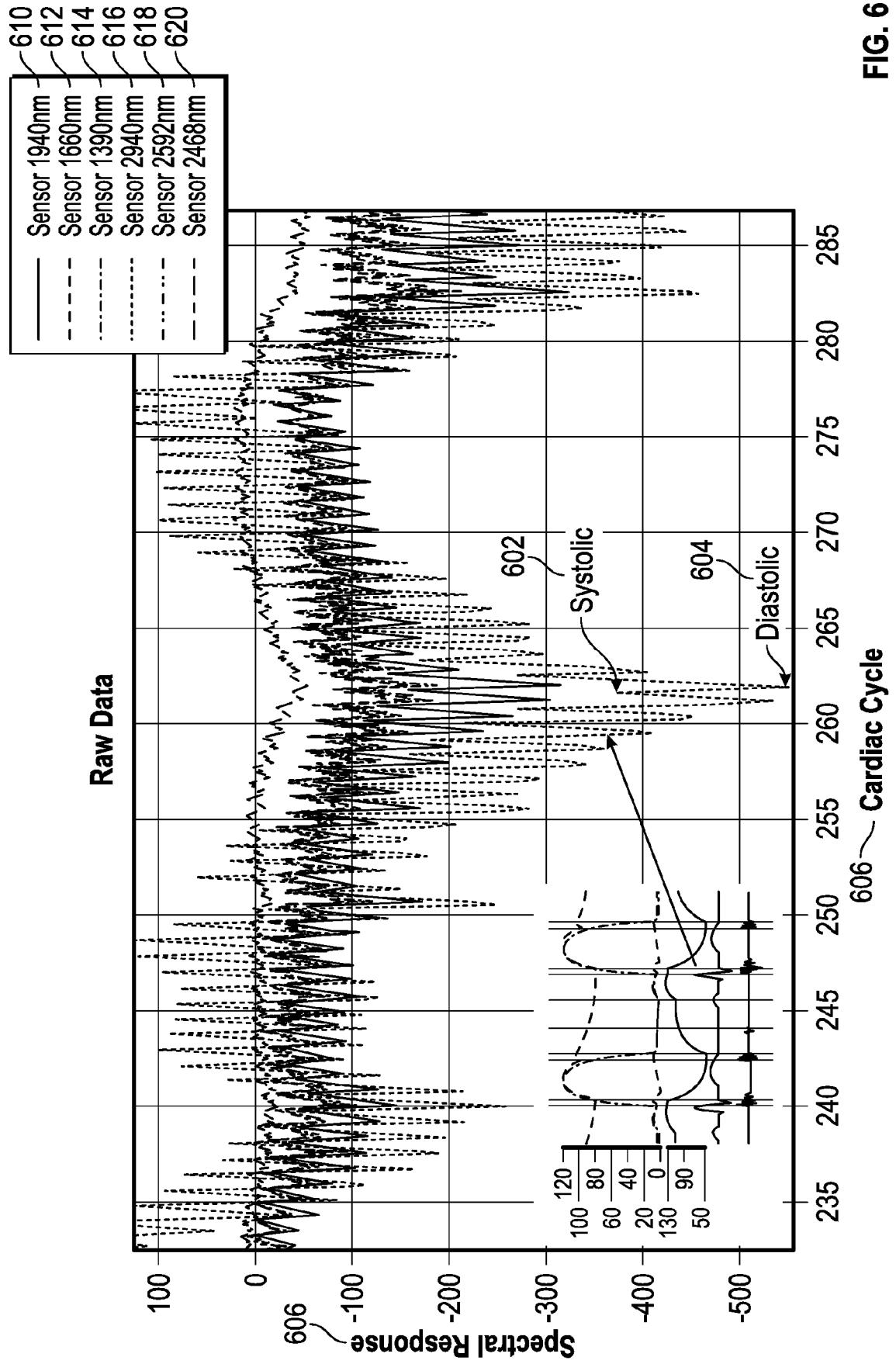
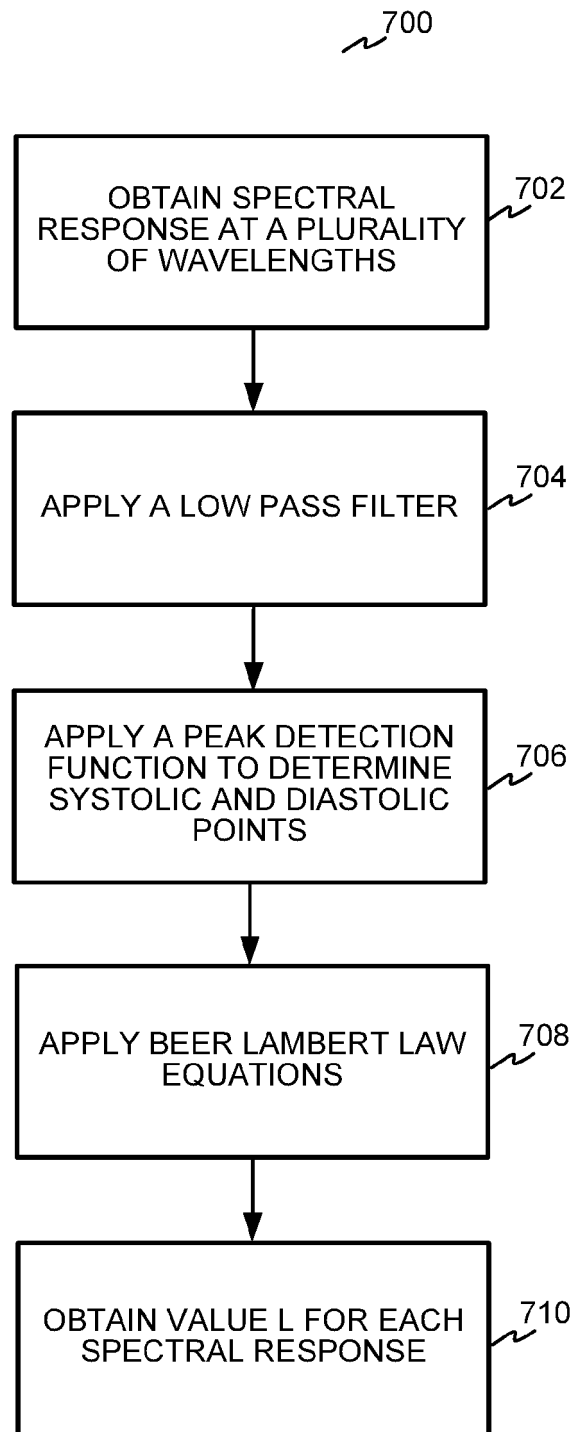


