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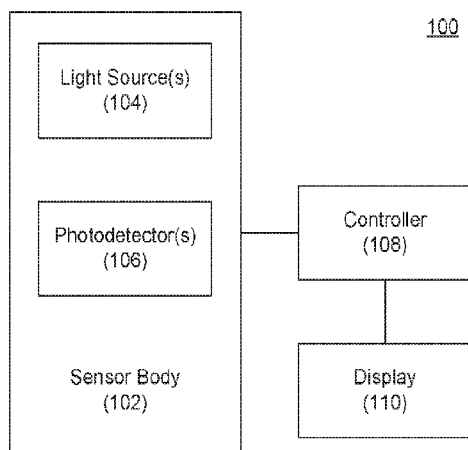


FIG. 1A

(57) Abstract: A non-invasive blood sensor includes a sensor body configured to mate with a tissue surface, light sources disposed on the sensor body, and a photodetector disposed on the sensor body in position for capturing light emanating from the tissue surface after emission from the blue light source by transmission, reflection or transreflection. A non-invasive hemoglobin sensor includes blue, green and red light sources. A non-invasive WBC sensor includes green, red and infrared light sources. The light source(s) and photodetector(s) may be supported on a support structure configured to register with a corresponding portion of human anatomy in a predetermined fashion, to arrange them in a defined spatial relationship. The sensor or an integrated meter may include a controller programmed to receive signals from the photodetector and calculate blood hemoglobin and/or white blood cell counts as a function of the signals received from the photodetector(s) after emission by the light source(s).



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**NON-INVASIVE HEMOGLOBIN AND WHITE BLOOD CELL SENSORS****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of priority of U.S. Provisional Patent Application Nos. 62/432,030, filed December 9, 2016, 62/432,037, filed December 9, 2016, and  
5 62/577,399, filed October 26, 2017, the entire disclosures of all of which are hereby incorporated herein by reference.

**FIELD OF THE INVENTION**

The present invention relates generally to and more particularly to hemoglobin and  
10 white blood cell count measuring devices, and more particularly, to sensors and methods for measuring hemoglobin and white blood cell count in the body without the need for a blood sample.

**BACKGROUND OF THE INVENTION**

Hemoglobin is the oxygen-transport component of blood. Hemoglobin levels can be  
15 an indicator of various diseases such as anemia.

White blood cells (also known as WBCs, leukocytes, and leucocytes) protect the body against infectious diseases and foreign objects. The number of WBCs can be an indicator of various diseases or various WBC disorders.

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**SUMMARY**

A non-invasive sensor includes a body configured to mate with a tissue surface; a plurality of light sources disposed on the sensor body; and a photodetector disposed on the sensor body at a suitable position for capturing light emanating from the tissue surface after emission from the light sources, *e.g.*, by one of: transmission, reflection, and transfection.  
25 The plurality of light sources of a non-invasive hemoglobin sensor includes a blue light source, a green light source, and a red light source. The plurality of light sources of a non-invasive WBC sensor includes a green light source, a red light source, and an infrared light source.

The light source(s) and photodetector(s) may be supported on a support structure  
30 configured to register with a corresponding portion of human anatomy in a predetermined fashion, and support the light sources and photodetectors in a defined spatial relationship. The sensor or an integrated meter may include a controller programmed to receive signals

from the photodetector and calculate blood hemoglobin and white blood cell count values as a function of the signals received from the photodetector(s) after emission by the light source(s).

### BRIEF DESCRIPTION OF THE DRAWINGS

5 For a fuller understanding of the nature and desired objects of the present invention, reference is made to the following detailed description taken in conjunction with the accompanying drawing figures wherein like reference characters denote corresponding parts throughout the several views.

10 FIG. 1A depicts a non-invasive blood (hemoglobin or WBC) sensor according to an embodiment of the invention.

FIGS. 1B and 1C depict an exemplary positioning of light sources and photodetectors along a subject's finger for measurement of reflectance/transflectance and transmission, respectively, according to embodiments of the invention.

15 FIGS. 1D and 1E depict an exemplary light source and photodetector assembly according to an embodiment of the invention.

FIG. 2 depicts the association of photodetector signals with a previously or concurrently applied color according to an embodiment of the invention.

FIG. 3 depicts a method of controlling a non-invasive hemoglobin sensor according to an embodiment of the invention.

20 FIGS. 4A-4J depict a non-invasive hemoglobin sensor according to an embodiment of the invention.

FIGS. 4K-4L illustrate exemplary embodiments of support structures designed to register with specific portions of human anatomy according to an embodiment of the invention.

25 FIG. 5 plots the relationship of the raw device results (*i.e.*, the *Hgb Factor*) to lab-measured hemoglobin levels. Example calibration Equation (3) is shown as the thick dashed line.

30 FIG. 6 plots the relationship of the raw device results (*i.e.*, the *WBC Factor*) to lab-measured white blood cell count levels. Example calibration Equation (6) is shown as the thick dashed line.

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## DEFINITIONS

The instant invention is most clearly understood with reference to the following definitions.

As used herein, the singular form “a,” “an,” and “the” include plural references unless  
5 the context clearly dictates otherwise.

Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. “About” can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear  
10 from context, all numerical values provided herein are modified by the term about.

As used in the specification and claims, the terms “comprises,” “comprising,” “containing,” “having,” and the like can have the meaning ascribed to them in U.S. patent law and can mean “includes,” “including,” and the like.

Unless specifically stated or obvious from context, the term “or,” as used herein, is  
15 understood to be inclusive.

Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,  
20 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 (as well as fractions thereof unless the context clearly dictates otherwise).

## DETAILED DESCRIPTION

Aspects of the invention provide non-invasive hemoglobin sensors and non-invasive white blood cell sensors. Without being bound by theory, Applicant believes that different  
25 components of blood are characterized by different absorption spectra such that the application of multiple wavelengths of light will yield different transmission, reflectance, and/or transreflectance spectra depending on the content of the subject’s blood (*e.g.*, the level of hemoglobin and/or white blood cells within the blood) that can act as “signatures” usable for analyzing the components of blood.

30 Pulse oximetry exploits a difference in absorption of red and infrared light between oxygenated and deoxygenated blood to calculate a saturation of peripheral oxygen (SpO<sub>2</sub>). However, the absorption of red and infrared wavelengths is not substantially impacted by hemoglobin or WBC levels to permit detection of hemoglobin or WBC levels solely from red

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and infrared absorption. That is, the absorption of red and infrared light is substantially the same regardless of whether a subject's hemoglobin or WBC levels are high, low, or in between. However, as discussed herein, hemoglobin levels can be measured using blue, green, and red light. WBC levels can be measured using green, red, and infrared light.

5 Applicant has discovered that hemoglobin levels reliably influence the absorption of certain wavelengths of light, particularly in the blue, green, and red spectra, and that WBC levels reliably influence the absorption of certain wavelengths of light, particularly in the green, red, and infrared spectra. Embodiments of the invention provide devices, methods, and computer-readable media that measure absorption at appropriate wavelengths and  
10 calculate hemoglobin and WBC levels based on that absorption.

Referring to FIG. 1A, one embodiment of the invention provides a non-invasive blood (hemoglobin or WBC) sensor 100 including a sensor body 102, one or more light sources 104, and one or more photodetectors 106. As discussed further herein and without being bound by theory, Applicant believes that blue, green, and red light absorption is a relatively  
15 strong predictor of hemoglobin levels, and that green, red, and infrared light absorption is a relatively strong predictor of WBC levels. Accordingly, embodiments of the invention can utilize only blue, green, and red light sources 104 or green, red, and infrared light sources 104. Other embodiments can add additional light sources 104 (*e.g.*, an infrared light source for the hemoglobin sensor or a blue light source for the WBC sensor), which can further  
20 improve the accuracy of a detected hemoglobin and/or WBC value and/or enable detection of other values of interest.

#### Light Sources

Light sources 104 can be light-emitting diodes (LEDs), fiber optics, or any other device capable of generating and/or transmitting a desired wavelength to a tissue (*e.g.*, skin)  
25 surface. Suitable LEDs are available from a variety of manufacturers and are detailed in the Appendix to this application.

Exemplary wavelength ranges and peak wavelengths are provided in Table 1 below.

<b>Table 1 – Exemplary Light Source Wavelengths</b>				
<b>Abbreviation</b>	<b>Color</b>	<b>Exemplary Wavelength Range</b>	<b>Exemplary Peak Wavelength</b>	<b>Exemplary Peak Wavelength Range</b>
B	Blue	380-495 nm	465 nm	454-476 nm
G	Green	495-590 nm	515 nm	497-533 nm
R	Red	590-750 nm	660 nm	650-670 nm
IR	Infrared	750-1000 nm	940 nm	915-965 nm

In one embodiment, one or more fiber optics function as the one or more light sources 104 by multiplexing and/or transmitting light from at least one LED or other light source located remote from the tissue surface.

5 In another embodiment, a broadband or white light source 104 can be filtered at the light source 104 to emit one or more wavelengths of interest. The filtering can change to emit a plurality of wavelengths in sequence or in parallel.

Photodetectors

10 Photodetector(s) 106 can be a photodiode such as a silicon photodiode (e.g., Product No. PDB-C171SM available from Luna Optoelectronics of Roanoke, Virginia), a phototransistor, and the like.

15 Photodetector(s) 106 detect light after partial absorption of light emitted by one of the light sources 104 and convert the light into electrical current. For example, at least a portion of the emitted light may be absorbed by various components of blood within tissue of the subject such that the amplitude of the detected light is less than from the amplitude of the emitted light.

Positioning of Light Sources and Photodetectors

20 In view of the prevalence of capillaries carrying blood skin or tissue surfaces, embodiments of the invention can be applied to most, if not all, tissue surfaces of a body without the need to position the sensor 100 over a particular blood vessel. However, particular embodiments can be configured for application to particular regions such as a finger, toe, forehead, head, ear, earlobe, chest, wrist, ankle, nostril, and the like.

The light source(s) 104 and the photodetector(s) 106 can be positioned along the tissue surface so that the photodetector(s) 106 detect light emitted by one or more light

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sources 104, after absorption of some of the emitted light by blood within the tissue. As illustrated in U.S. Patent Nos. 6,763,256, 8,818,476, and 9,314,197, photodetector(s) 106 can be located on the same surface as the light sources 104 to detect reflectance and/or transfectance of emitted light through the tissue (as also depicted in FIG. 1B) and/or the opposite side (*e.g.*, perpendicularly opposite) of the tissue (*e.g.*, finger) to detect transmission of the light through the tissue (as also depicted in FIG. 1C). In reflectance oximetry, the light sources 104 are typically placed around a central photodetector 106 (*e.g.*, on a single body for abutting a tissue surface), which can be surrounded by a light shield (*e.g.*, an optically opaque sensor body 102) to minimize detection of light that has not traveled through the subject's tissue as depicted in FIGS. 1D and 1E. Such an embodiment having an approximately 8 mm diameter is depicted in FIG. 3.11 of John TB Moyle, Pulse Oximetry 31 (2d ed. 2002).

#### Sensor Housings

Referring still to FIGS. 1D and 1E, the sensor body 102 can be a wand or probe that can be placed or held over a desired tissue surface.

This assembly can be further mounted to, coupled to, and/or incorporated within a support structure component for securing the assembly against a tissue surface. Exemplary components include a strap adapted to wrap around a body part (*e.g.*, an about 6 cm to about 10 cm strap to accommodate placement over a finger, an about 15 cm to about 23 cm strap to accommodate placement around a wrist, and the like) that can be secured to itself after wrapping around a tissue, a sleeve, a glove, and the like. The strap, sleeve, glove, cuff, spring-loaded case or clip, or other component can include one or more elastic members, hook-and-loop fasteners (*e.g.*, those available under the VELCRO® trademark from Velcro Industries B.V. of the Netherlands Antilles), and the like.

In each case, the sensor body 102 can be designed to abut and/or register or mate with the intended anatomical structure and further support the light source(s) 104 and photodetector(s) 106 in a defined spatial relationship so that they will be properly positioned during use, according to the reflectance, transmittance, or transfectance mode of operation for which the sensor 100 is designed.

Sensor body 102 can be configured for application to one or more specific tissue surfaces. For example, sensor body 102 can be configured for application to a subject's finger and/or fingertip such as depicted in FIGS. 1B and 1C and disclosed in U.S. Patent Nos. 4,825,879, 8,554,297, 8,818,476, and 9,314,197 and U.S. Patent Application Publication Nos. 2006/0224058 and 2007/0244377, on a wrist as disclosed in U.S. Patent No. 9,314,197,

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in a contact lens as disclosed in U.S. Patent No. 8,971,978, on a heel (*e.g.*, an infant's heel), and the like. For example, non-invasive hemoglobin sensor 100 can be, or can be incorporated within, a watch and/or an activity tracker (*e.g.*, devices sold under the APPLE WATCH® trademark by Apple, Inc. of Cupertino, California, the FITBIT® trademark by  
5 Fitbit, Inc. of San Francisco, California, and the like).

In various embodiments, the sensor body 102 shields or substantially shields the light source(s) 104, the photodetector 106, and/or the tissue from ambient light. For example, in FIGS. 1D and 1E, a shell 102 surrounds light sources 104 and/or photodetector 106 such that light is directed (and sometimes collimated) toward tissue 200 and/or such that  
10 photodetector 106 can only receive light that emanates from the tissue 200. While four light sources and a single photodetector are shown in FIGS. 1D and 1E, in other embodiments, more or less light sources 104 and/or photodetectors 106 can be implemented. For other, *e.g.*, transmission implementations, the light sources 104 and photodetector(s) 106 can be spaced on opposite sides of tissue 200 as discussed herein, for example, in a spaced linear array  
15 along a flexible wrap.