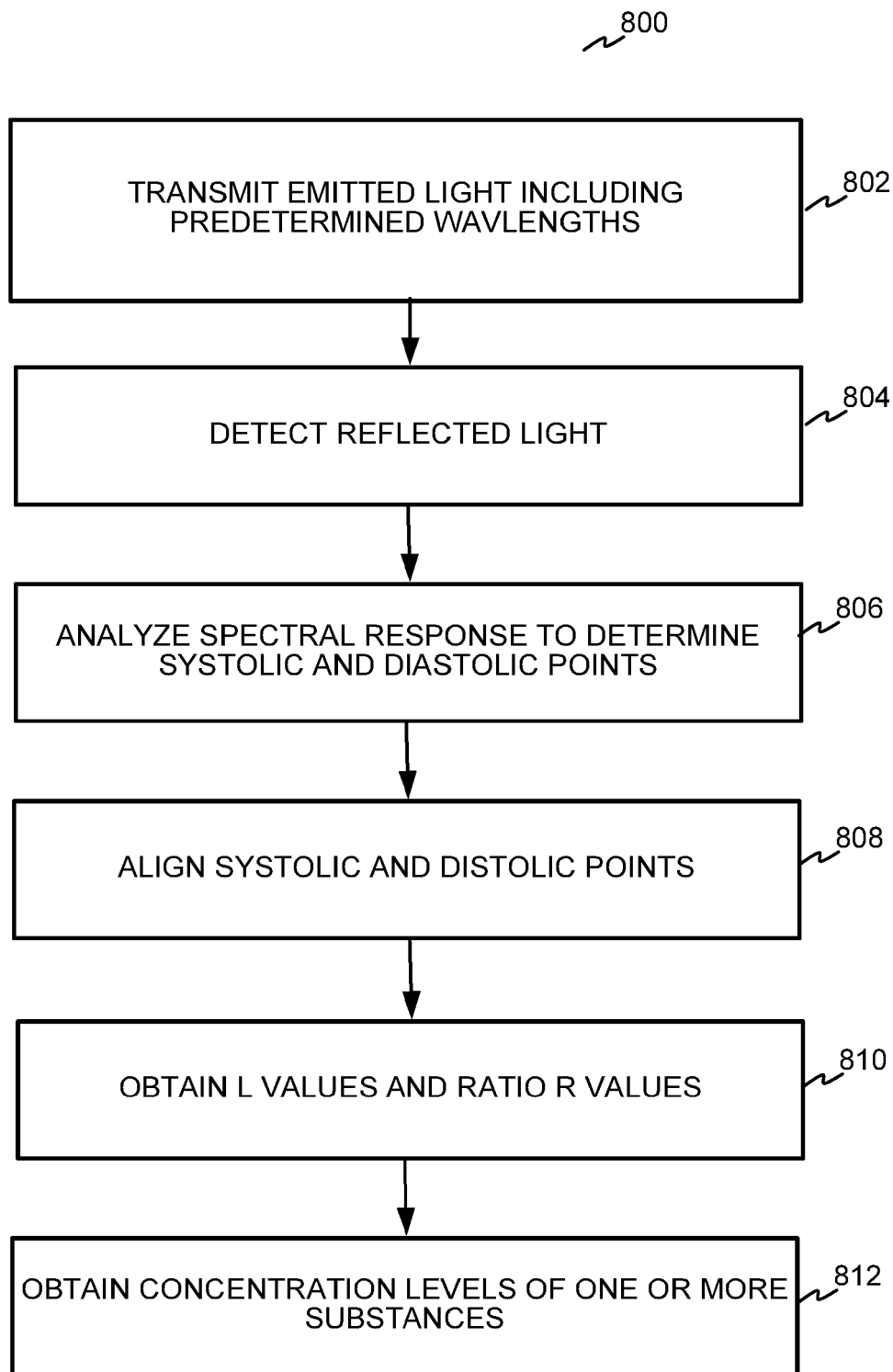
FIG. 5B







**FIG. 7**



**FIG. 8**

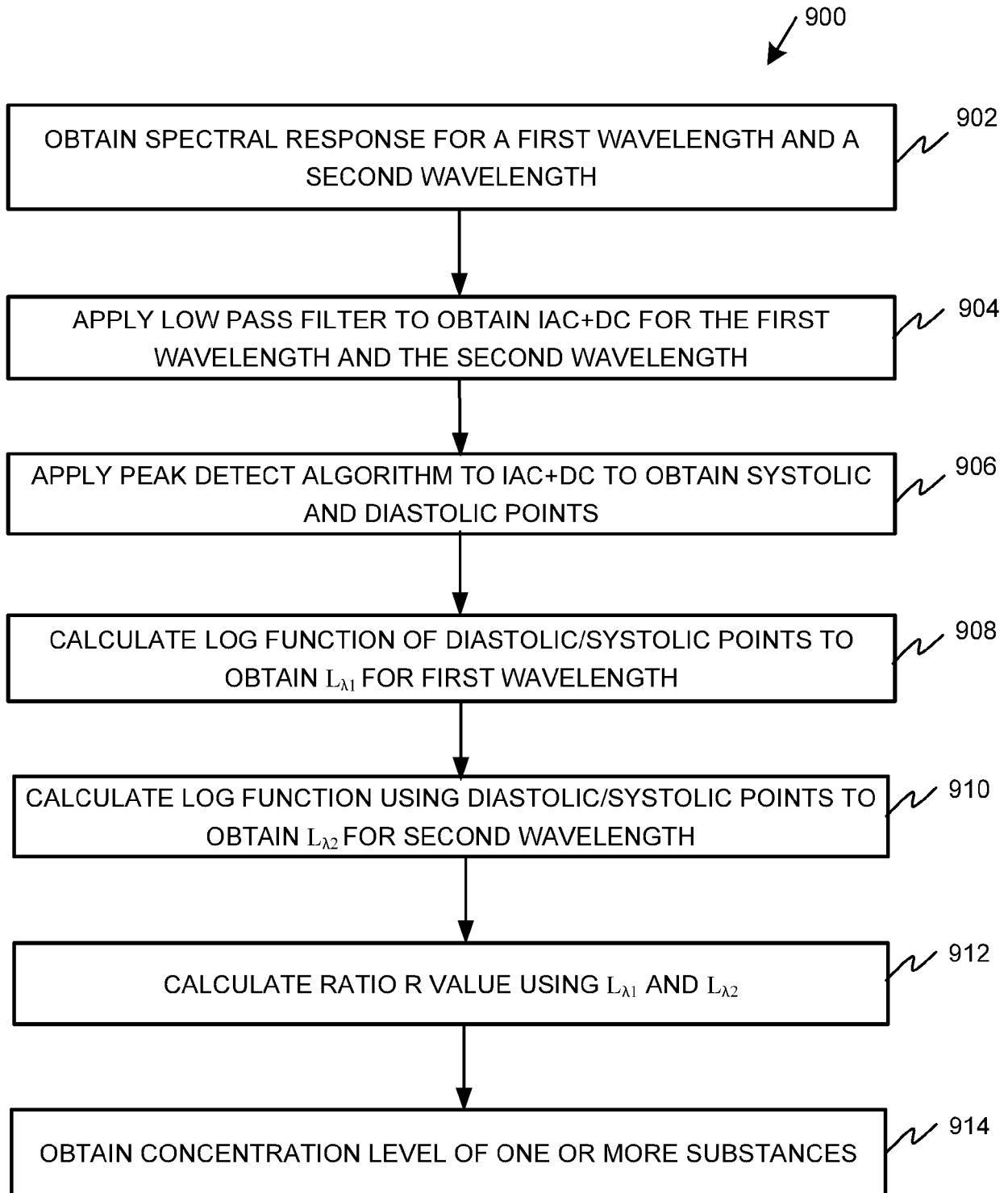


FIG. 9

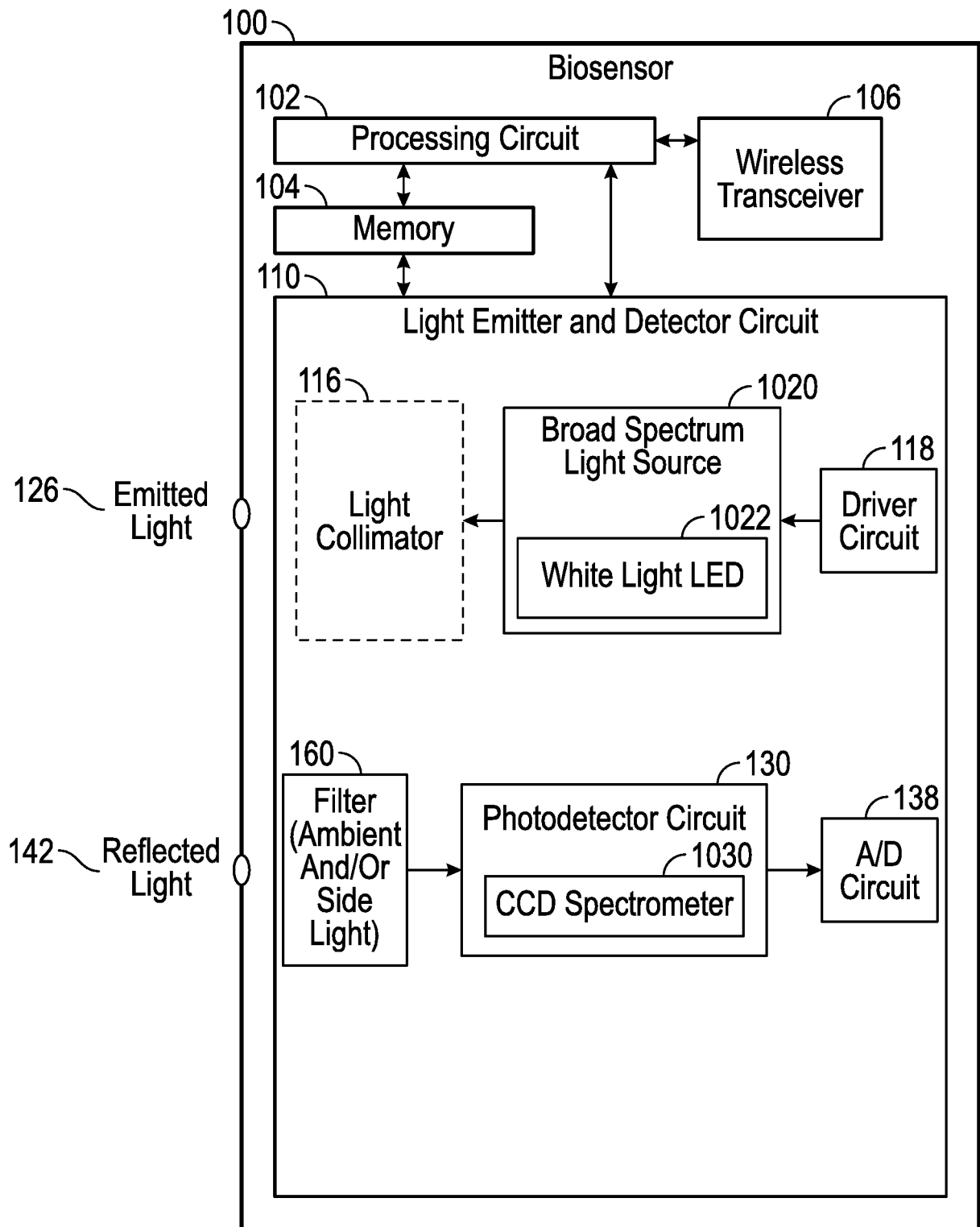
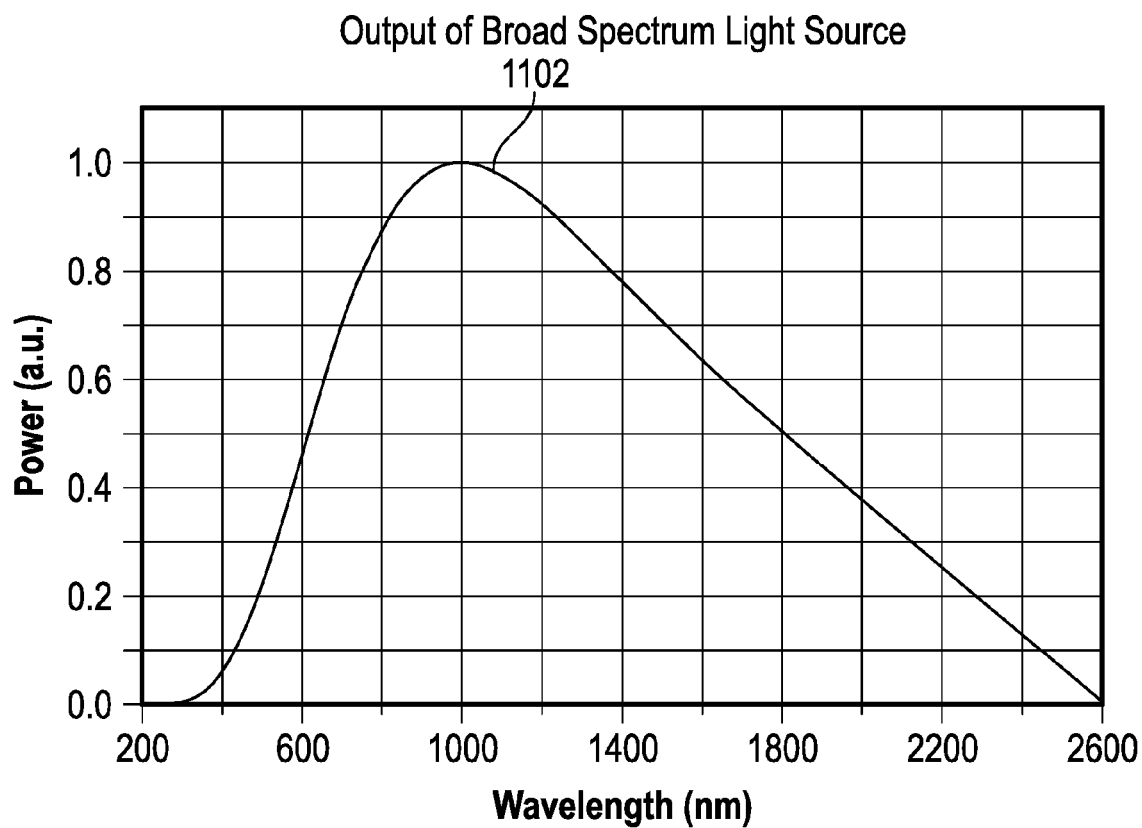
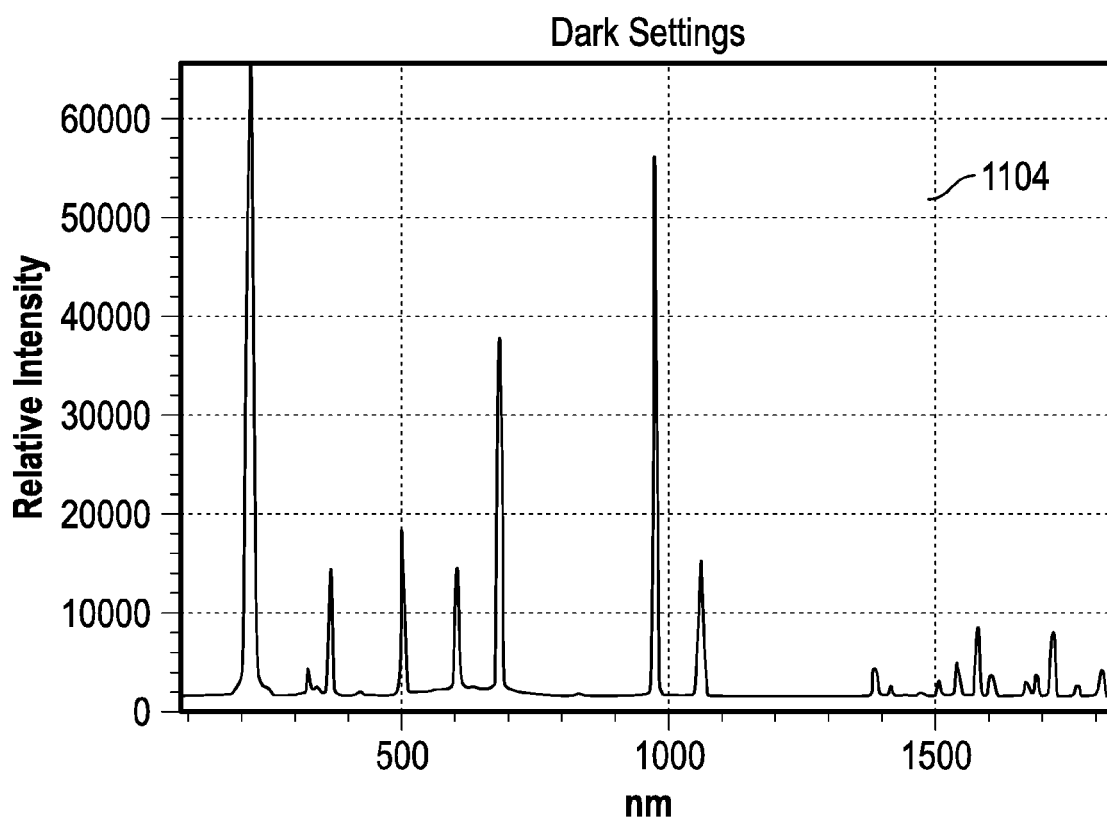


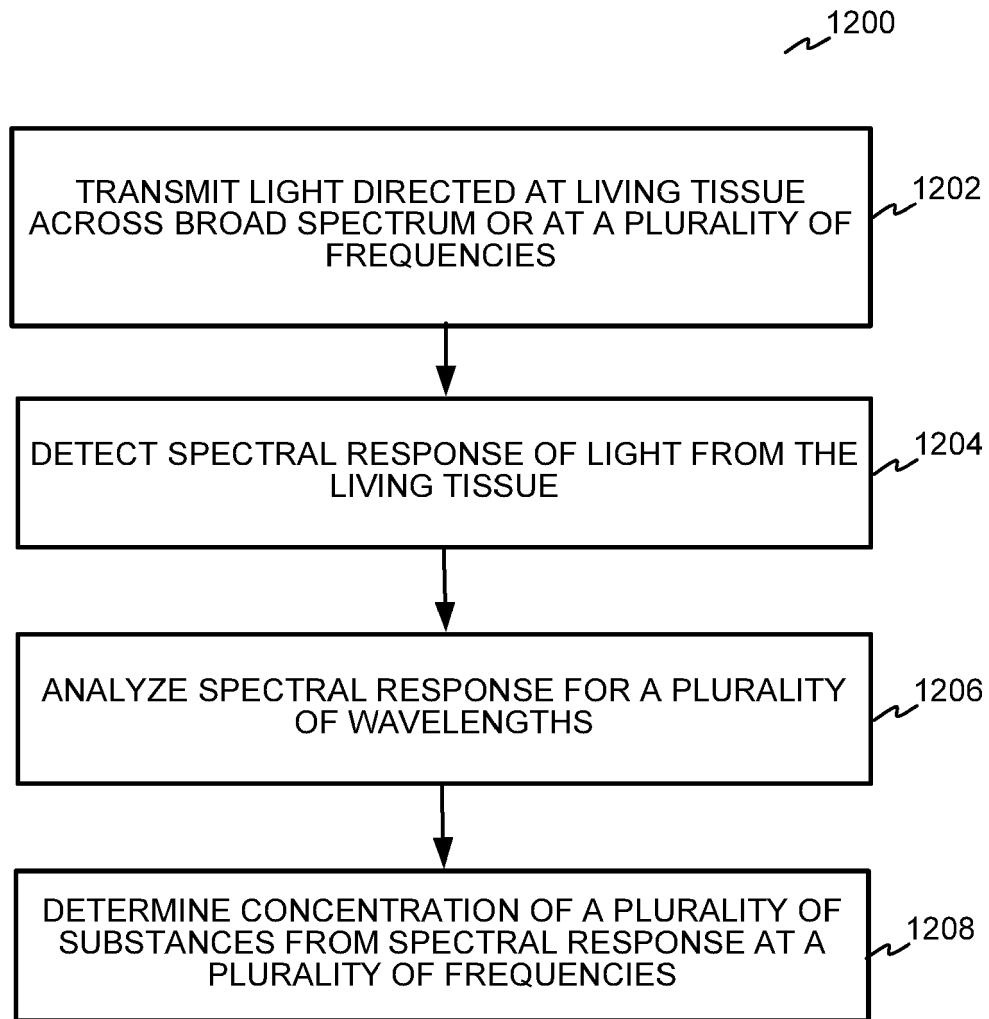
FIG. 10



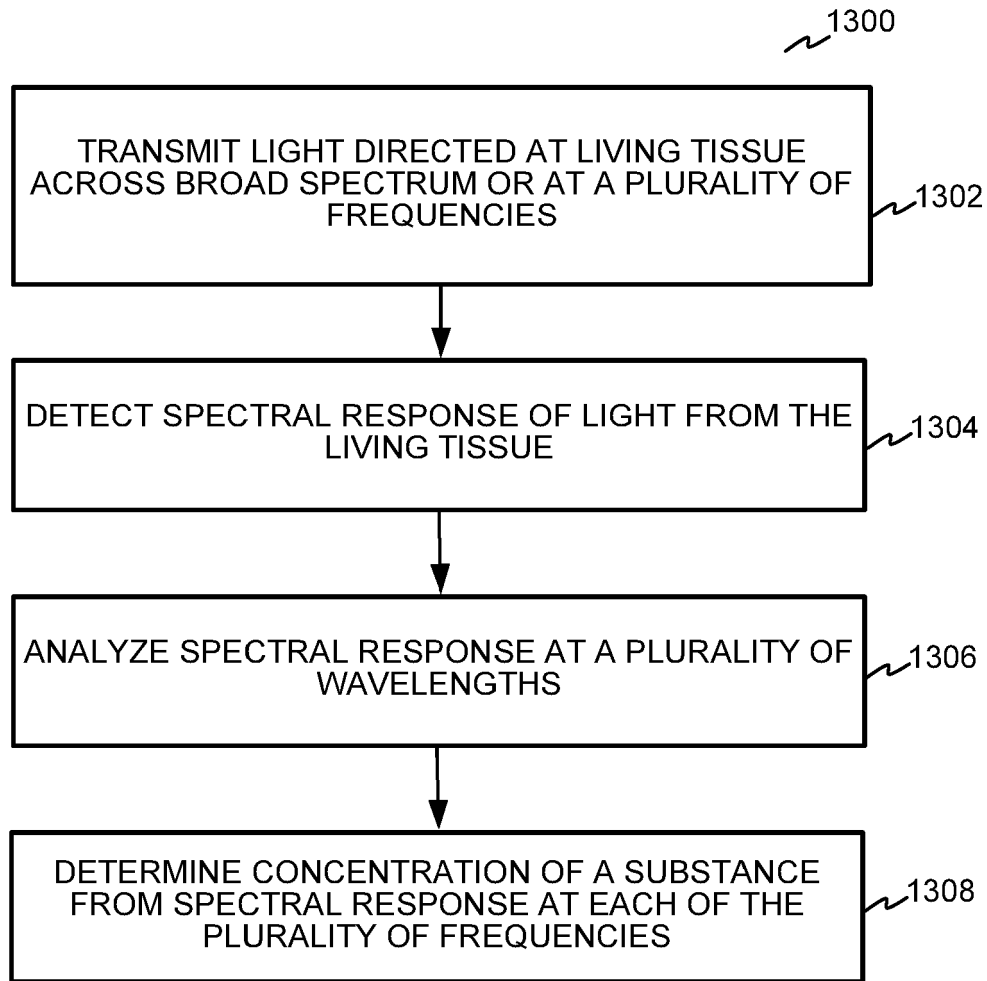
**FIG. 11A**



**FIG. 11B**



**FIG. 12**



**FIG. 13**

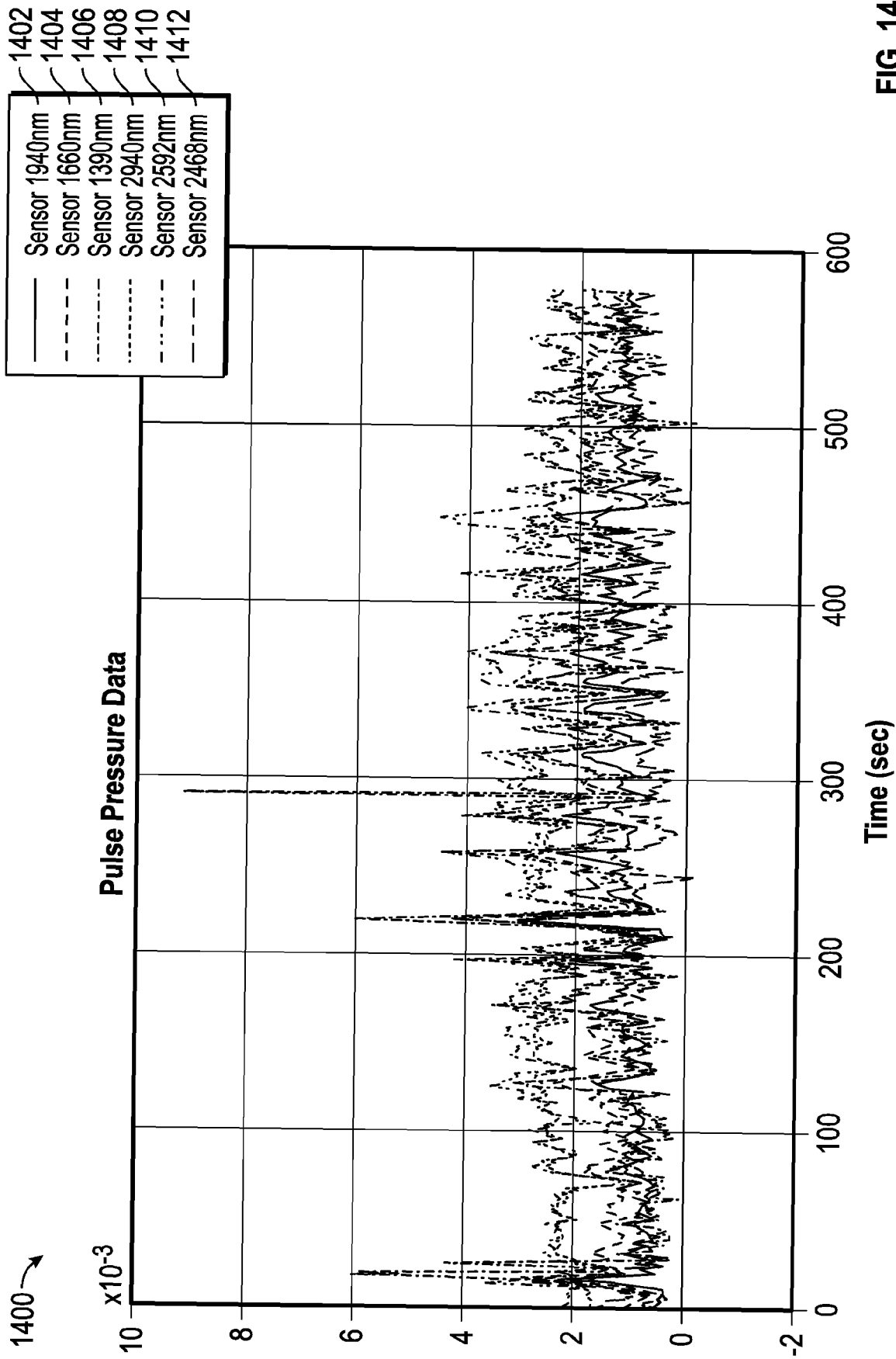
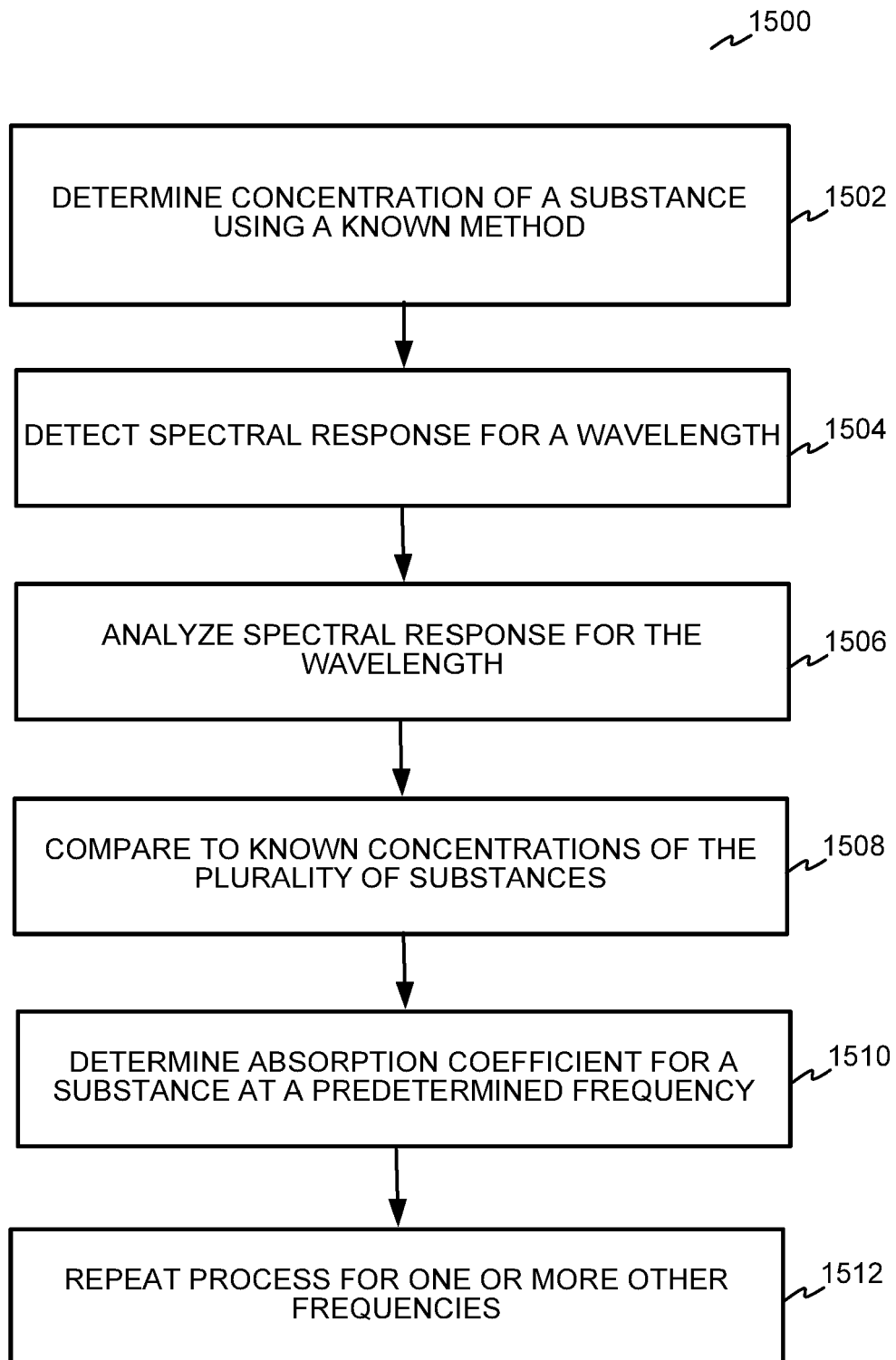