In one embodiment, the sensor 100 includes a support structure (*e.g.*, a tether, sock, glove or sleeve) having a configuration specifically designed to register with a specific portion of the human anatomy, *e.g.*, a finger, a hand, a forearm, etc., and one or more sensor bodies are arranged on the support structure in one or more predetermined locations  
20 corresponding to the intended locations on the human anatomy, *e.g.*, by mounting them on or to a substrate such as a flexible glove or flexible sleeve. The support structure thereby acts somewhat like a three-dimensional template or jig for arranging the sensor(s) on the human anatomy in a desired spatial arrangement. An exemplary embodiment of such a support structure is shown in FIGS. 4A-4J. FIGS. 4K-4L illustrate exemplary embodiments of  
25 support structures designed to register with specific portions of human anatomy according to an embodiment of the present invention. In this manner, the meter's/sensor's structure assists the user in using the meter/sensor properly, as it does not require the user to follow extensive directions, anatomical knowledge or medical expertise for proper sensor placement relative to anatomical structures, but rather simplifies the process in a manner suitable for a layperson –  
30 *e.g.*, requiring merely placing one's hand in a glove or one's foot in a sock.

In other embodiments, the sensor may include a support structure that is more generic, and capable of registering with distinctly different parts of the human anatomy, such a spring-loaded clip or clamp.

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As described further below, FIGS. 4A-4J depict an exemplary embodiment of a sensors capable of measuring hemoglobin, WBC and/or other vital signs. Embodiments of the invention are not limited to finger-worn devices.

#### Control of Non-Invasive Hemoglobin/WBC Sensor

5           In various embodiments, each light source of one or more light sources 102 can be activated at different times such that only one light source 102 is activated at a time. For example, as depicted in FIG. 2, the resulting light received by photodetector(s) 106 can be associated with a particular light source 104 (and color) based on a time delay between activation of a particular light source 104 and later detection by the photodetector(s) 106.

10           Referring now to FIG. 3, a method 300 of controlling a non-invasive hemoglobin and/or WBC sensor is provided. While specific steps in a predetermined order are illustrated in FIG. 3, in various embodiments, one or more of the steps may be excluded and/or additional steps can be added. Further, the steps may be performed in any order.

          In step S302, a light source is controlled to emit a first light signal. In various  
15           embodiments, this can include controlling the light source to emit a light signal at a specific wavelength of light. In one embodiment, each of the light sources can be controlled to serially apply each light signal at a specific wavelength (*e.g.*, blue, then green, then red, then infrared, although any order can be used). The light sources can be applied at non-overlapping periods of time. In various embodiments, the light sources can be turned on and  
20           off at such a frequency (*e.g.*, 60 Hz or greater) that the light sources may appear to be continuously illuminated to the human eye.

          In step S304, a resulting light can be detected by the one or more photodetectors. A controller can be programmed to monitor and record detected light based on the sequence of emission on step S302. For example, light can be first detected in the blue wavelength, then  
25           green, then red, then infrared. A waveform is observed wherein the peaks correspond to the pulsatile blood flow during systole and the trough is the resting phase of diastole. The difference between the peak and the trough is the measured amplitude of interest.

          In step S306, the resulting light signal can be validated based on expected ranges of values (*e.g.*, to confirm that the light sources and photodetector(s) are properly positioned).  
30           For example, the resulting light signals can be assessed to ensure that each exhibits a pulsatile waveform of the type expected from blood flow within a subject. In various embodiments, validation is performed each time a measurement is performed. In other embodiments, validation is performed after the meter has been applied to a subject and once the device has

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been validated, validation is no longer performed. In yet other embodiments, validation is performed based upon subject-supplied commands or when the measured hemoglobin levels deviate from an expected range.

In step S308, the resulting light signal can be preprocessed (*e.g.*, by averaging over  
5 several heartbeats and/or other statistical techniques over several heartbeats, data points, or period of time) to remove or minimize noise, outliers, or other variations. For example, a last-in, first-out (LIFO) queue of  $n$  data points (*e.g.*, on the order of 10, 100, and the like) can be maintained for statistical processing.

Various techniques for validating and preprocessing data in the pulse oximetry field  
10 as well as hardware for implementing the same are described in John TB Moyle, Pulse Oximetry (2d ed. 2002) and can be applied prior to calculating of a hemoglobin level.

In step S310, the subject's hemoglobin or WBC level can be calculated as described below.

The method can then be repeated continuously or periodically to provide updated  
15 hemoglobin or WBC levels.

#### Calculation of Hemoglobin Level

Embodiments of the invention can calculate hemoglobin levels based on the amplitudes received from the one or more photodetector(s) 106 in response to the application of one or more frequencies of light. The amplitudes may be normalized with regard to the  
20 base of the waveform (*i.e.*, the ambient or dark signal) for one or more frequencies of light.

The equations described herein and equivalent equations act to isolate the effect of hemoglobin level on absorption of particular colors from the effects of other absorbents along the optical path.

Equation (1) below provides one exemplary equation for calculating a hemoglobin  
25 level using a device such as depicted in FIGS. 4A-4J using blue, green, and red light measurements.

$$Hgb\ Factor = (\alpha) \left( \frac{B + G}{R} \right) + (\delta) \ln \left( (\epsilon) \frac{G}{B} \right) + (\zeta) \quad (1)$$

Equation (2) below provides one exemplary equation for calculating a hemoglobin level using a device such as depicted in FIGS. 4A-4J using blue, green, red, and infrared light measurements.

$$Hgb\ Factor = (\alpha) \left( \frac{B + G}{R} \right) + (\beta) \ln \left( (\gamma) \frac{B + G}{IR} \right) + (\delta) \ln \left( (\epsilon) \frac{G}{B} \right) + (\zeta) \quad (2)$$

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Exemplary calibration values for Equations (1) and (2) are provided in Table 2 below.

<b>Table 2 – Hemoglobin Sensor Calibration Values</b>	
$\alpha$	1.0
$\beta$	1.0
$\gamma$	2500
$\delta$	250
$\varepsilon$	1.0
$\zeta$	0.0

Equation (3) below provides another exemplary equation for calculating a hemoglobin level using a device such as depicted in FIGS. 4A-4J using blue, green, red, and infrared light measurements.

$$Hgb\ Factor = \frac{\alpha + \beta \frac{B}{G} + \gamma^{B/G} + \delta \ln\left(\frac{G}{B}\right) + \ln\left(\frac{IR}{G}\right) + \varepsilon \ln\left(\frac{BG}{IR}\right)}{\zeta} \quad (3)$$

5 Exemplary calibration values for Equation (3) are provided in Table 3 below.

<b>Table 3 – Hemoglobin Sensor Calibration Values</b>	
$\alpha$	20
$\beta$	2
$\gamma$	3
$\delta$	-2
$\varepsilon$	-1
$\zeta$	25

Although exemplary calibration values are provided for Equations (1) and (2), a person of ordinary skill in the art will appreciate that these calibration values may vary for a particular implementation (e.g., using light source(s) 104 of varying spectra and/or intensity, photodetector(s) 106 of varying spectra and/or sensitivity, contemplated placement of sensor 100, and the like). Particular calibration values for a given embodiment, including those embodiments using Equations (1) and (2), can be determined by obtaining amplitude values for a plurality of wavelengths and hemoglobin levels obtained by other methods for a test population of subjects. Various fitting algorithms can be used to optimize the calibration values to minimize errors in prediction as will be appreciated by those skilled in the art.

15 Exemplary algorithms are described in treatises such as Rudolf J. Freund et al., Regression Analysis (2d ed. 2006); P.G. Guest, Numerical Methods of Curve Fitting (1961); and Harvey Motulsky & Arthur Christopoulos, Fitting Models to Biological Data Using Linear and Nonlinear Regression (2003).

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Additionally or alternatively, calibrations can be performed on a subject-level. For example, one or more ground-truth hemoglobin values can be obtained, *e.g.*, through queries to the user (*e.g.*, through a user interface) or from one or more sources such as the user's electronic medical record, a computer application or service (*e.g.*, software/services available under the APPLE® HEALTHKIT™ trademark by Apple, Inc. of Cupertino, California, the GOOGLE FIT® trademark by Google Inc. of Mountain View, California, and the like). For example, a user can enter one or more hemoglobin levels obtained using another hemoglobin meter that can be associated with a particular date and time. Those levels can be used as a ground truth and associated with light intensity measurements from the same date and time. This allows for calibration to a particular subject and deviations from the ground-truth hemoglobin level to be measured using light intensity.

Likewise, other functions can be utilized to calculate hemoglobin levels based on light absorption. Such functions can use any or all of the terms:  $\frac{R+B}{B}$ ,  $\frac{IR+B}{B}$ ,  $\frac{R+IR+B}{B}$ ,  $\frac{R+G}{G}$ ,  $\frac{IR+G}{G}$ ,  $\frac{R+IR+G}{G}$ ,  $\frac{R+B+G}{B}$ ,  $\frac{IR+B+G}{B}$ ,  $\frac{R+IR+B+G}{B}$ ,  $\frac{R+B+G}{G}$ ,  $\frac{IR+B+G}{G}$ , and  $\frac{R+IR+B+G}{G}$ . Any or all of these terms can be modified by a logarithm to any base, modified by a natural logarithm, raised by *e* or any other power, arithmetically combined in any way, modified by one or more calibration factors, or otherwise modified algebraically.

A hemoglobin count can be determined based on a calculated *Hgb Factor* using a lookup table such as Table 4 below.

<b>Table 4 – Hgb Factor to Hgb Level Lookup Table</b>	
<b>Hgb Factor</b>	<b>Hgb Level</b>
≤ 0	> 15
1 to 69.9	14 to 15
71 to 139.9	12.0 to 13.9
140 to 209.9	7.1 to 11.9
≥ 210	≤ 7.0

Alternatively, a hemoglobin level can be determined using the *Hgb Factor* calculated using Equations (1)-(3) and a calibration equation. One example of a calibration equation is:

$$Device\ Calculated\ Hemoglobin\ Level = 5.389e^{1.026(Hgb\ Factor)} \tag{4}$$

Calculation of WBC Level

Embodiments of the invention can calculate WBC levels based on the amplitudes received from the one or more photodetector(s) 106 in response to the application of one or more frequencies of light.

5           The equations described herein and equivalent equations act to isolate the effect of WBC level on absorption of particular colors from the effects of other absorbents along the optical path.

Equation (5) below provides one exemplary equation for calculating a WBC level using a device such as depicted in FIGS. 4A-4J using green, red, and infrared light  
10   measurements.

$$WBC\ Factor = (\beta)(G) + (\gamma)(R) + (\delta)(IR) + (\epsilon)\ln\left(\frac{IR}{G}\right) + (\zeta) \quad (5)$$

Equation (6) below provides one exemplary equation for calculating a WBC level using a device such as depicted in FIGS. 4A-4J using blue, green, red, and infrared light measurements.

$$WBC\ Factor = (\alpha)(B) + (\beta)(G) + (\gamma)(R) + (\delta)(IR) + (\epsilon)\ln\left(\frac{IR}{G}\right) + (\zeta) \quad (6)$$

Exemplary calibration values for Equations (5) and (6) are provided in Table 5 below.

<b>Table 5 – WBC Sensor Calibration Values</b>	
$\alpha$	0.002
$\beta$	0.002
$\gamma$	0.004
$\delta$	0.002
$\epsilon$	40
$\zeta$	0.0

15           Although exemplary calibration values are provided for Equations (5) and (6), a person of ordinary skill in the art will appreciate that these calibration values may vary for a particular implementation (e.g., using light source(s) 104 of varying spectra and/or intensity, photodetector(s) 106 of varying spectra and/or sensitivity, contemplated placement of  
20   sensor 100, and the like). Particular calibration values for a given embodiment, including those embodiments using Equations (5) and (6), can be determined by obtaining amplitude values for a plurality of wavelengths and WBC levels obtained by other methods for a test population of subjects. Various fitting algorithms can be used to optimize the calibration

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values to minimize errors in prediction as will be appreciated by those skilled in the art. Exemplary algorithms are described in treatises such as Rudolf J. Freund et al., Regression Analysis (2d ed. 2006); P.G. Guest, Numerical Methods of Curve Fitting (1961); and Harvey Motulsky & Arthur Christopoulos, Fitting Models to Biological Data Using Linear and  
 5 Nonlinear Regression (2003).

Likewise, other functions can be utilized to calculate WBC levels based on light absorption. Such functions can use any or all of the terms:  $\frac{R+B}{B}$ ,  $\frac{IR+B}{B}$ ,  $\frac{R+IR+B}{B}$ ,  $\frac{R+G}{G}$ ,  $\frac{IR+G}{G}$ ,  $\frac{R+IR+G}{G}$ ,  $\frac{R+B+G}{B}$ ,  $\frac{IR+B+G}{B}$ ,  $\frac{R+IR+B+G}{B}$ ,  $\frac{R+B+G}{G}$ ,  $\frac{IR+B+G}{G}$ , and  $\frac{R+IR+B+G}{G}$ . Any or all of these terms can be modified by a logarithm to any base, modified by a natural logarithm, raised by *e* or  
 10 any other power, arithmetically combined in any way, modified by one or more calibration factors, or otherwise modified algebraically.