FIG. 14





**FIG. 15**

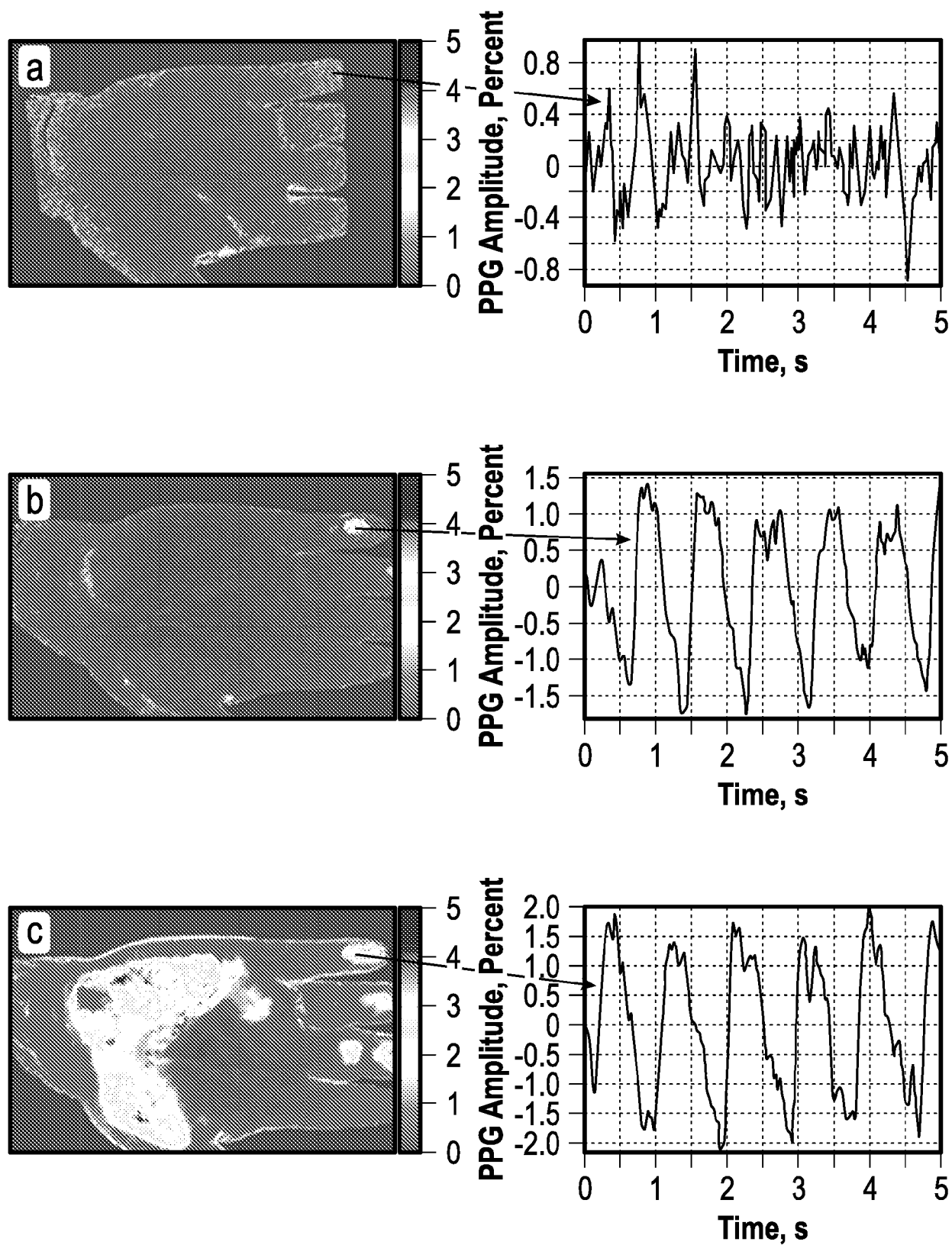


FIG. 16

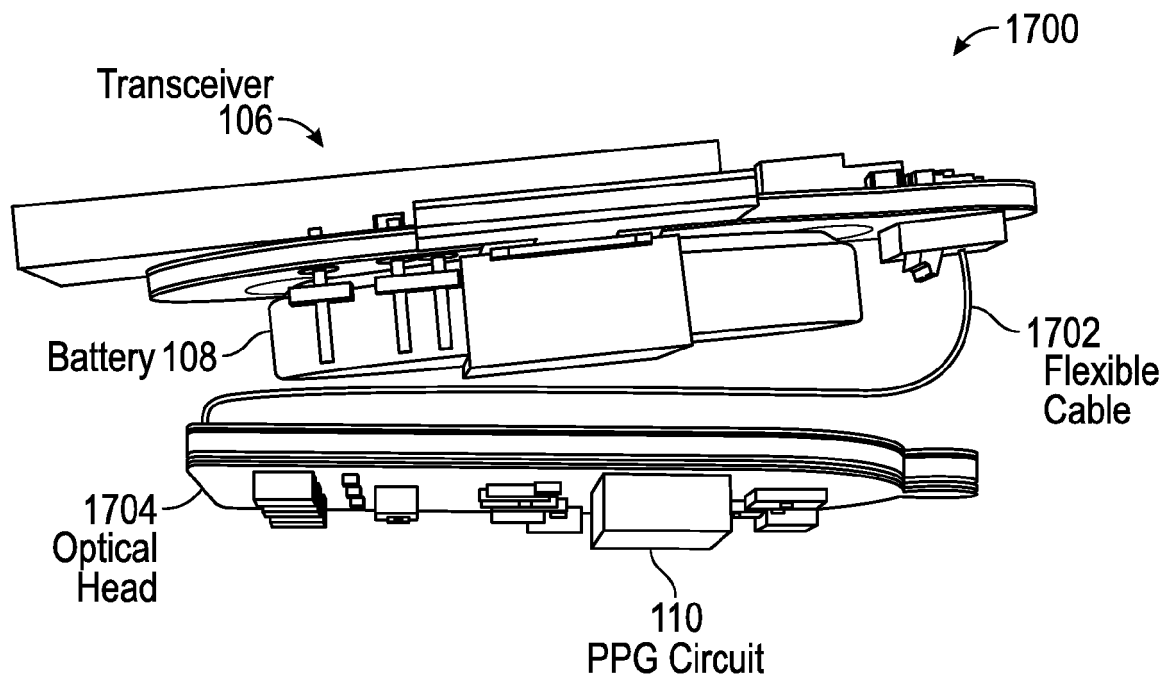


FIG. 17A

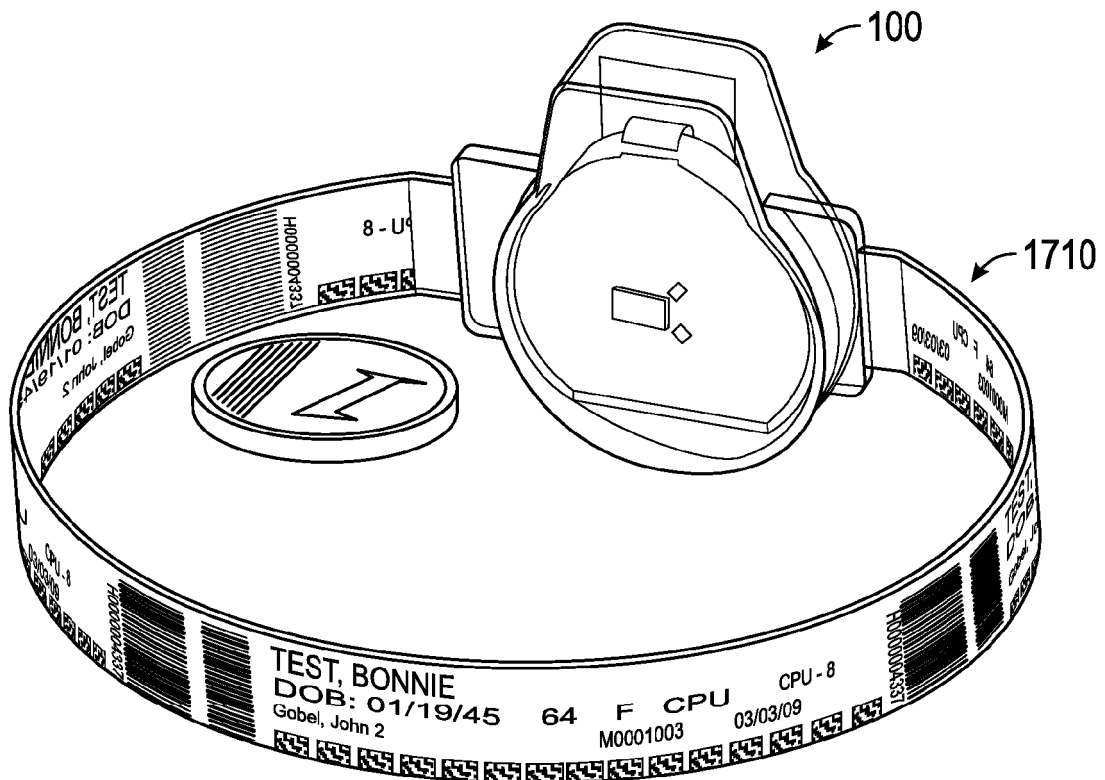
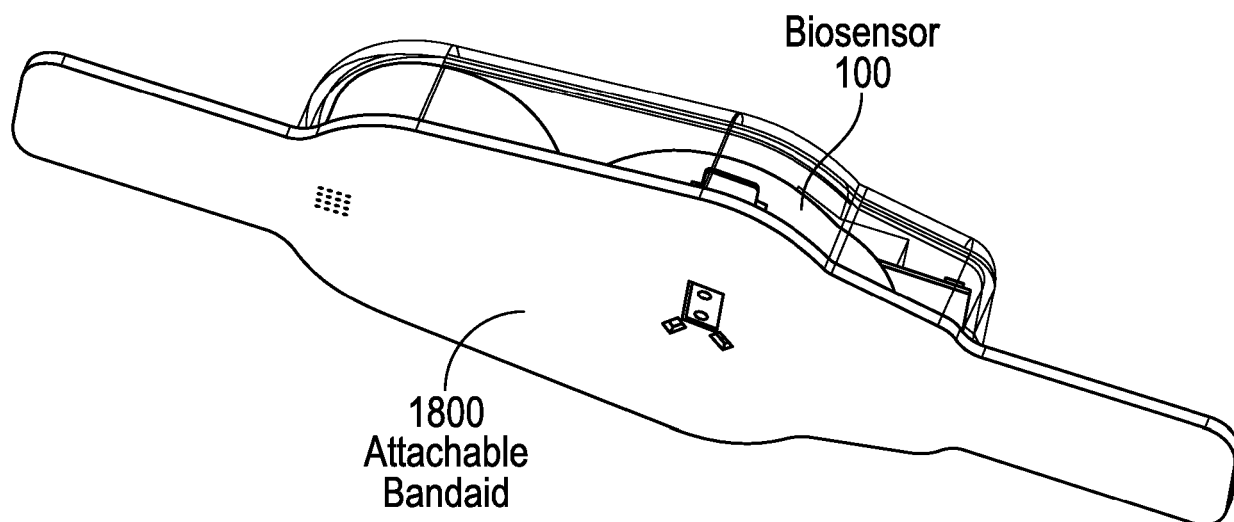
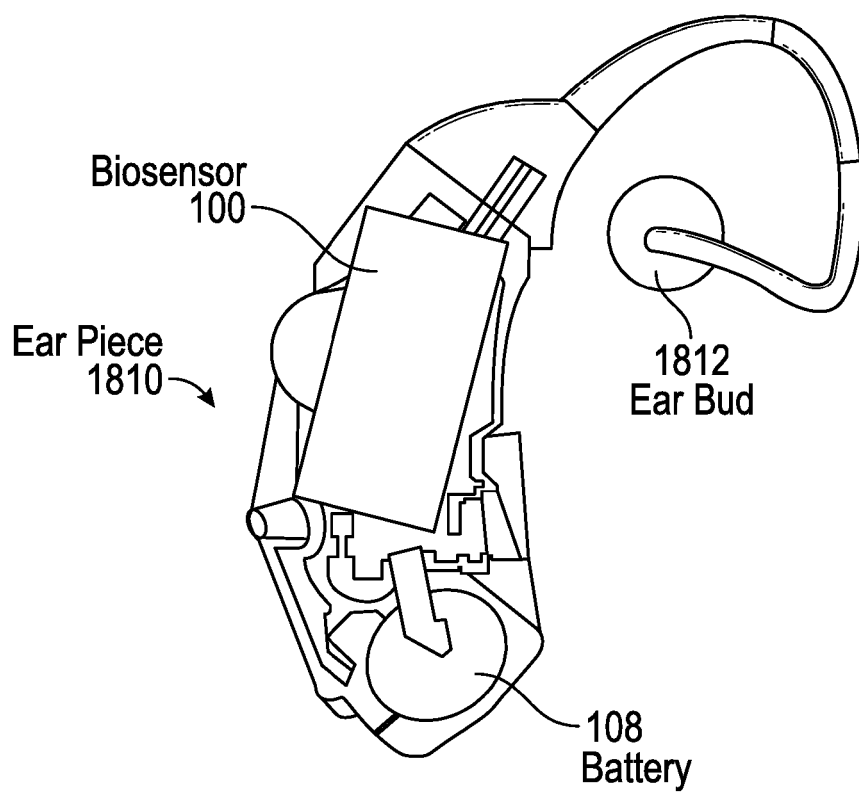


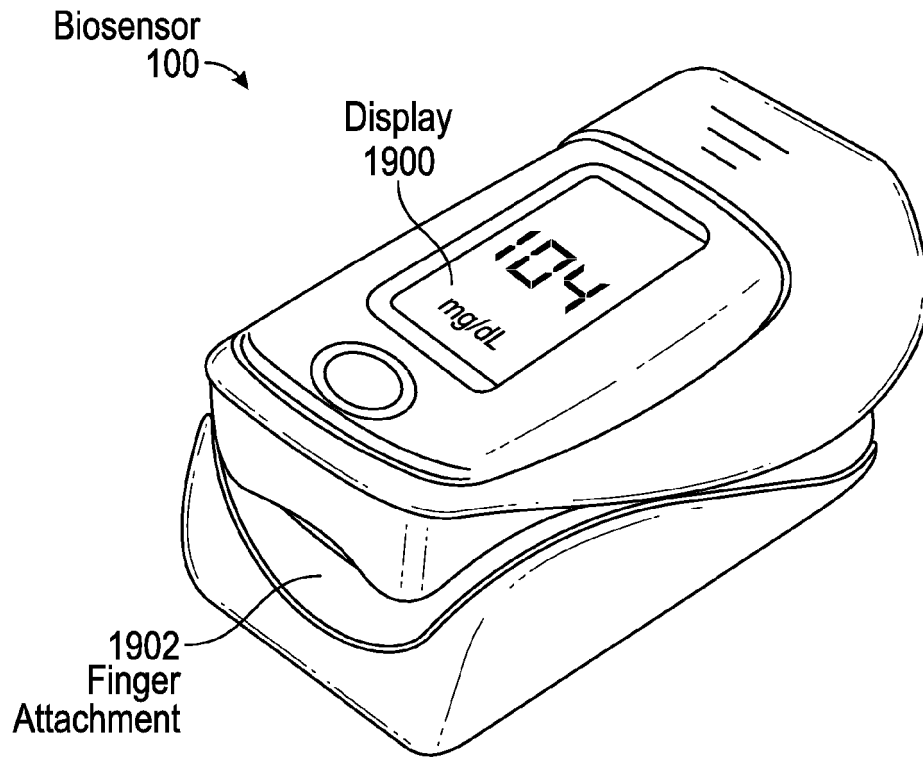
FIG. 17B



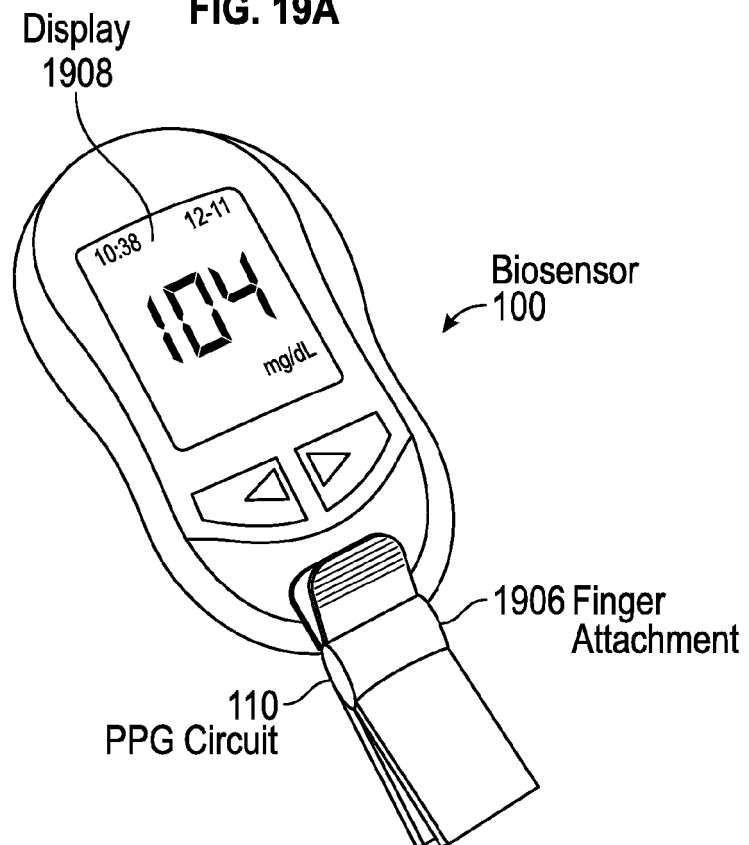
**FIG. 18A**



**FIG. 18B**



**FIG. 19A**



**FIG. 19B**

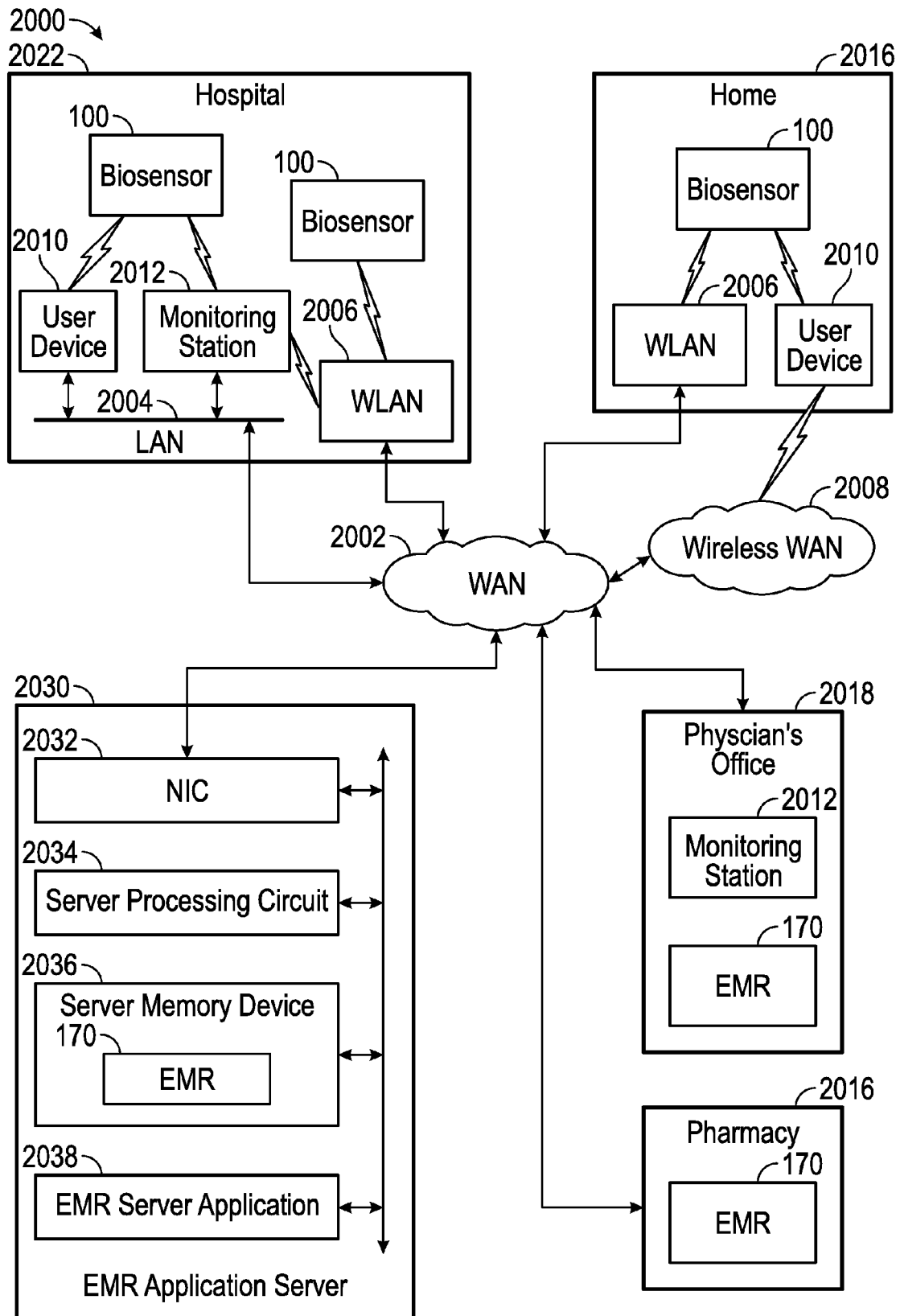
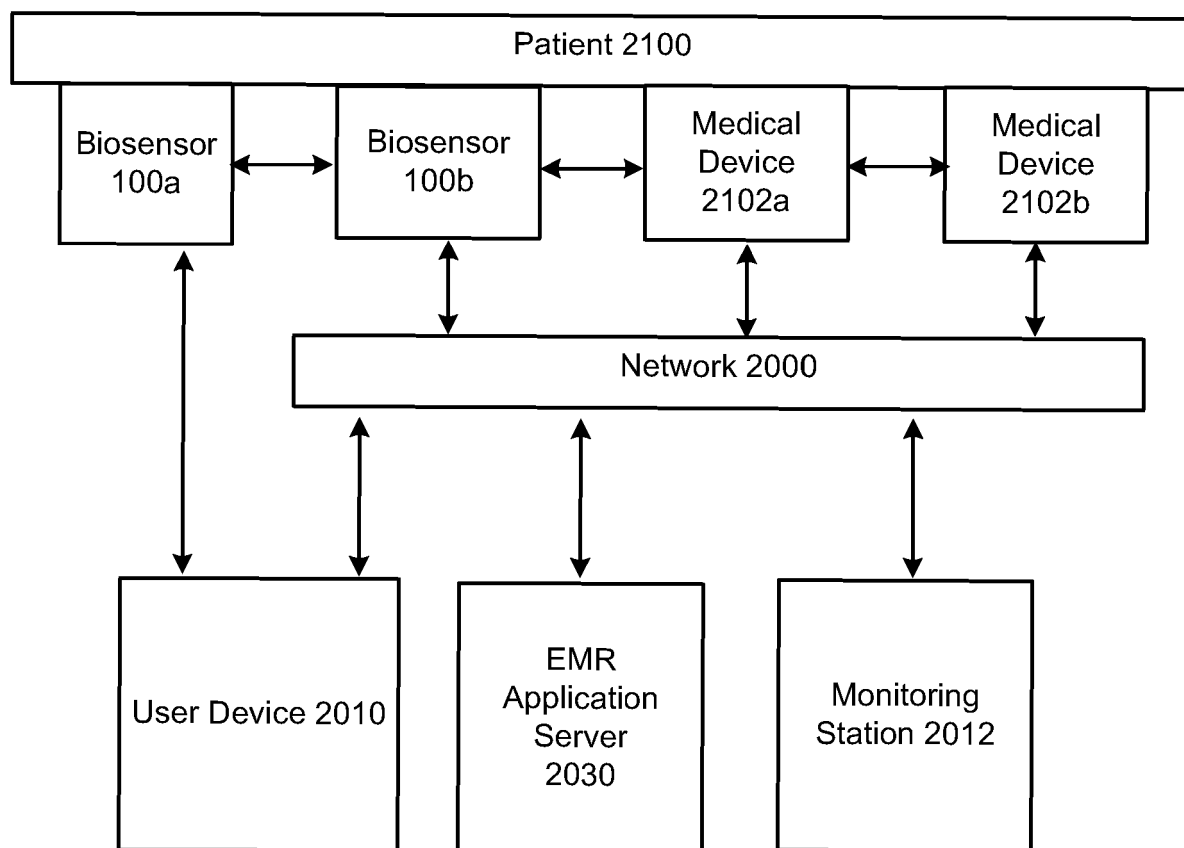
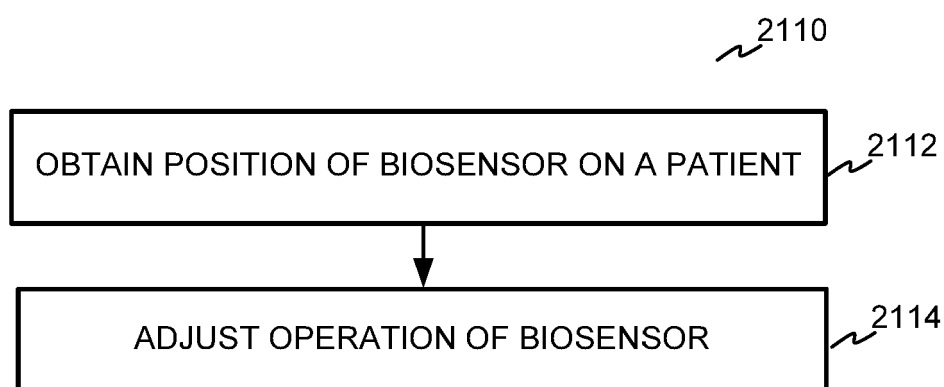