A WBC count can be determined based on a calculated *WBC Factor* using a lookup table such as Table 6 below.

<b>WBC Factor</b>	<b>WBC Count</b>
≤ 0	< 7
1 to 69.9	7 to 9.4
71 to 139.9	9.5 to 11.9
140 to 209.9	12 to 16.9
≥ 210	≥ 17.0

Multi-Band Implementations

Some embodiments of the invention utilize multiple bands within each nominal color (e.g., blue, green, red, infrared, and the like). For example, two bands can be measured for each color according to Table 7 below.

**Table 7 – Exemplary Light Source Wavelengths**

Color	Abbreviation	Exemplary Peak Wavelength	Exemplary Peak Wavelength Range
Blue	B <sub>1</sub>	400 nm	380-430 nm
	B <sub>2</sub>	450 nm	430-495 nm
Green	G <sub>1</sub>	500 nm	495-545 nm
	G <sub>2</sub>	550 nm	545-590 nm
Red	R <sub>1</sub>	600 nm	590-660 nm
	R <sub>2</sub>	700 nm	650-750 nm
Infrared	IR <sub>1</sub>	800 nm	570-850 nm
	IR <sub>2</sub>	900 nm	850-1,000 nm

5 In some embodiments, all eight light sources are provided at the same location (e.g., at fingertip). The fingertip is particularly advantageous for all implementations because its anatomy is fairly constant across subjects of various ages and sizes.

Communication with Other Devices

10 Embodiments of the non-invasive hemoglobin or WBC blood sensor 100 can be designed for repeated use or single use and can use one or more communication links for communicating with a controller 108 as will be further described herein. For example, the non-invasive hemoglobin sensor 100 can implement one or more wired or wireless communication protocols.

15 In one embodiment, the non-invasive hemoglobin/WBC sensor 100 can include the appropriate hardware and/or software to implement one or more of the following communication protocols: Universal Serial Bus (USB), USB 2.0, IEEE 1394, Peripheral Component Interconnect (PCI), Ethernet, Gigabit Ethernet, and the like. The USB and USB 2.0 standards are described in publications such as Andrew S. Tanenbaum, Structured Computer Organization Section § 3.6.4 (5th ed. 2006); and Andrew S. Tanenbaum, Modern Operating Systems 32 (2d ed. 2001). The IEEE 1394 standard is described in Andrew S. Tanenbaum, Modern Operating Systems 32 (2d ed. 2001). The PCI standard is described in Andrew S. Tanenbaum, Modern Operating Systems 31 (2d ed. 2001); Andrew S. Tanenbaum, Structured Computer Organization 91, 183-89 (4th ed. 1999). The Ethernet and

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Gigabit Ethernet standards are discussed in Andrew S. Tanenbaum, Computer Networks 17, 65-68, 271-92 (4th ed. 2003).

In other embodiments, the non-invasive hemoglobin or WBC sensor 100 can include appropriate hardware and/or software to implement one or more of the following  
5 communication protocols: BLUETOOTH®, IEEE 802.11, IEEE 802.15.4, and the like. The BLUETOOTH® standard is discussed in Andrew S. Tanenbaum, Computer Networks 21, 310-17 (4th ed. 2003). The IEEE 802.11 standard is discussed in Andrew S. Tanenbaum, Computer Networks 292-302 (4th ed. 2003). The IEEE 802.15.4 standard is described in Yu-Kai Huang & Ai-Chan Pang, “A Comprehensive Study of Low-Power Operation in IEEE  
10 802.15.4” in MSWiM'07 405-08 (2007).

### Controller

The non-invasive hemoglobin sensor 100 or the non-invasive WBC sensor 100 can be sold as a stand-alone peripheral device or as an integrated meter device including a controller 108 and/or a display device 110.

15 In one embodiment, the non-invasive hemoglobin/WBC sensor 100 includes a controller 108 configured to obtain resulting signals from the one or more photodetectors 106. Controller 108 can be further configured to provide current and/or instructions to each light source 104 to emit light and to each photodetector 106 to measure resulting light intensities.

20 Controller 108 can be disposed on sensor body 102 or on a substrate separate from sensor body 102. In one embodiment, the controller 108 filters, processes and/or converts the resulting signal or signals to determine a hemoglobin and/or WBC value for a subject.

Controller 108 can either be a fixed unit that handles all aspects of control and measurement and outputs a hemoglobin and/or WBC level (and potentially other  
25 measurements), *e.g.*, through a display or communication with another device, or can rely on an external device (*e.g.*, a smartphone or a computer) including software and/or hardware including instructions for controlling the operation of light source(s) 104 and photodetectors 106 and calculating hemoglobin and/or WBC levels based on the received values. For example, controller 108 (or one component thereof) can be worn by the patient (*e.g.*, in a  
30 watch, activity tracker, and the like) and control light source(s) 104 and photodetectors 106, but communicate the signals from photodetectors 106 to another component of controller 108 or another device (*e.g.*, a smartphone) for calculation of hemoglobin and/or WBC value(s). Collected signals can further be passed from a wearable device to a smartphone and then

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(*e.g.*, via the internet or other network) to a remote service (*e.g.*, “in the cloud”) implementing a hemoglobin and/or WBC calculation algorithm.

Controller 108 can be an electronic device programmed to control the operation of the system to achieve a desired result. The controller 108 can be programmed to autonomously  
5 determine a hemoglobin and/or WBC level in a subject based upon emission and detection of light.

Controller 108 can be a computing device such as a general purpose computer (*e.g.*, a personal computer (“PC”), laptop, desktop), workstation, mainframe computer system, a patient telemetry device, a smartphone (*e.g.*, devices sold under the IPHONE® trademark by  
10 Apple, Inc. of Cupertino, California, the WINDOWS® trademark by Microsoft Corporation of Redmond Washington, the ANDROID® trademark by Google Inc. of Mountain View, California, and the like), a tablet (*e.g.*, devices sold under the IPAD® trademark from Apple Inc. of Cupertino, California and the KINDLE® trademark from Amazon Technologies, LLC of Reno, Nevada and devices that utilize WINDOWS® operating systems available from  
15 Microsoft Corporation of Redmond, Washington or ANDROID® operating systems available from Google Inc. of Mountain View, California), a video game console (*e.g.*, the WII U® console available from Nintendo of America Inc. of Redmond, Washington; the SONY® PLAYSTATION® console available from Kabushiki Kaisha Sony Corporation of Tokyo, Japan; the MICROSOFT® XBOX® console available from Microsoft Corporation of  
20 Redmond, Washington), smart speaker devices (*e.g.*, devices sold under the HOMEPOD™ trademark by Apple, Inc. of Cupertino, California, the AMAZON ECHO™ trademark from Amazon Technologies, LLC of Reno, Nevada, the GOOGLE HOME™ trademark by Google Inc. of Mountain View, California, and the CASTLEHUB® trademark by CastleOS Software, LLC of Johnston, Rhode Island), medical devices (*e.g.*, insulin pumps, hospital  
25 monitoring systems, intravenous (IV) pumps), electronic medical record (EMR) systems, electronic health record (EHR) systems, and the like.

Controller 108 can be or can include a processor device (or central processing unit “CPU”), a memory device, a storage device, a user interface, a system bus, and/or a communication interface.

30 A processor can be any type of processing device for carrying out instructions, processing data, and so forth.

A memory device can be any type of memory device including any one or more of random access memory (“RAM”), read-only memory (“ROM”), Flash memory, Electrically Erasable Programmable Read Only Memory (“EEPROM”), and so forth.

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A storage device can be any data storage device for reading/writing from/to any removable and/or integrated optical, magnetic, and/or optical-magneto storage medium, and the like (e.g., a hard disk, a compact disc-read-only memory “CD-ROM”, CD-ReWritable “CD-RW”, Digital Versatile Disc-ROM “DVD-ROM”, DVD-RW, and so forth). The storage  
5 device can also include a controller/interface for connecting to a system bus. Thus, the memory device and the storage device can be suitable for storing data as well as instructions for programmed processes for execution on a processor.

The user interface can include a touch screen, control panel, keyboard, keypad, display, voice recognition and control unit, or any other type of interface, which can be  
10 connected to a system bus through a corresponding input/output device interface/adaptor.

The communication interface can be adapted and configured to communicate with any type of external device. The communication interface can further be adapted and configured to communicate with any system or network, such as one or more computing devices on a local area network (“LAN”), wide area network (“WAN”), the internet, and so  
15 forth. The communication interface can be connected directly to a system bus or can be connected through a suitable interface.

The controller 108 can, thus, provide for executing processes, by itself and/or in cooperation with one or more additional devices, that can include algorithms for controlling various components of the light source(s) 104 and photodetector(s) 106 in accordance with  
20 the present invention. Controller 108 can be programmed or instructed to perform these processes according to any communication protocol and/or programming language on any platform. Thus, the processes can be embodied in data as well as instructions stored in a memory device and/or storage device or received at a user interface and/or communication interface for execution on a processor.

The controller 108 can control the operation of the system components in a variety of  
25 ways. For example, controller 108 can modulate the level of electricity provided to a component. Alternatively, the controller 108 can transmit instructions and/or parameters a system component for implementation by the system component.

#### Implementation in Computer-Readable Media and/or Hardware

The methods described herein can be readily implemented in software that can be  
30 stored in computer-readable media for execution by a computer processor. For example, the computer-readable media can be volatile memory (e.g., random access memory and the like),

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non-volatile memory (*e.g.*, read-only memory, hard disks, floppy disks, magnetic tape, optical discs, paper tape, punch cards, and the like).

Additionally or alternatively, the methods described herein can be implemented in computer hardware such as an application-specific integrated circuit (ASIC).

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## WORKING EXAMPLES

### Working Example 1

Referring now to FIGS. 4A-4G, a first pair of light sources 404a, 404b (*e.g.*, blue light source 404a and green light source 404b) and a first photodetector 406a is located within a first unit 412a at the base (*e.g.*, over a proximal phalanx) of a finger while a second pair of  
10 light sources 404c, 404d (*e.g.*, red light source 404c and infrared light source 404d) and a second photodetector 406b is located within a second unit 412b positioned over a tip of the same finger. As further described in U.S. Provisional Patent Application Serial No. 62/417,231, filed November 3, 2016, and U.S. Provisional Patent Application Serial No. 62/432,131, filed December 9, 2016, distribution of light sources 404a, 404b, 404c, 404d and  
15 photodetectors 406a, 406b along a limb (*e.g.*, a finger) facilitates measurement of blood pressure using pulse transit time. (An additional optional pulse oximetry sensor 414 is also depicted in FIGS. 4A and 4B, but is not essential to the invention described herein.)

### Working Example 2

20 FIG. 5 plots the relationship of the raw device results (*i.e.*, the *Hgb Factor*) to lab-measured hemoglobin levels. The exemplary calibration equation is shown as the thick dashed line.

### Working Example 3

25 FIG. 6 plots the relationship of the raw device results (*i.e.*, the *WBC Factor*) to lab-measured white blood cell count levels. The exemplary calibration equation is shown as the thick dashed line.

## EQUIVALENTS

30 Although preferred embodiments of the invention have been described using specific terms, such description is for illustrative purposes only, and it is to be understood that

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changes and variations may be made without departing from the spirit or scope of the following claims.

#### INCORPORATION BY REFERENCE

The entire contents of all patents, published patent applications, and other references  
 5 cited herein are hereby expressly incorporated herein in their entireties by reference.

#### APPENDIX

<b>Table 8 – Exemplary Components</b>		
<b>Component</b>	<b>Source</b>	<b>Product No.</b>
Blue LED	Kingbright	APT1608LVBC/D
Green LED	Kingbright	APT1608LZGCK
Red LED	Lite-On Electronics, Inc.	LTST-C171CKT
Infrared LED	SunLED	XZTNI54W

## CLAIMS

1. A non-invasive sensor comprising:
  - a sensor body configured to mate with a tissue surface;
  - a blue light source disposed on the sensor body;
  - a green light source disposed on the sensor body;
  - a red light source disposed on the sensor body;
  - a photodetector disposed on the sensor body at a suitable position for capturing light emanating from the tissue surface after emission from the blue light source, the green light source, and the red light source; and
  - a controller programmed to:
    - receive one or more signals from the photodetector; and
    - calculate a hemoglobin value as function of at least the one or more signals received from the photodetector after emission by the blue light source, the green light source, and the red light source.
  
2. A non-invasive sensor comprising:
  - a sensor body configured to mate with a tissue surface;
  - a green light source disposed on the sensor body;
  - a red light source disposed on the sensor body;
  - an infrared light source disposed on the sensor body;
  - a photodetector disposed on the sensor body at a suitable position for capturing light emanating from the tissue surface after emission from the green light source, the red light source, and the infrared light source; and
  - a controller programmed to:
    - receive one or more signals from the photodetector; and
    - calculate a white blood count (WBC) value as function of at least the one or more signals received from the photodetector after emission by the green light source, the red light source, and the infrared light source.
  
3. The non-invasive sensor of claims 1 or 2, wherein the controller is further programmed to control selective actuation of the light sources.

4. The non-invasive sensor of claims 1 or 2, wherein the controller is further programmed to control selective actuation of the light sources during discrete time intervals.

5. The non-invasive sensor of claim 1, wherein the controller is further programmed to calculate the hemoglobin value using the equation  $Hgb\ Factor = (\alpha) \left(\frac{B+G}{R}\right) + (\delta) \ln \left(\left(\varepsilon\right) \frac{G}{B}\right) + (\zeta)$ , wherein:

$B$  is a measure of amplitude of detected blue light;

$G$  is a measure of amplitude of detected green light;

$R$  is a measure of amplitude of detected red light; and

$\alpha$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants.

6. The non-invasive sensor of claim 1, further comprising:  
an infrared light source disposed on the sensor body proximate to the blue light source, the green light source, and the red light source.

7. The non-invasive sensor of claim 6, wherein the controller is further programmed to calculate the hemoglobin value using the equation

$Hgb\ Factor = (\alpha) \left(\frac{B+G}{R}\right) + (\beta) \ln \left(\left(\gamma\right) \frac{B+G}{IR}\right) + (\delta) \ln \left(\left(\varepsilon\right) \frac{G}{B}\right) + (\zeta)$ , wherein:

$B$  is a measure of amplitude of detected blue light;

$G$  is a measure of amplitude of detected green light;

$R$  is a measure of amplitude of detected red light;

$IR$  is a measure of amplitude of detected infrared light; and

$\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants.

8. The non-invasive sensor of claim 7, wherein:

$\beta$  is about 1.0;

$\gamma$  is about 2500;

$\delta$  is about 250;

$\varepsilon$  is about 1.0; and

$\zeta$  is about 0.0.

9. The non-invasive sensor of claim 8, wherein:  
 $\alpha$  is about 1.0.

10. The non-invasive sensor of claim 6, wherein the controller is further programmed to calculate the hemoglobin value using the equation

$$Hgb\ Factor = \frac{\alpha + \beta \frac{B}{G} + \gamma \frac{B}{G} + \delta \ln\left(\frac{G}{B}\right) + \ln\left(\frac{IR}{G}\right) + \varepsilon \ln\left(\frac{BG}{IR}\right)}{\zeta}, \text{ wherein:}$$

$B$  is a measure of amplitude of detected blue light;  
 $G$  is a measure of amplitude of detected green light;  
 $R$  is a measure of amplitude of detected red light;  
 $IR$  is a measure of amplitude of detected infrared light; and  
 $\alpha, \beta, \gamma, \delta, \varepsilon,$  and  $\zeta$  are calibration constants.

11. The non-invasive sensor of claim 10, wherein:  
 $\beta$  is about 2;  
 $\gamma$  is about 3;  
 $\delta$  is about -2;  
 $\varepsilon$  is about -1; and  
 $\zeta$  is about 25.

12. The non-invasive sensor of claim 11, wherein:  
 $\alpha$  is about 20.

13. The non-invasive sensor of claim 2, wherein the controller is further programmed to calculate the WBC value using the equation  $WBC\ Factor = (\beta)(G) + (\gamma)(R) + (\delta)(IR) + (\varepsilon)\ln\left(\frac{IR}{G}\right) + (\zeta)$ , wherein:

$G$  is a measure of amplitude of detected green light;  
 $R$  is a measure of amplitude of detected red light;  
 $IR$  is a measure of amplitude of detected infrared light; and  
 $\beta, \gamma, \delta, \varepsilon,$  and  $\zeta$  are calibration constants.

14. The non-invasive sensor of claim 2, further comprising:  
a blue light source disposed on the sensor body proximate to the green light source, the red light source, and the infrared light source.
15. The non-invasive sensor of claim 14, wherein the controller is further programmed to calculate the WBC value using the equation  $WBC\ Factor = (\alpha)(B) + (\beta)(G) + (\gamma)(R) + (\delta)(IR) + (\varepsilon)\ln\left(\frac{IR}{G}\right) + (\zeta)$ , wherein:  
*B* is a measure of amplitude of detected blue light;  
*G* is a measure of amplitude of detected green light;  
*R* is a measure of amplitude of detected red light;  
*IR* is a measure of amplitude of detected infrared light; and  
 $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants.
16. The non-invasive sensor of claims 13 or 15, wherein:  
 $\beta$  is about 0.002;  
 $\gamma$  is about 0.004;  
 $\delta$  is about 0.002;  
 $\varepsilon$  is about 40; and  
 $\zeta$  is about 0.0.
17. The non-invasive WBC sensor of claim 16, wherein:  
 $\alpha$  is about 0.002.
18. The non-invasive sensor of claims 1 or 2, wherein the sensor body is rigid.
19. The non-invasive sensor of claims 1 or 2, wherein the sensor body is selected from the group consisting of: a clamp, a case, a clip, a wand, and a probe, each of which has a tissue-engaging member on which the light sources are supported.
20. The non-invasive sensor of claims 1 or 2, wherein the sensor body is or is mounted on a flexible member.

21. The non-invasive sensor of claim 20, wherein the flexible member is selected from the group consisting of: a strap, a glove, a cuff, and a sleeve, each of which is configured to register with a corresponding portion of human anatomy in a predetermined fashion, to support the light sources and photodetector in a pre-determined spatial relationship with respect to the corresponding portion of human anatomy.
22. The non-invasive sensor of claims 1 or 2, wherein the suitable position is selected to facilitate capturing light emanating from the tissue surface after one or more selected from the group consisting of: transmission, reflection, and transflection.
23. The non-invasive sensor of claims 1 or 2, wherein the suitable position is selected to cause the photodetector to lie adjacent to the light sources when the sensor body mates with the tissue surface and to receive light emitted by the light sources after reflection or transflection.
24. The non-invasive sensor of claims 1 or 2, wherein the suitable position is selected to cause the photodetector to lie on an opposite tissue surface from the light sources when the sensor body mates with the tissue surface and to receive light emitted by the light sources after transmission.
25. The non-invasive sensor of claims 1 or 2, wherein the sensor body is configured to hold the light sources and the photodetector such that when the sensor body is pressed against the tissue surface, the photodetector is shielded from ambient light such that the photodetector only measures light emerging from the tissue surface after emission by at least the light sources.
26. The non-invasive sensor of claims 1 or 2, wherein the opaque sensor body is optically opaque.
27. A method of non-invasively determining a hemoglobin level, the method comprising:  
receiving one or more measurements of the absorption of at least green light, red light, and infrared light; and

calculating a hemoglobin value based on an equation  $Hgb\ Factor = (\alpha) \left(\frac{B+G}{R}\right) + (\delta) \ln\left(\left(\varepsilon\right)\frac{G}{B}\right) + (\zeta)$ , wherein:

- $B$  is a measure of amplitude of detected blue light;
- $G$  is a measure of amplitude of detected green light;
- $R$  is a measure of amplitude of detected red light; and
- $\alpha$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants.

28. The method of claim 27, wherein:

- $\alpha$  is about 1.0;
- $\gamma$  is about 0.004;
- $\delta$  is about 0.002;
- $\varepsilon$  is about 40; and
- $\zeta$  is about 0.0.

29. A method of non-invasively determining a hemoglobin level, the method comprising: receiving one or more measurements of the absorption of at least blue light, green light, red light, and infrared light; and

calculating a hemoglobin value based on an equation

$$Hgb\ Factor = \frac{\alpha + \beta \frac{B}{G} + \gamma \frac{B}{G} + \delta \ln\left(\frac{G}{B}\right) + \ln\left(\frac{IR}{G}\right) + \varepsilon \ln\left(\frac{BG}{IR}\right)}{\zeta}, \text{ wherein:}$$

- $B$  is a measure of amplitude of detected blue light;
- $G$  is a measure of amplitude of detected green light;
- $R$  is a measure of amplitude of detected red light;
- $IR$  is a measure of amplitude of detected infrared light; and
- $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants.

30. The method of claim 29, wherein:

- $\alpha$  is about 20;
- $\beta$  is about 2;
- $\gamma$  is about 3;
- $\delta$  is about -2;

$\varepsilon$  is about -1; and

$\zeta$  is about 25.

31. A method of non-invasively determining a WBC level, the method comprising:  
receiving one or more measurements of the absorption of at least green light, red light,  
and infrared light; and

calculating a white blood cell value based on an equation  $WBC\ Factor = (\beta)(G) + (\gamma)(R) + (\delta)(IR) + (\varepsilon)\ln\left(\frac{IR}{G}\right) + (\zeta)$ , wherein  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants,

wherein:

$G$  is a measure of amplitude of detected green light;

$R$  is a measure of amplitude of detected red light;

$IR$  is a measure of amplitude of detected infrared light; and

$\beta$ ,  $\gamma$ ,  $\delta$ ,  $\varepsilon$ , and  $\zeta$  are calibration constants.

32. The method of claim 31, wherein:

$\beta$  is about 0.002;

$\gamma$  is about 0.004;

$\delta$  is about 0.002;

$\varepsilon$  is about 40; and

$\zeta$  is about 0.0.