FIG. 20



**FIG. 21A**



**FIG. 21B**

## 42 Year Old Female - Healthy

2200

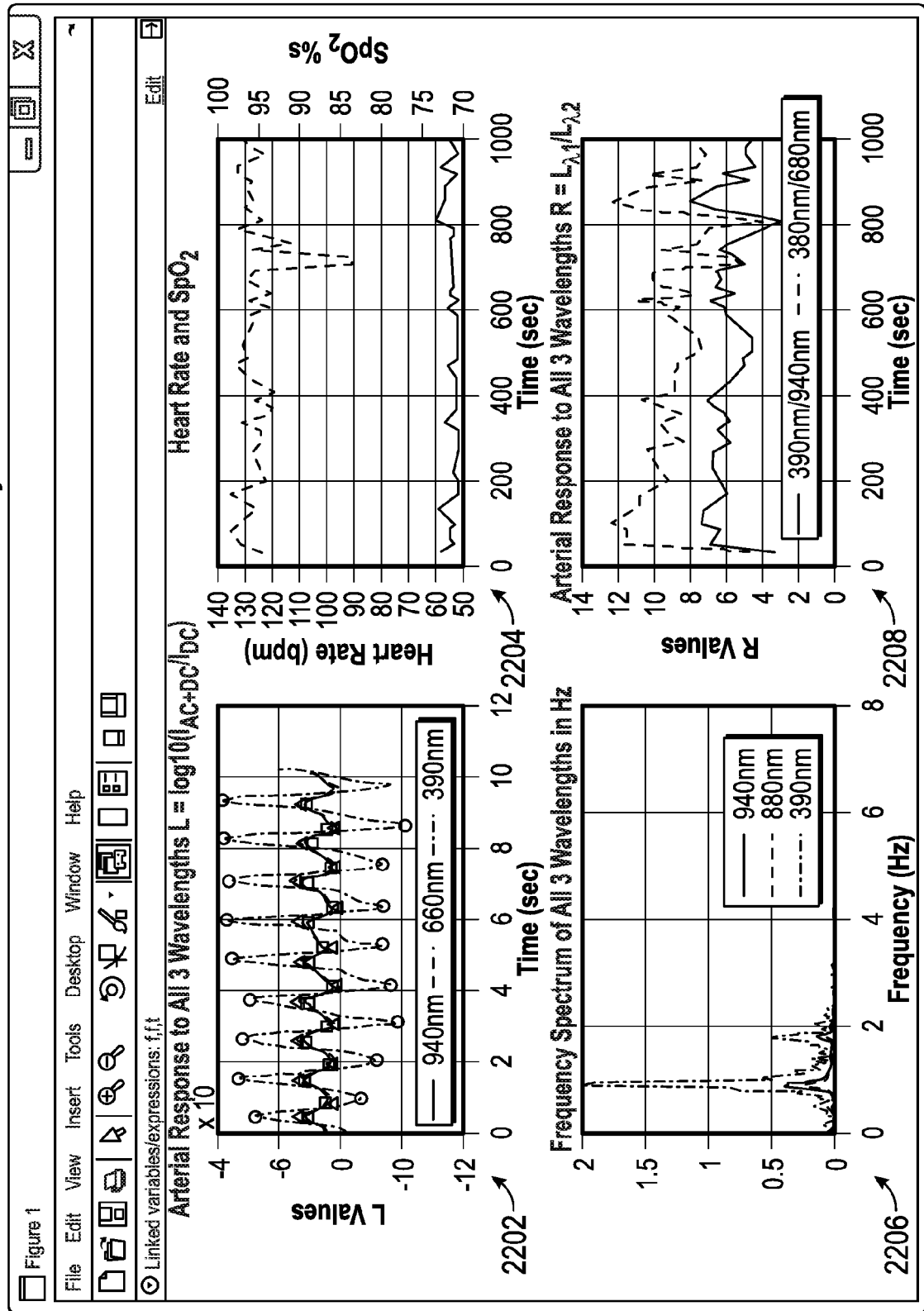
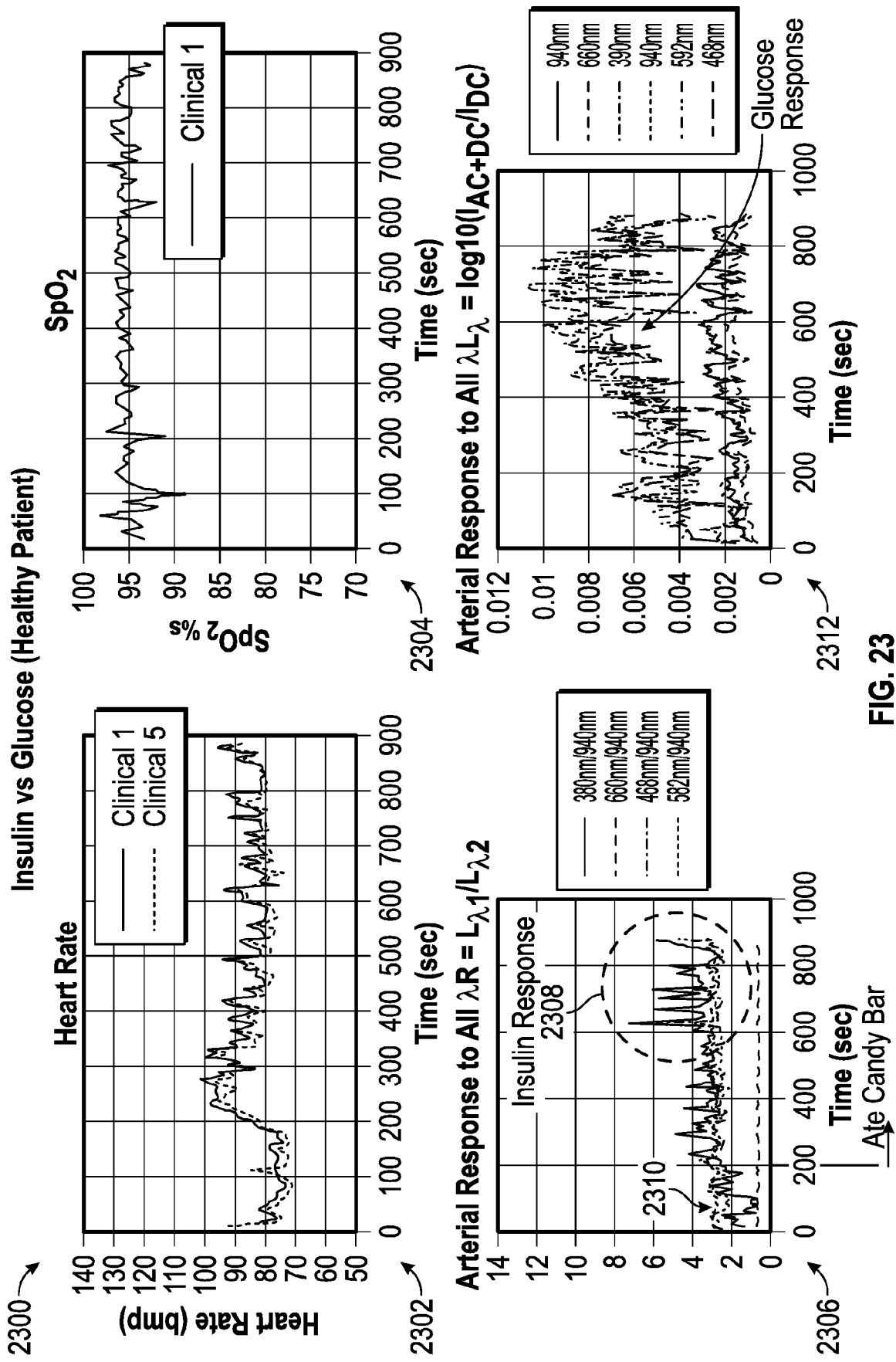
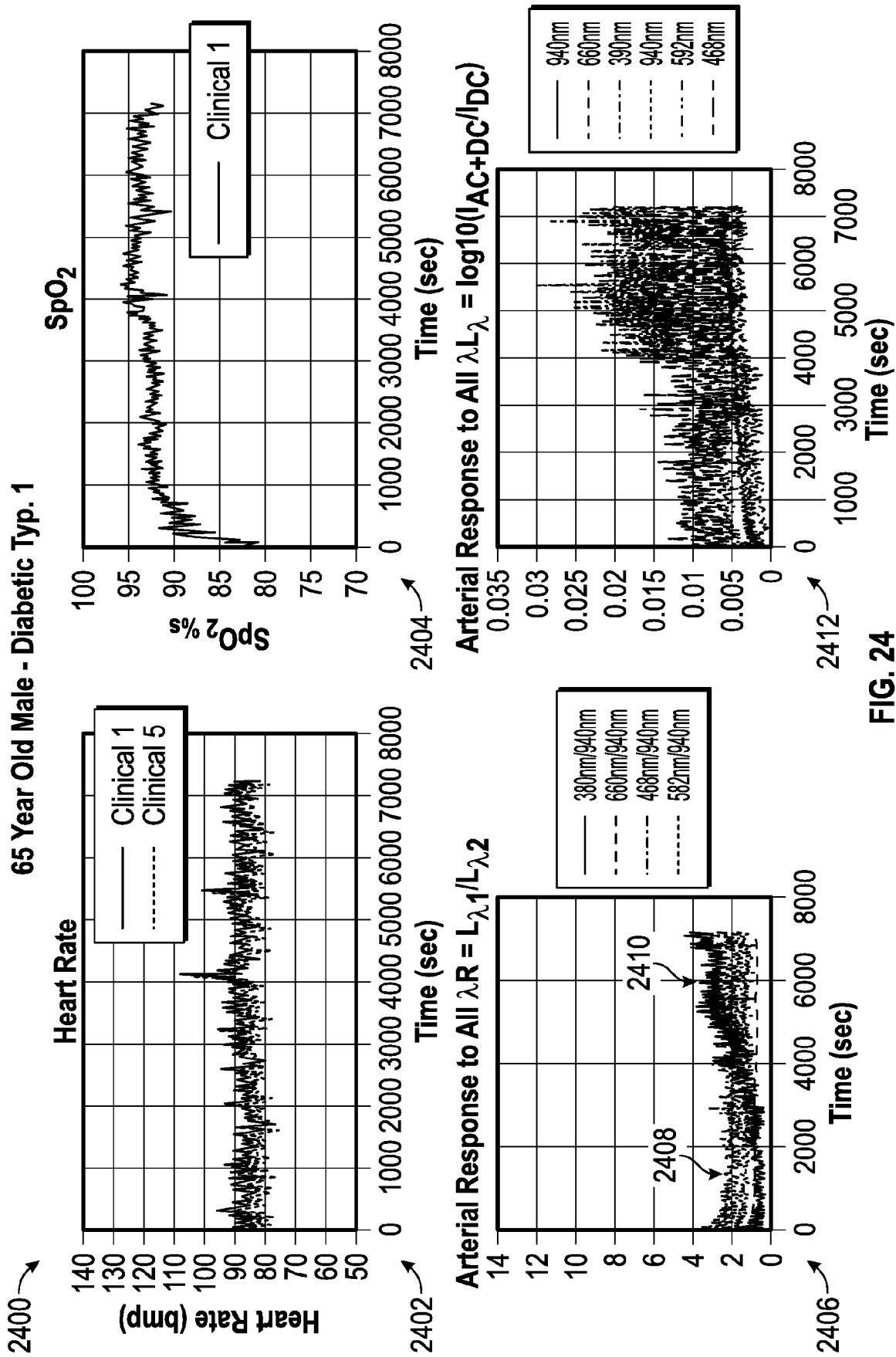


FIG. 22







## 65 Year Old Male Type 1 Diabetic

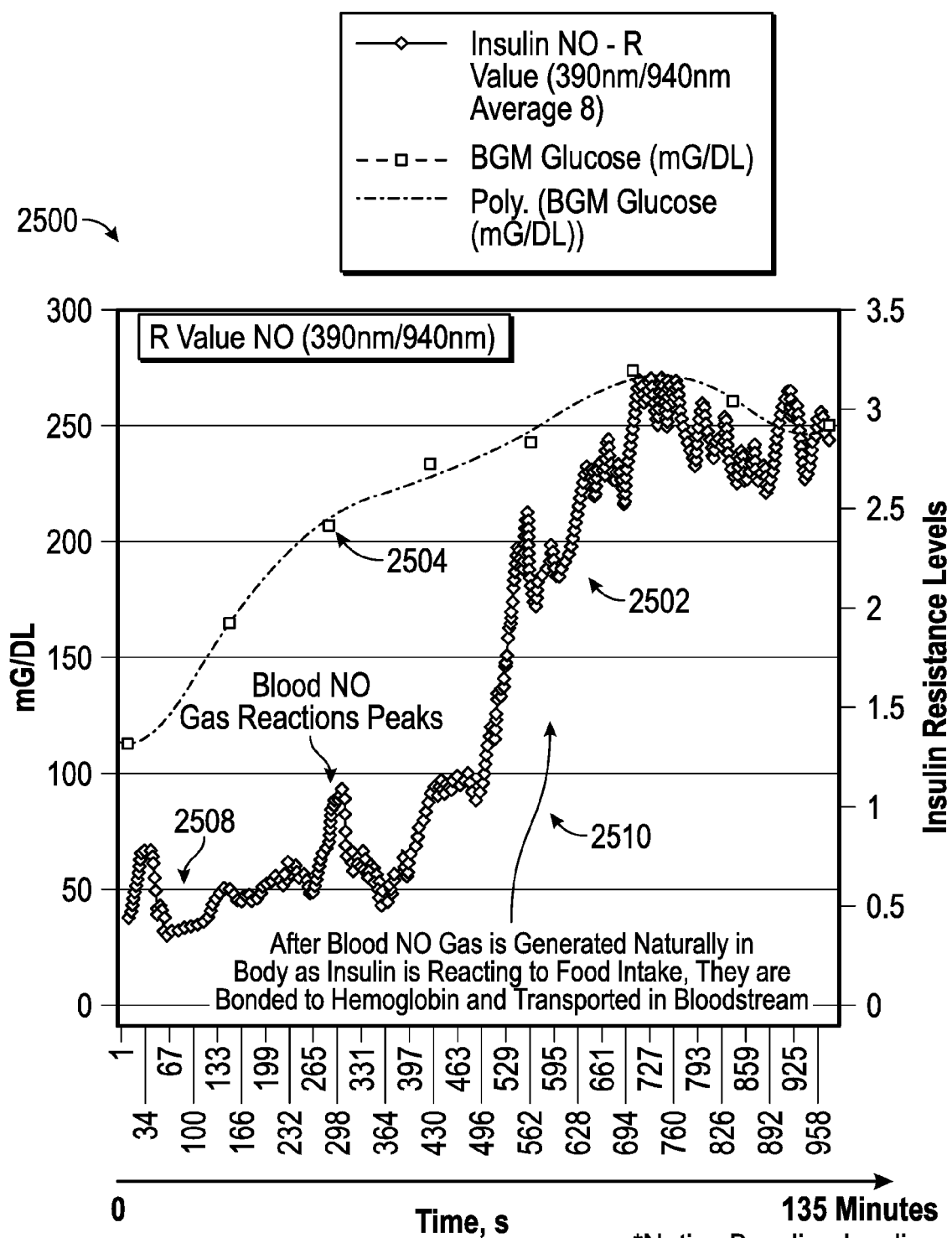
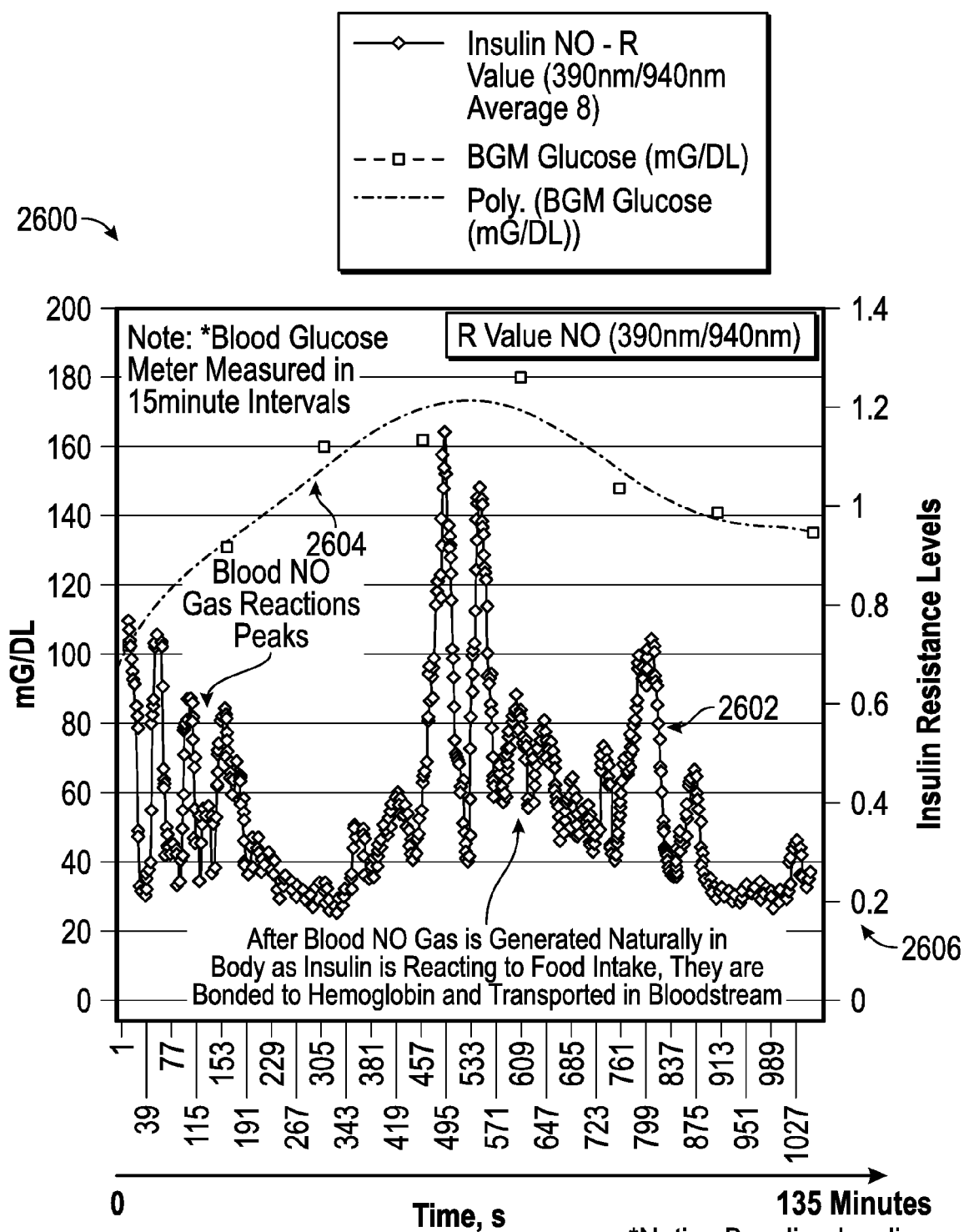