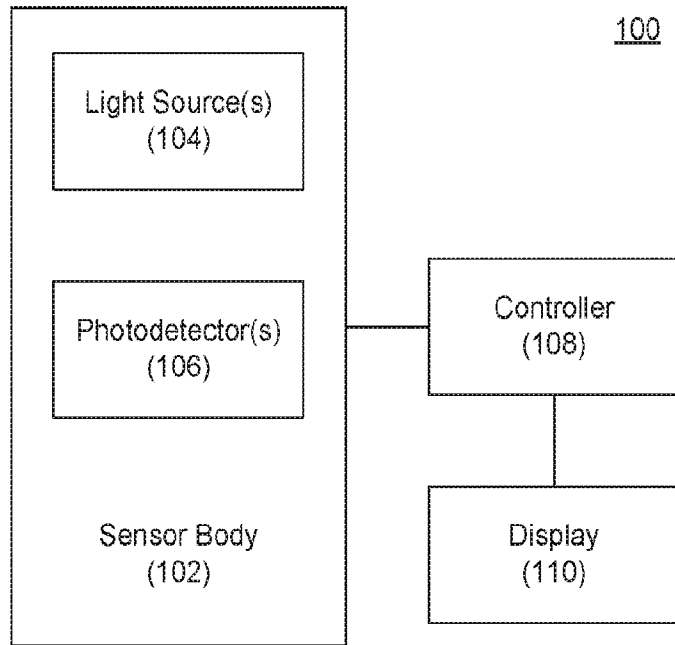


FIG. 1A

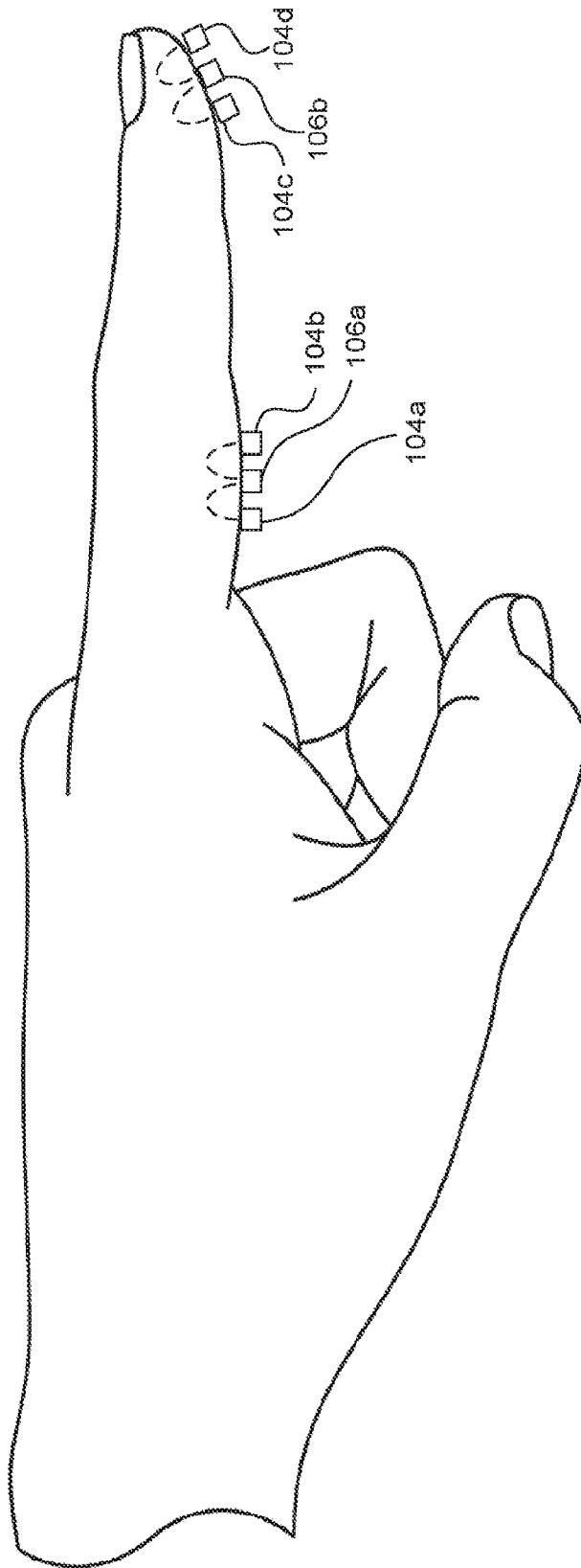


FIG. 1B

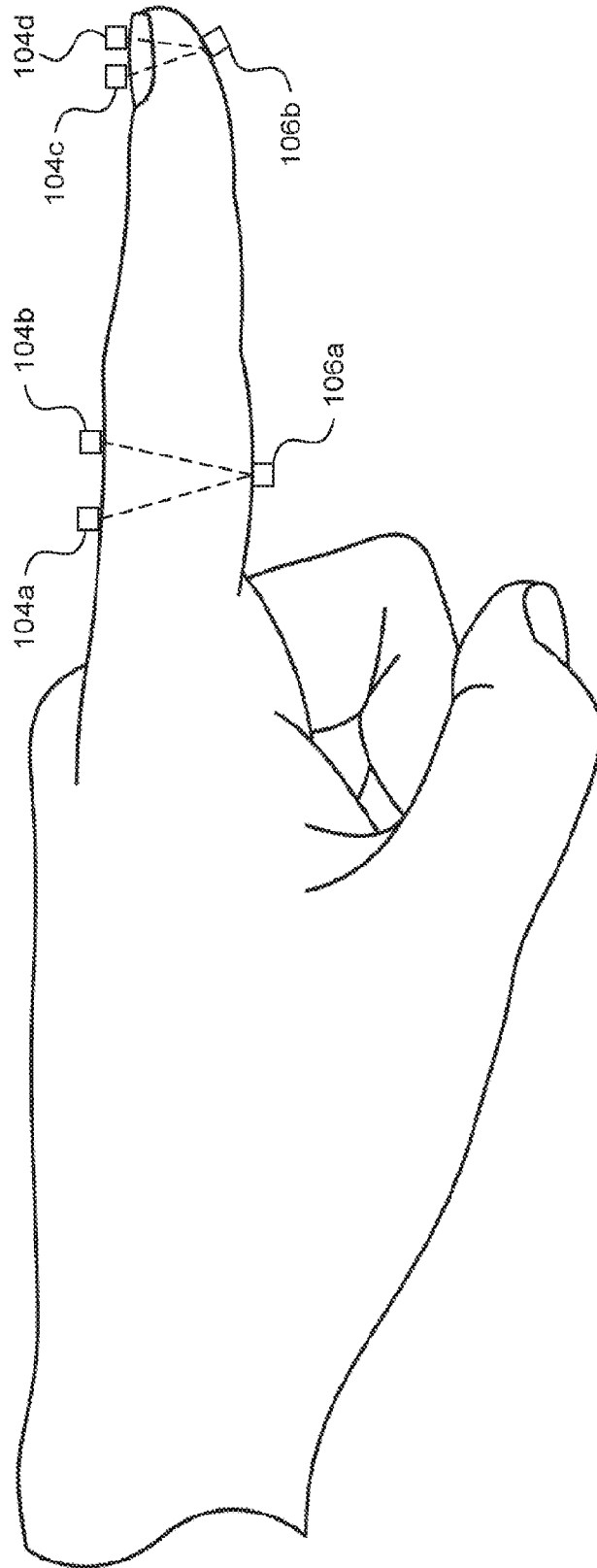


FIG. 1C

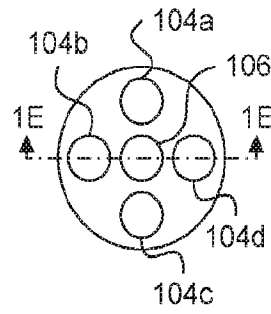


FIG. 1D

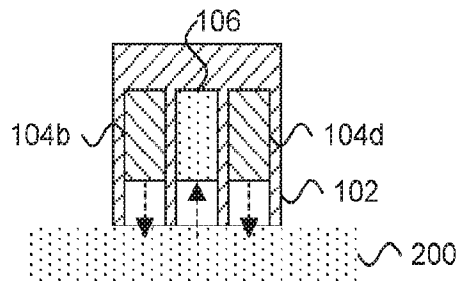


FIG. 1E

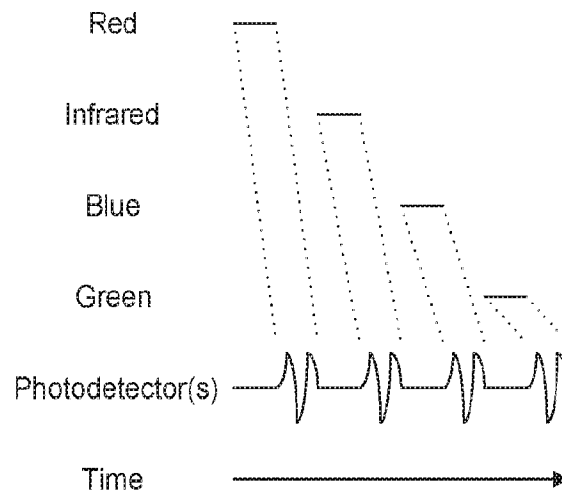


FIG. 2

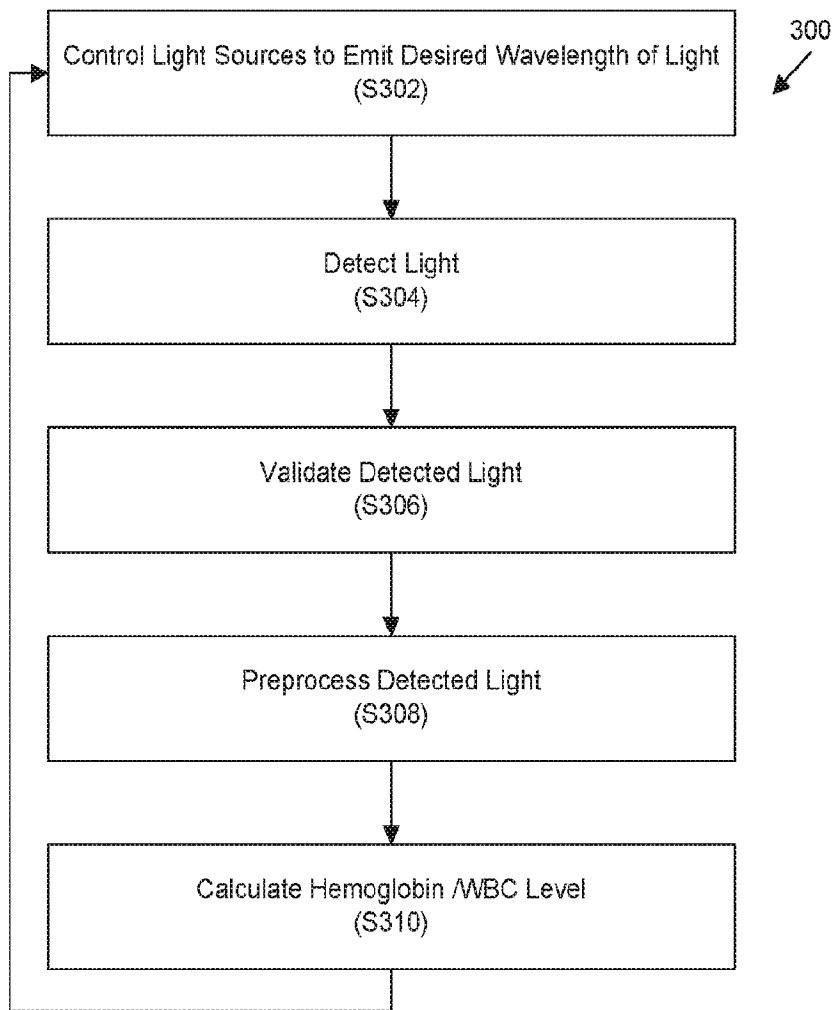


FIG. 3

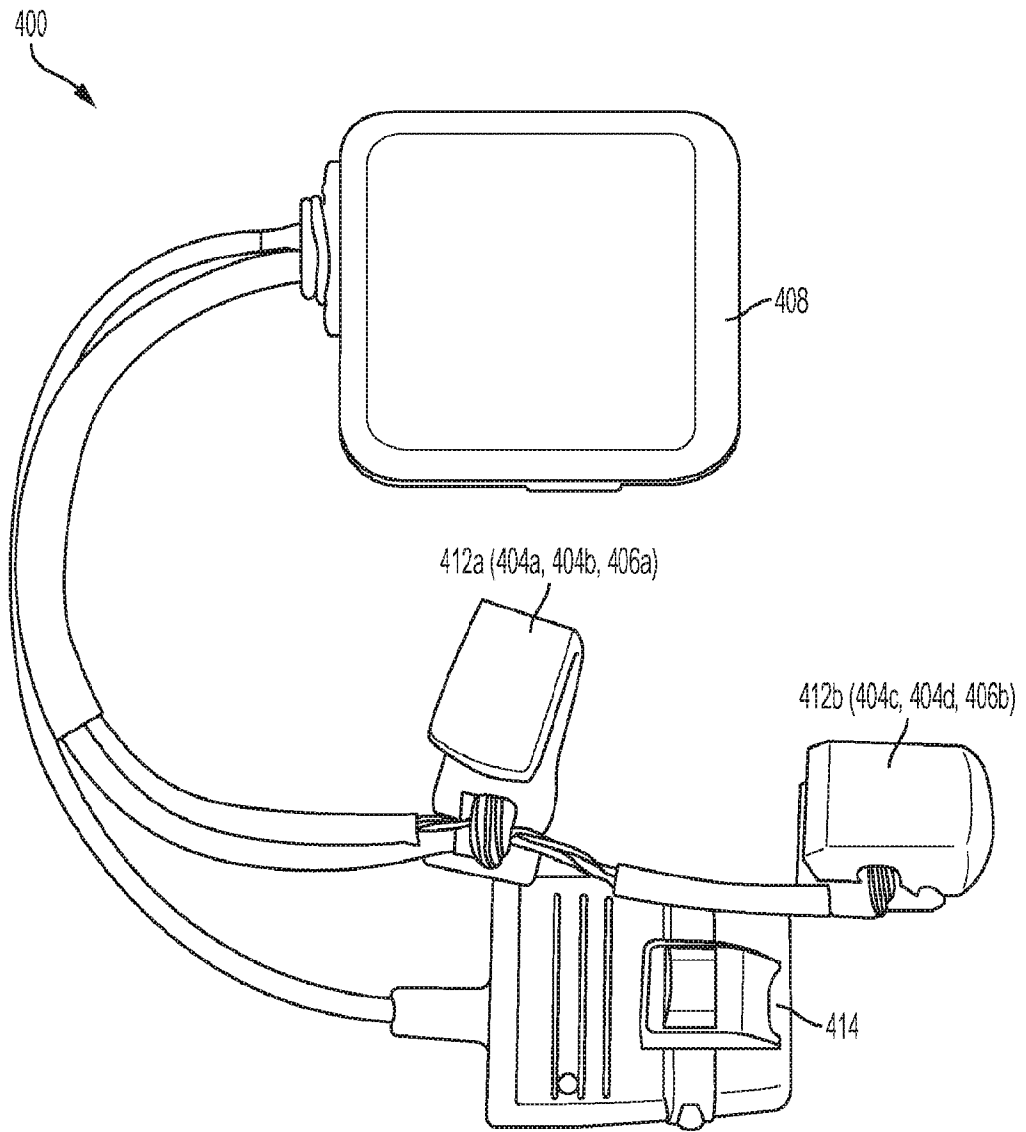


FIG. 4A

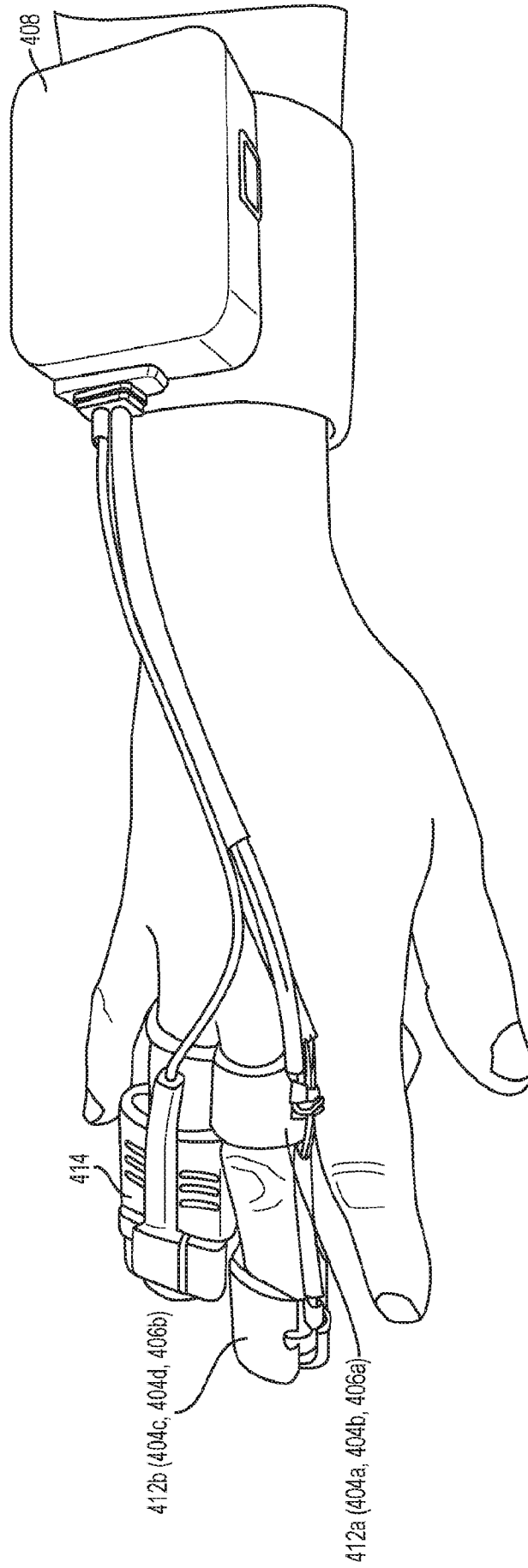


FIG. 4B

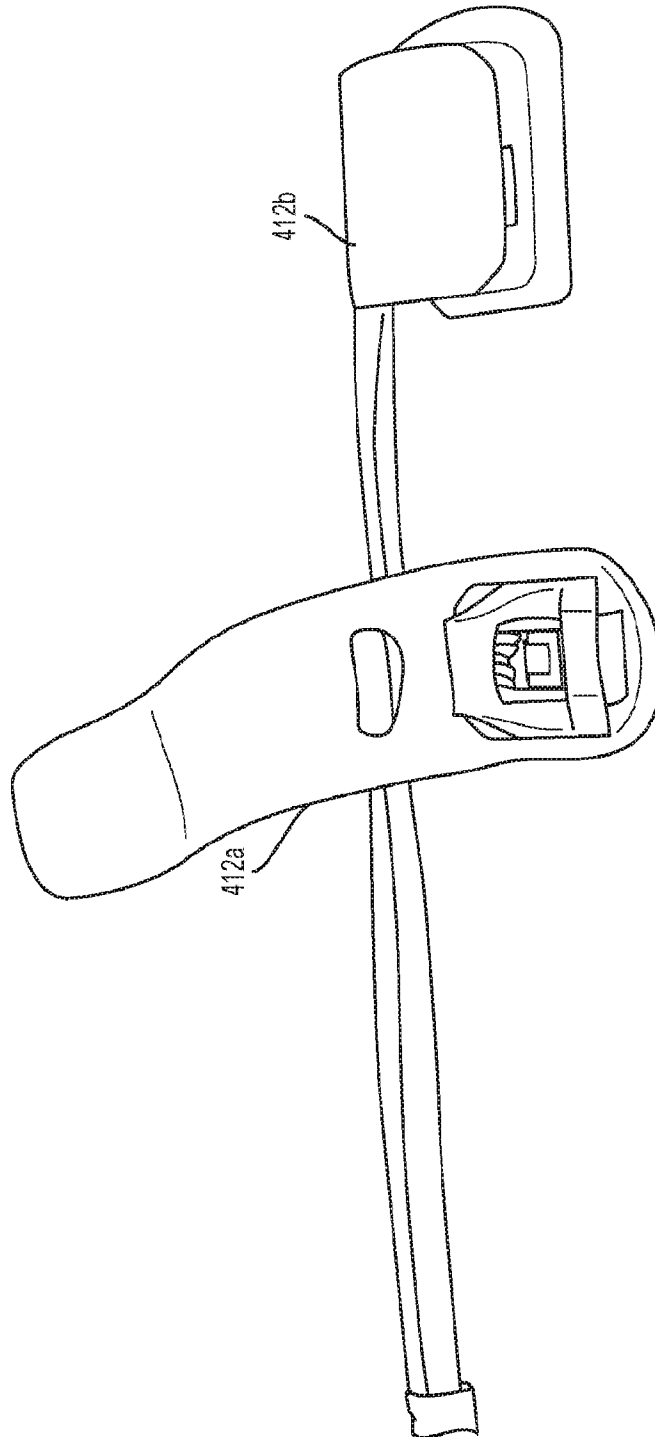


FIG. 4C

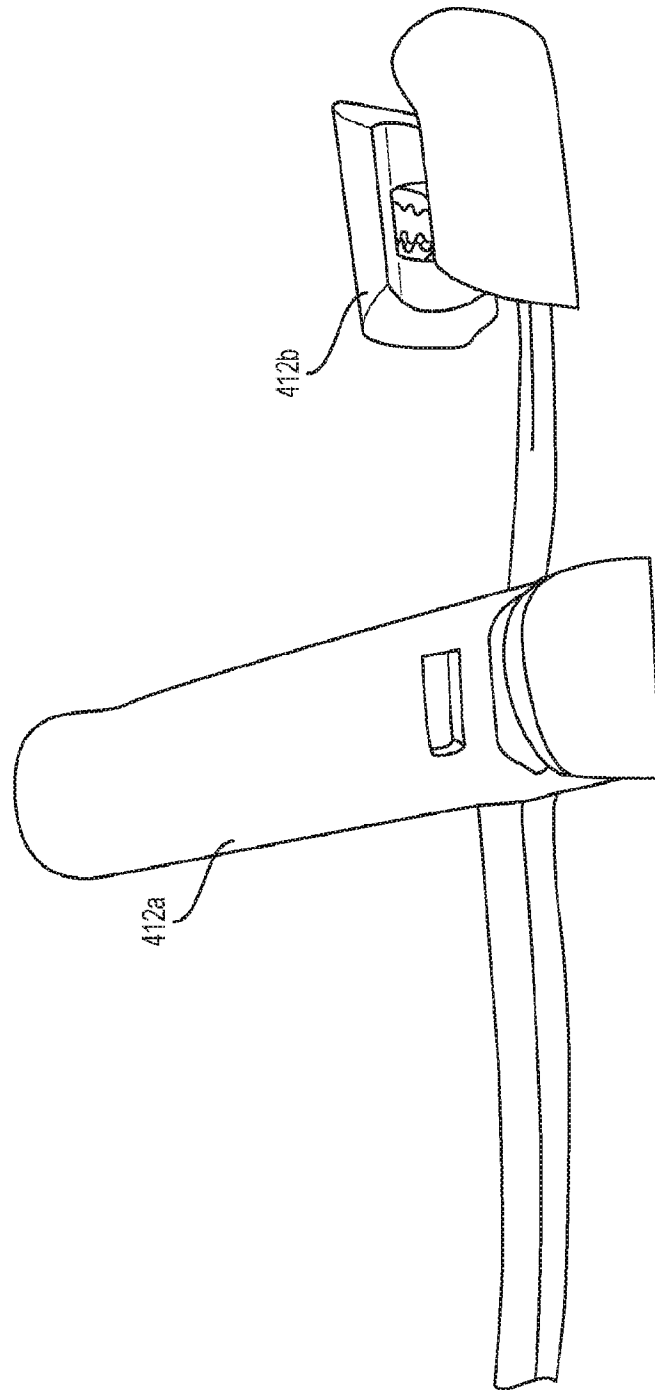


FIG. 4D

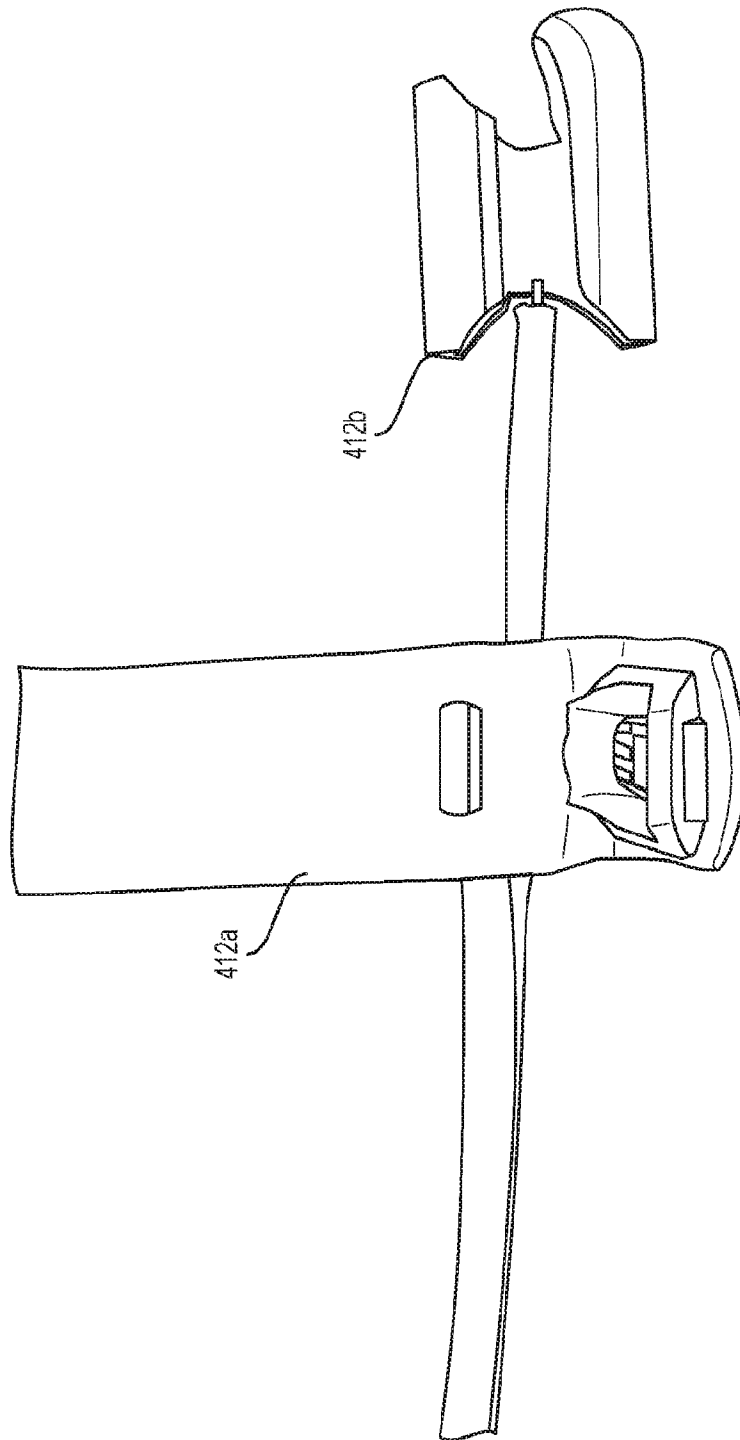


FIG. 4E

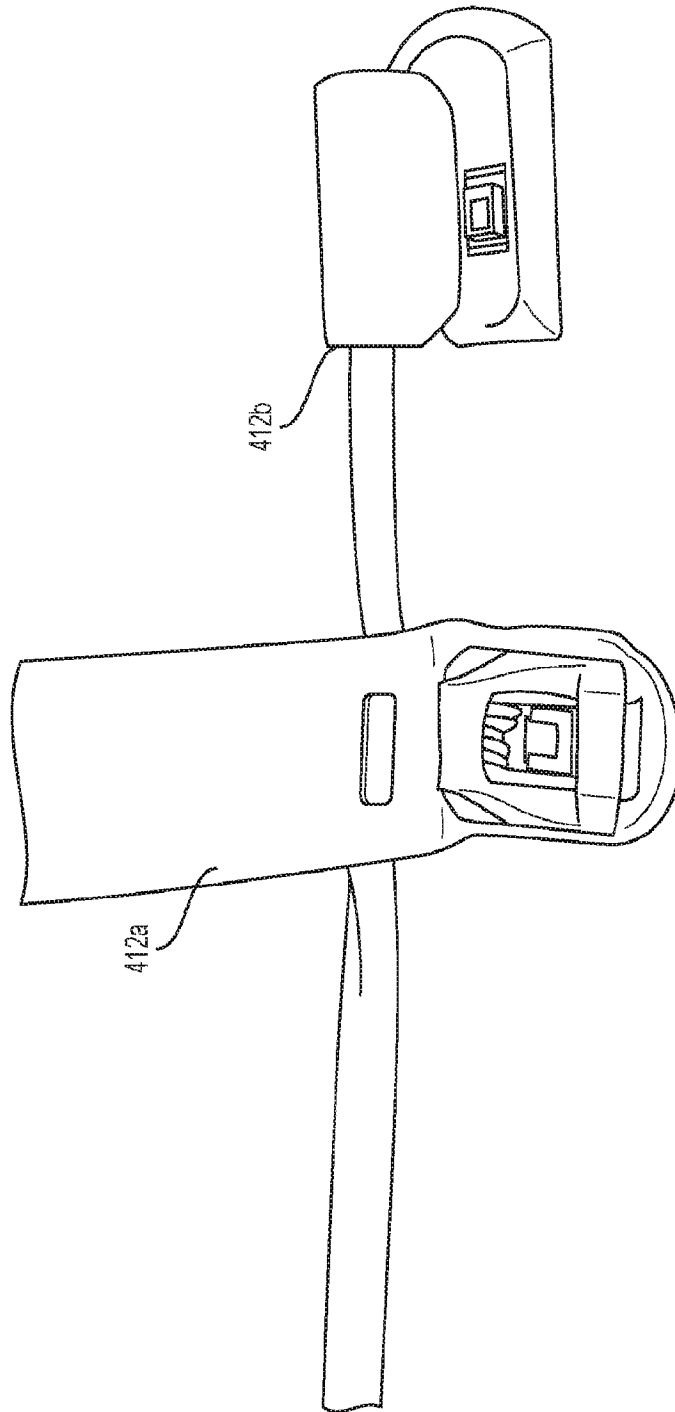


FIG. 4F