FIG. 25

\*Notice Baseline Insulin Resistance Level is <0.8 (R Value 390/940nm) for Every Diabetic Before Eating @ Time 0

## 37 Year Old Female - Diabetic Typ. 1



\*Notice Baseline Insulin Resistance Level is <0.8 (R Value 390/940nm) for Every Diabetic Before Eating @ Time 0

FIG. 26

## 59 Year Old Male Type 2 Diabetic

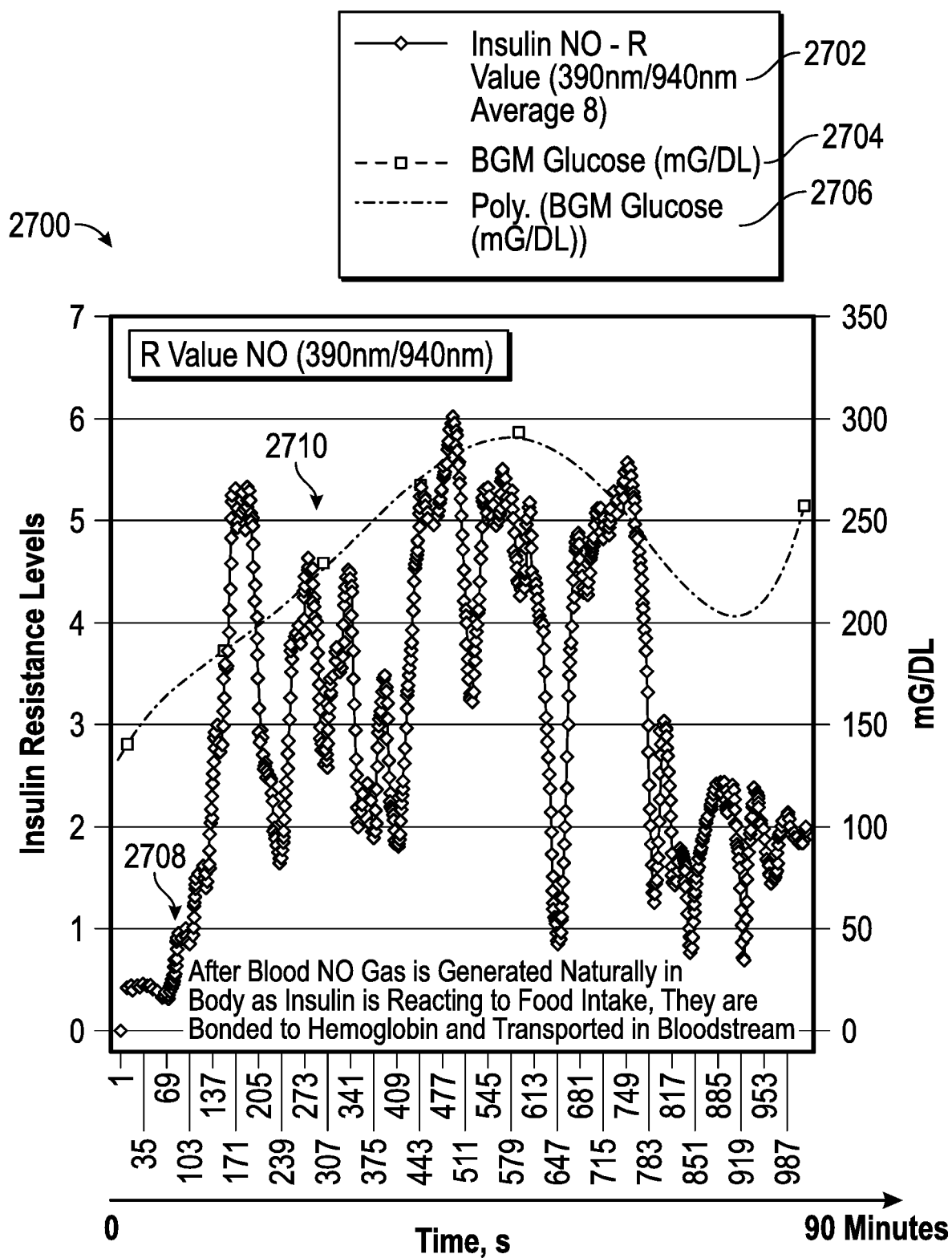
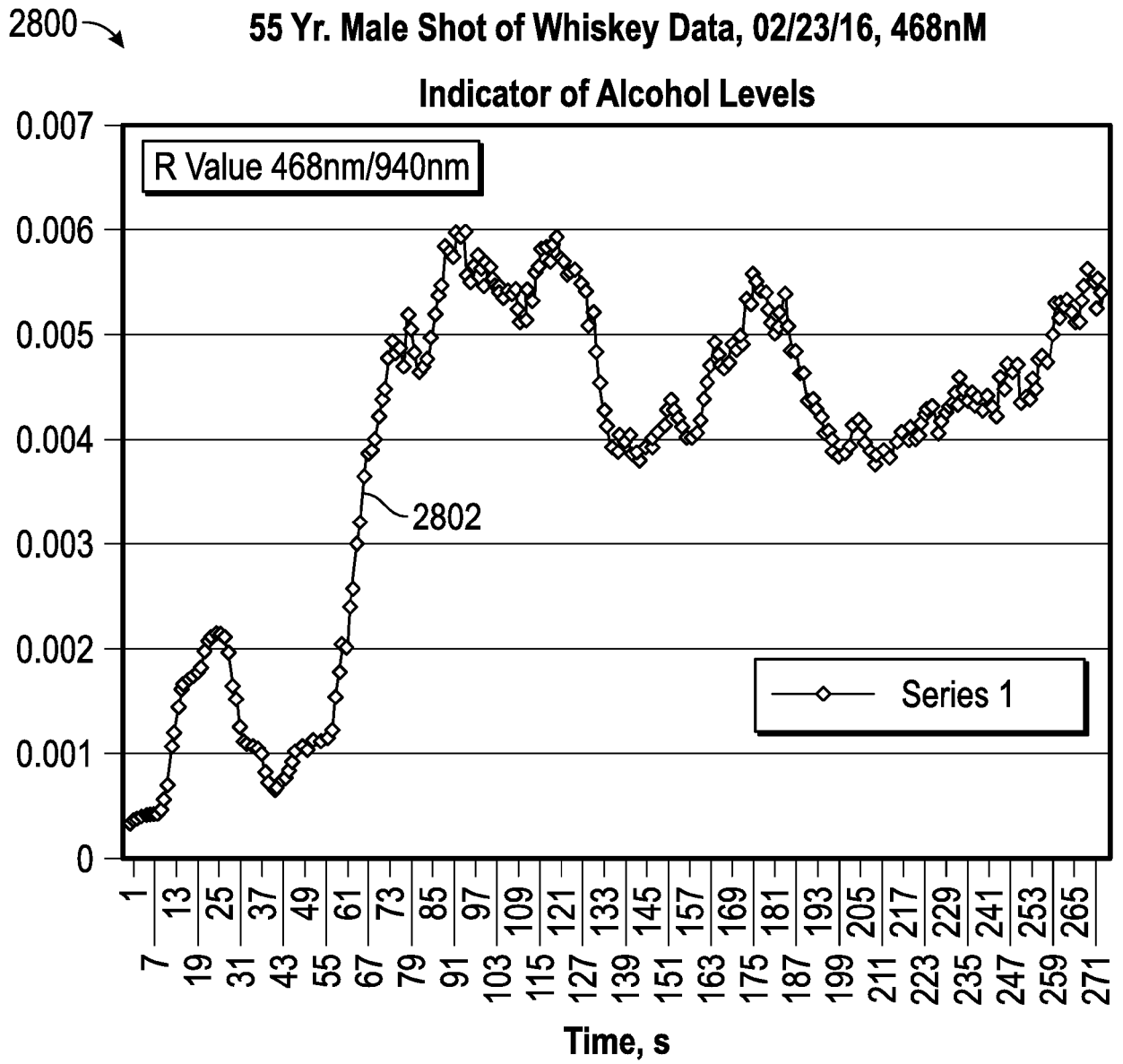
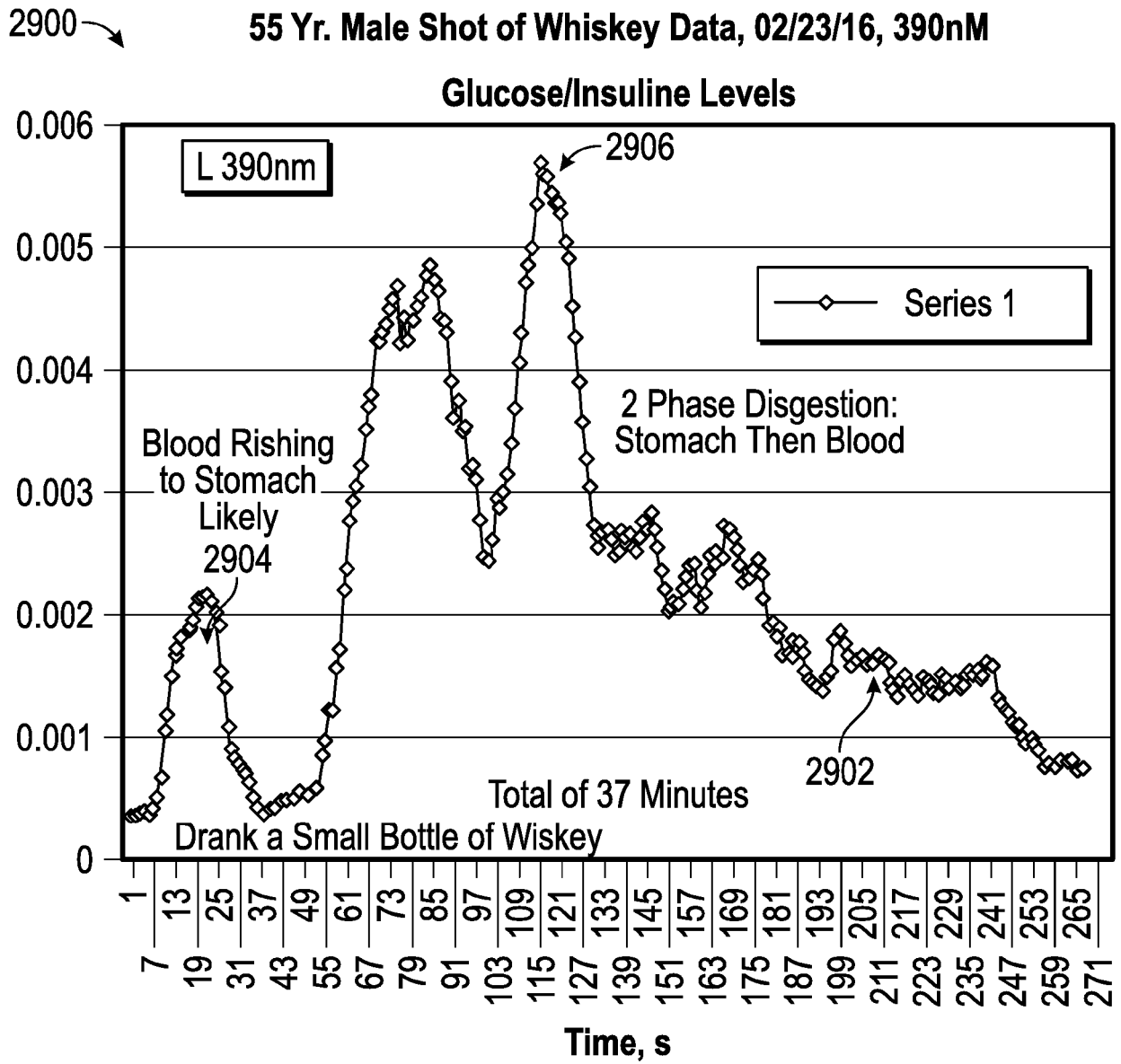


FIG. 27

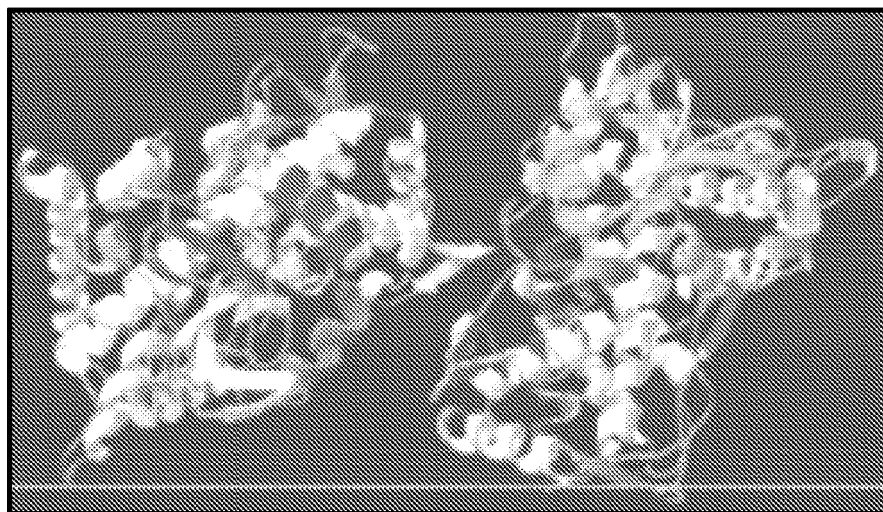
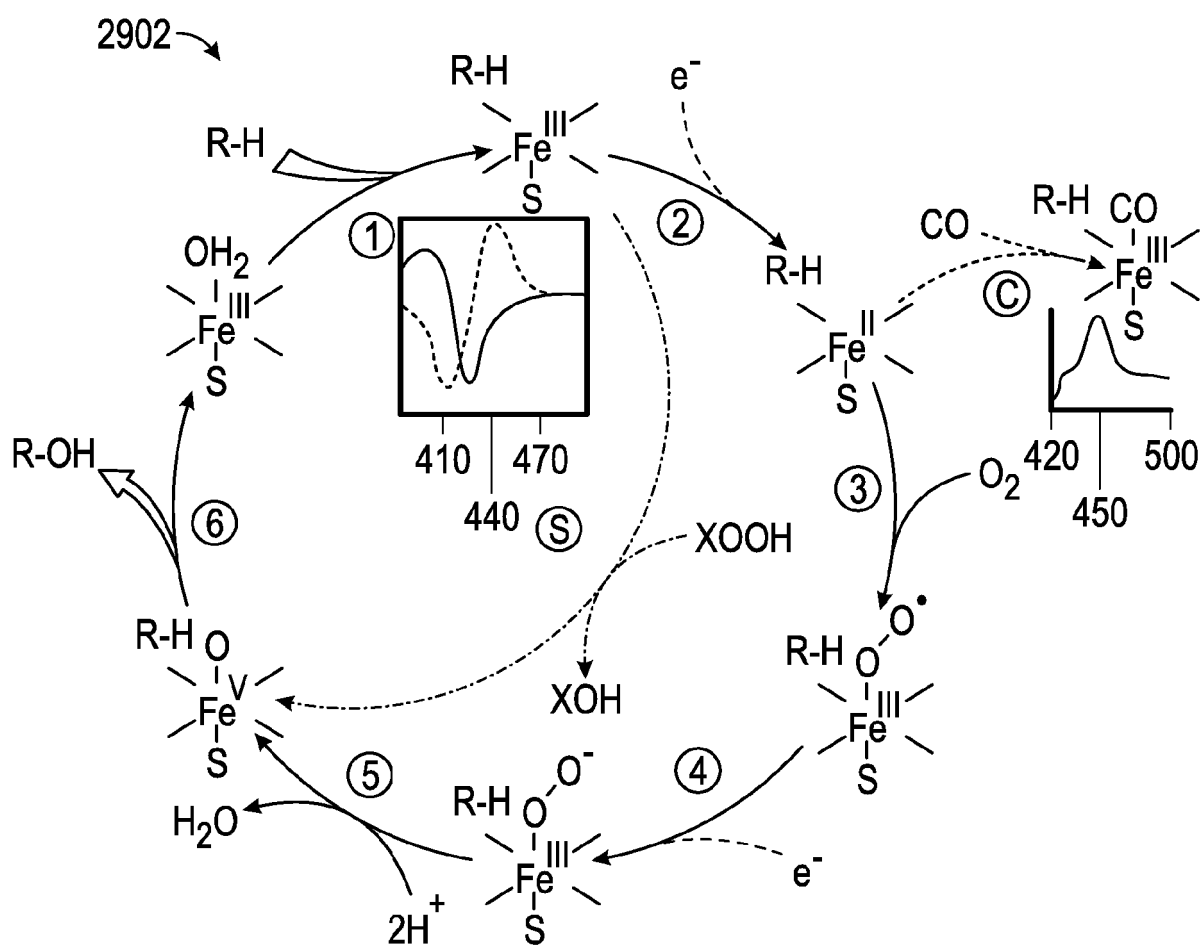


**FIG. 28**



**FIG. 29**

2900

**Cytochrome P450****Cytochrome P450 Oxidase (CYP2C9)****FIG. 30**



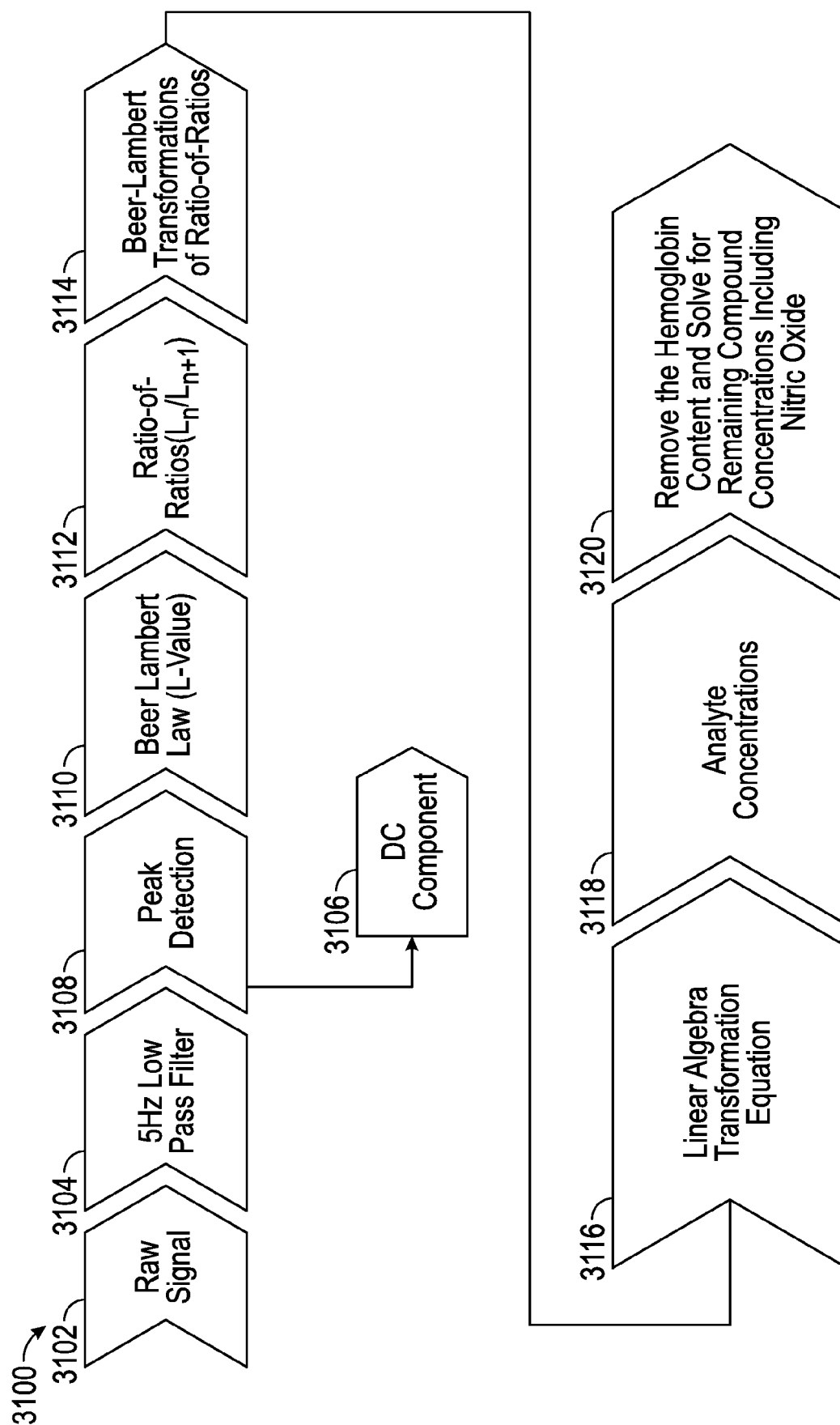


FIG. 31

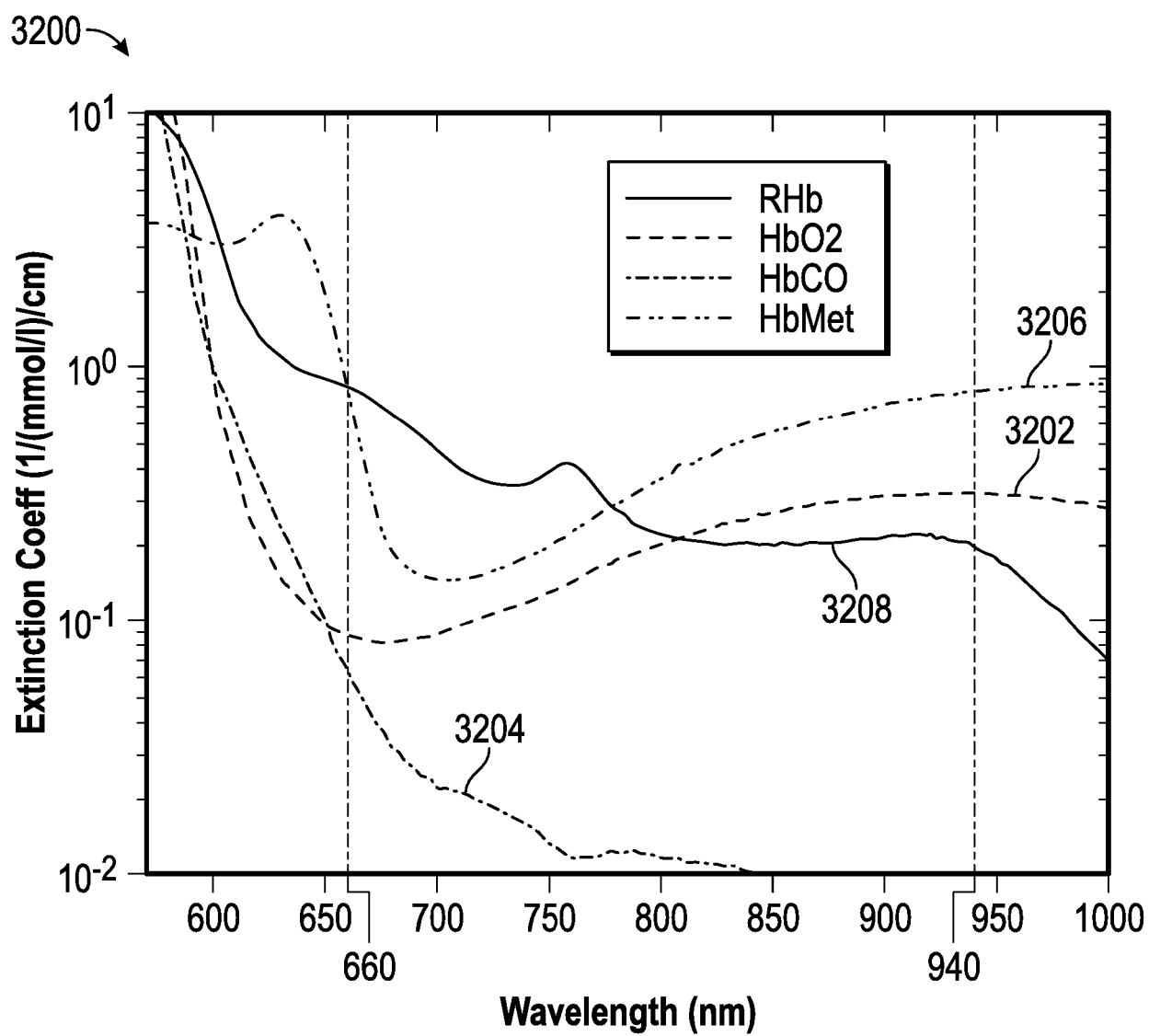


FIG. 32

## REFERENCES CITED IN THE DESCRIPTION

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