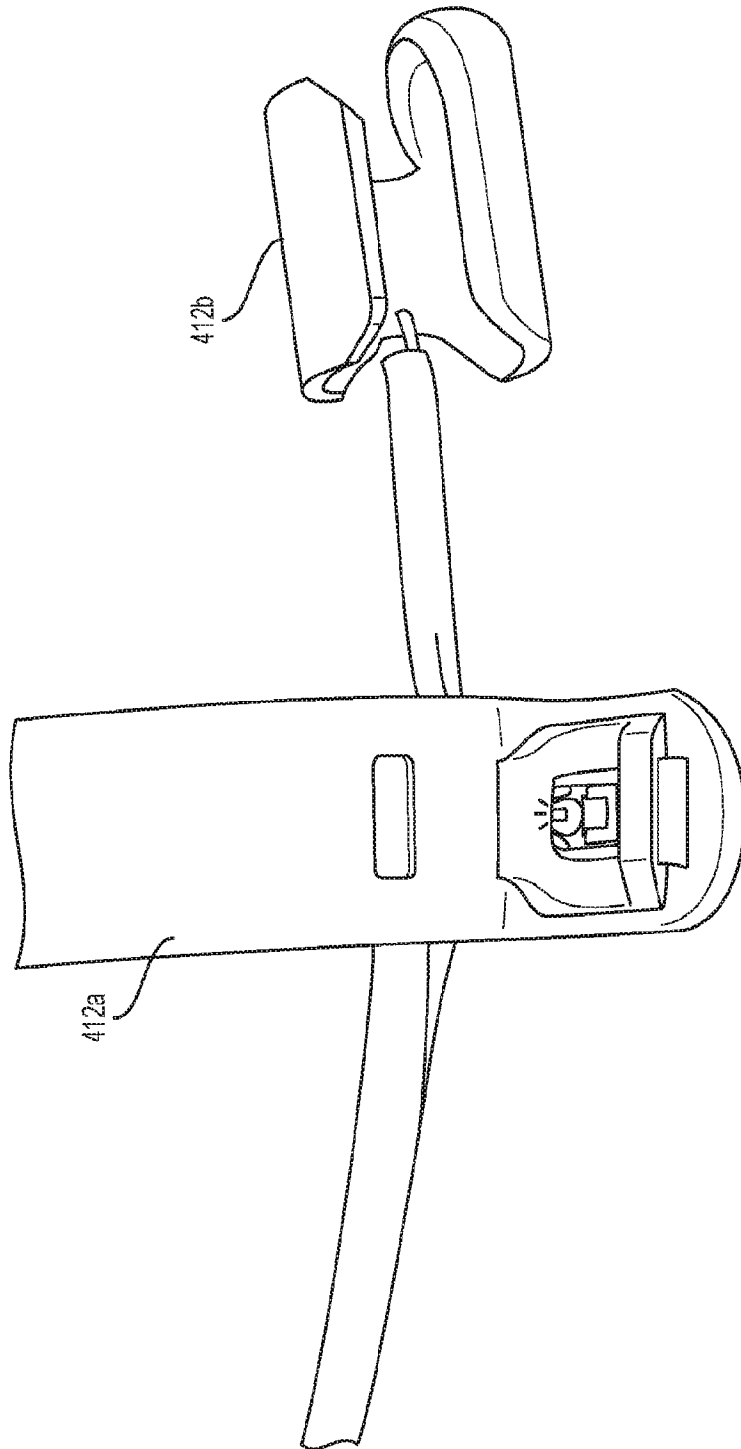


FIG. 4G

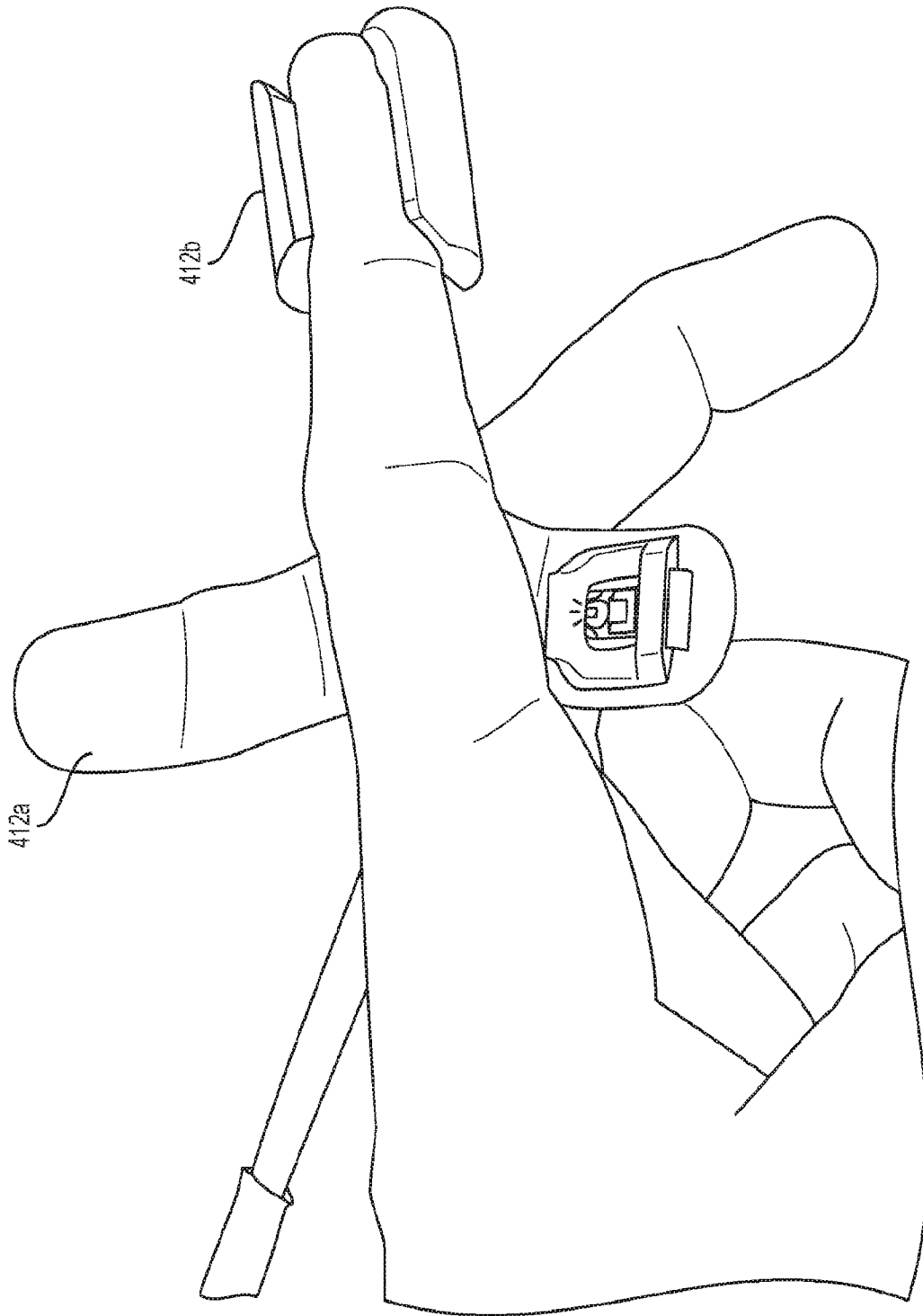


FIG. 4H

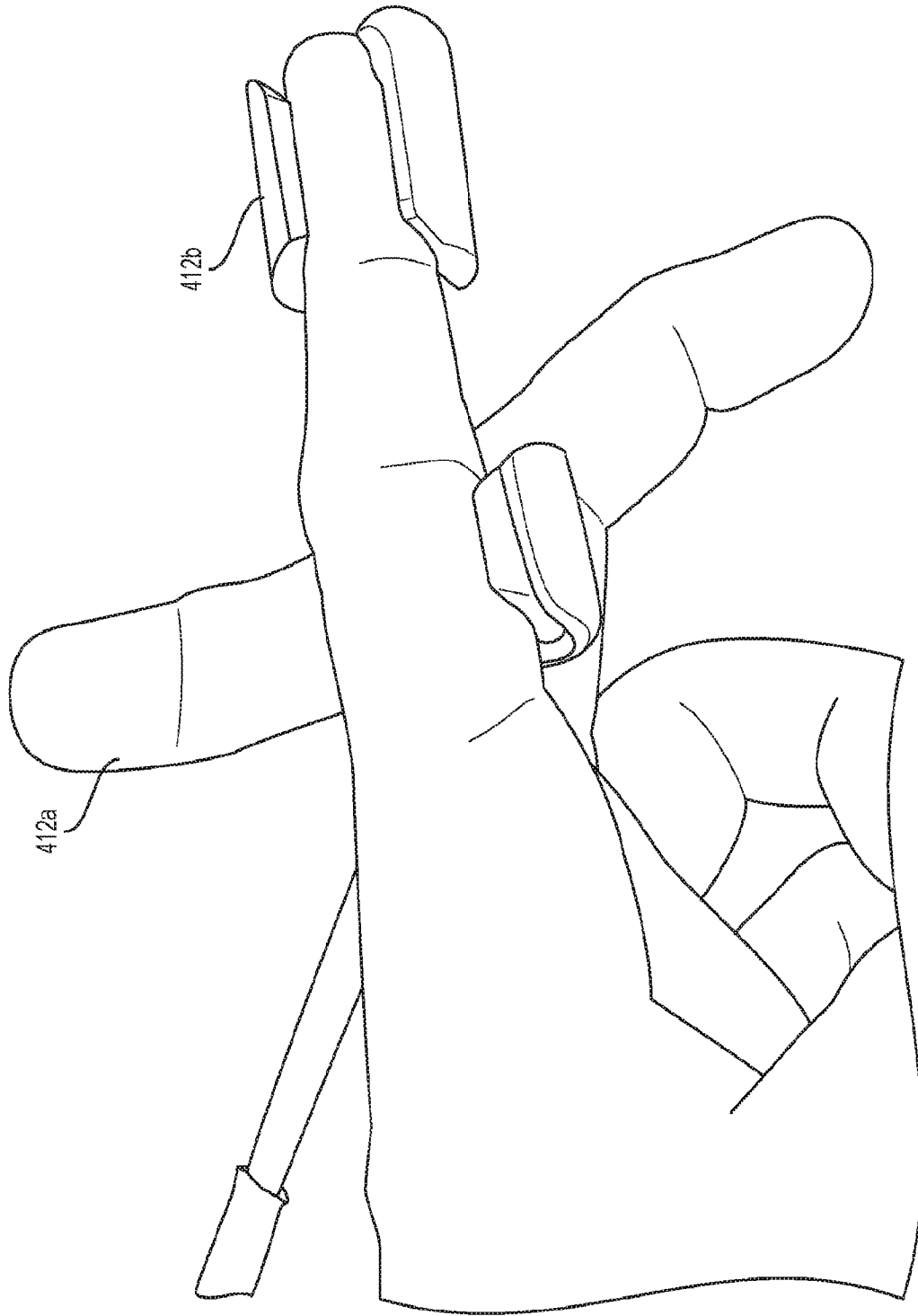


FIG. 4I

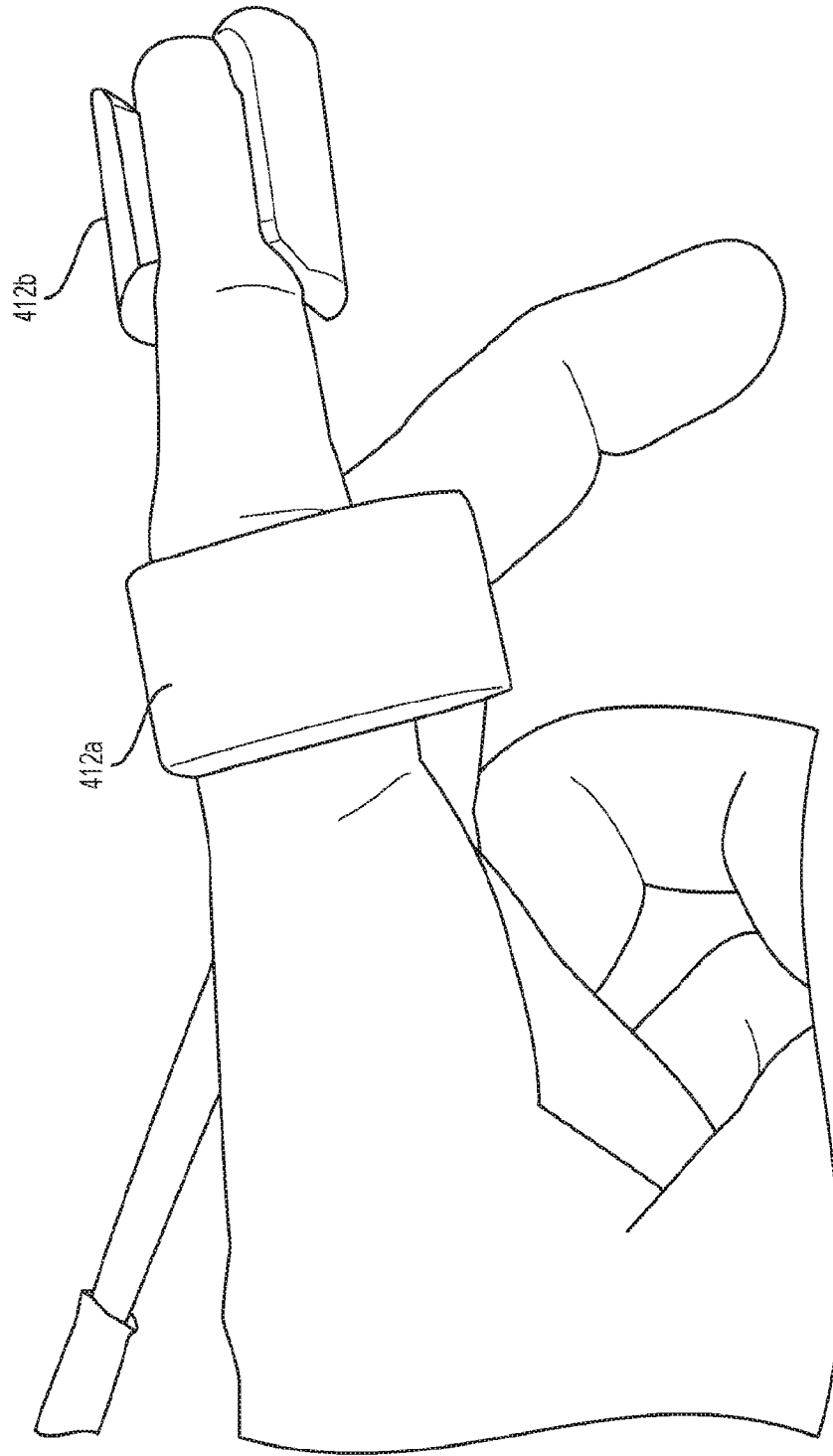


FIG. 4J

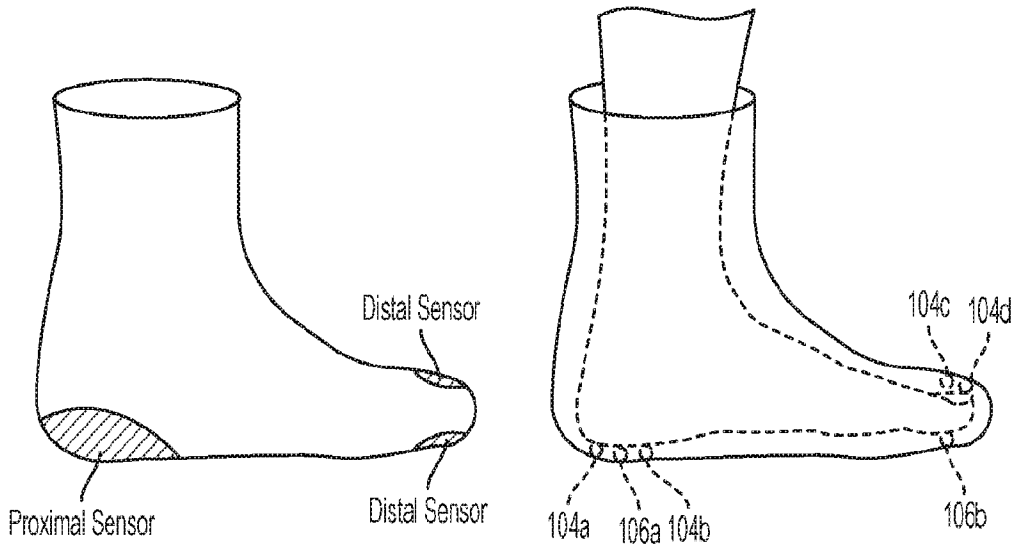


FIG. 4K

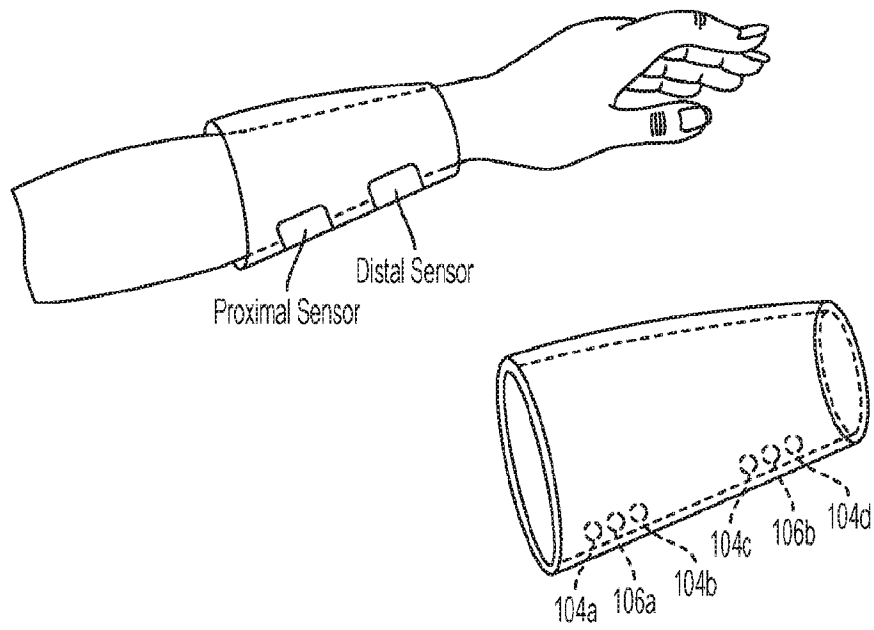


FIG. 4L

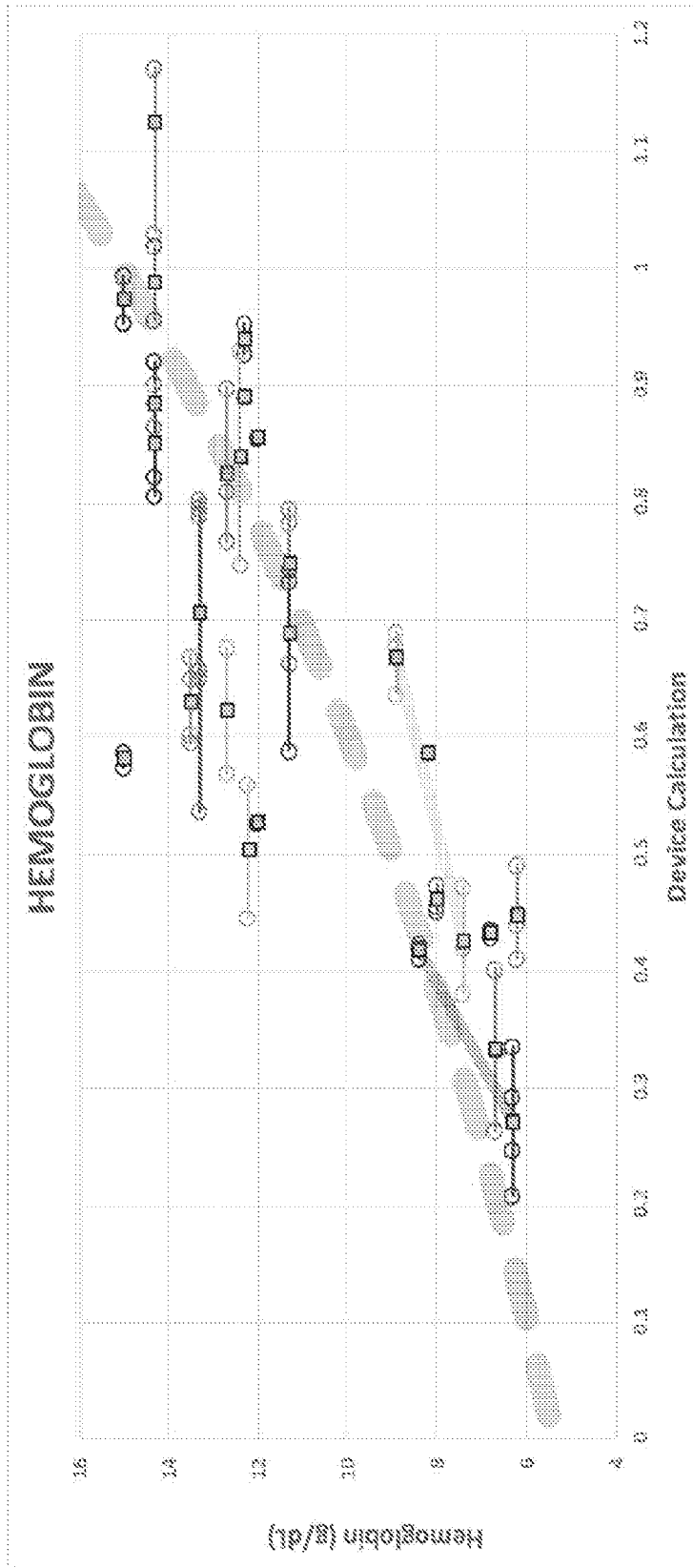


FIG. 5

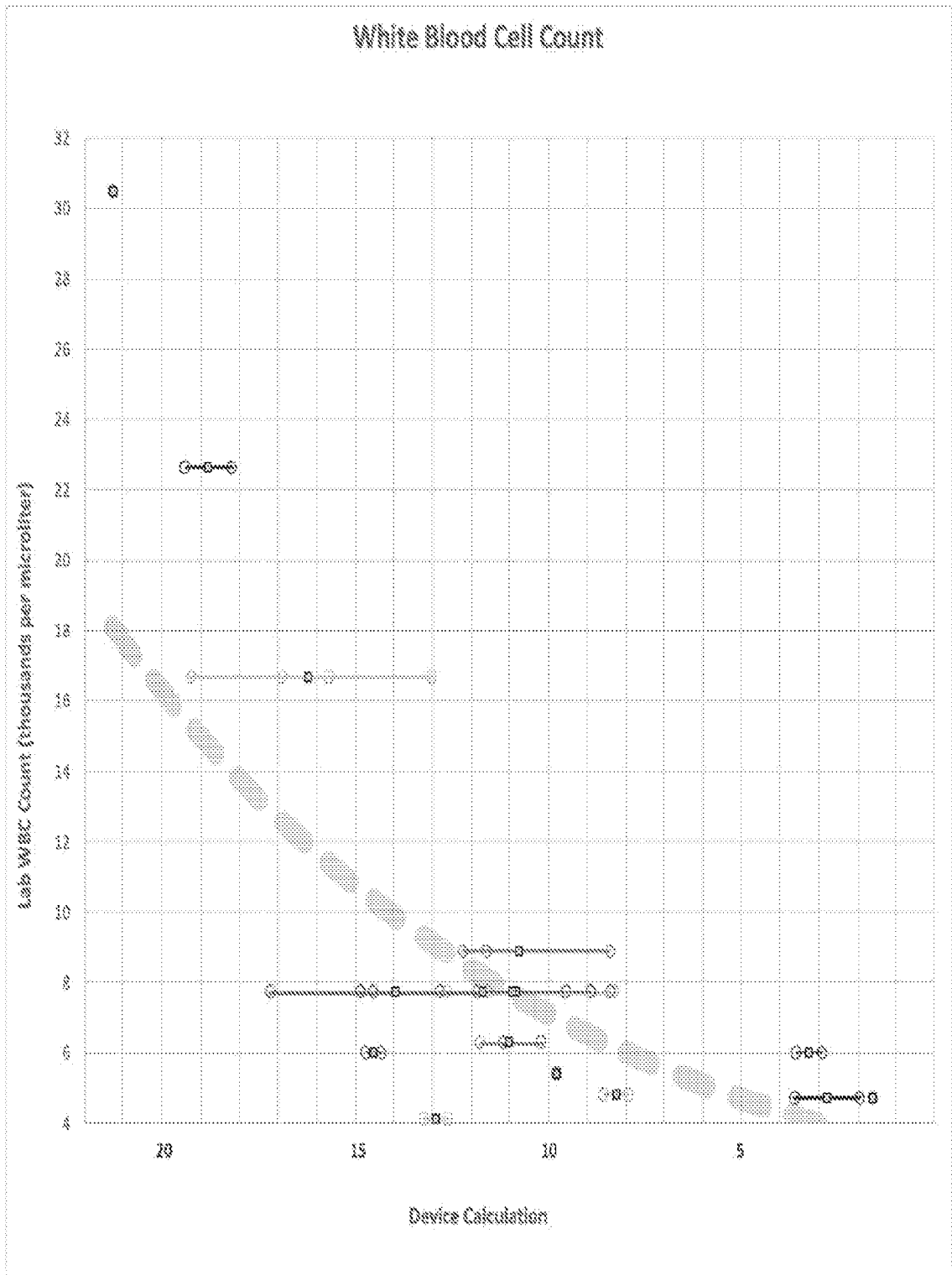


FIG. 6

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/59873

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC - A61B 5/026, 5/145, 5/1455 (2017.01)  
 CPC - A61B 5/0261, 5/145, 5/1455, 5/14551

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 See Search History document

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

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,104,939 A (GRONER, W. et al.) August 15, 2000; abstract; figures 2, 15A, 15B, 17A, and 17B; column 8, lines 8-25; column 16, lines 40-64; column 20, lines 22-48; column 24, lines 1-11; column 24, line 55- column 25, line 45; column 28, line 62- column 29, line 26; column 30, lines 43-54; column 30, line 43 - column 31, line 44.	1-4, 6, 14, 18-20, 22-23 --- 21, 24,-26
Y	US 2015/0018647 A1 (XEROX CORPORATION) January 15, 2015; figures 1-5; paragraphs [0020, 0022, 0026, 0027].	21, 24
Y	WO 2016/003269 A1 (SCINT B.V.) January 7, 2016; figures 1 and 7; page 13, lines 1-15; page 24, lines 19-26; page 28, line 18- page 29, line 4; page 34, lines 1-10.	25, 26
A	WO 2011/070357 A1 (MOOR INSTRUMENTS, LTD:) June 16, 2011; entire document.	1-32
A	US 5,791,345 A (ISHIHARA, K. et al.) August 11, 1998; entire document.	1-32

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

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

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

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

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Date of the actual completion of the international search

20 December 2017 (20.12.2017)

Date of mailing of the international search report

17 JAN 2018

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