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(54) **METHOD FOR SPECTROPHOTOMETRIC BLOOD OXYGENATION MONITORING**

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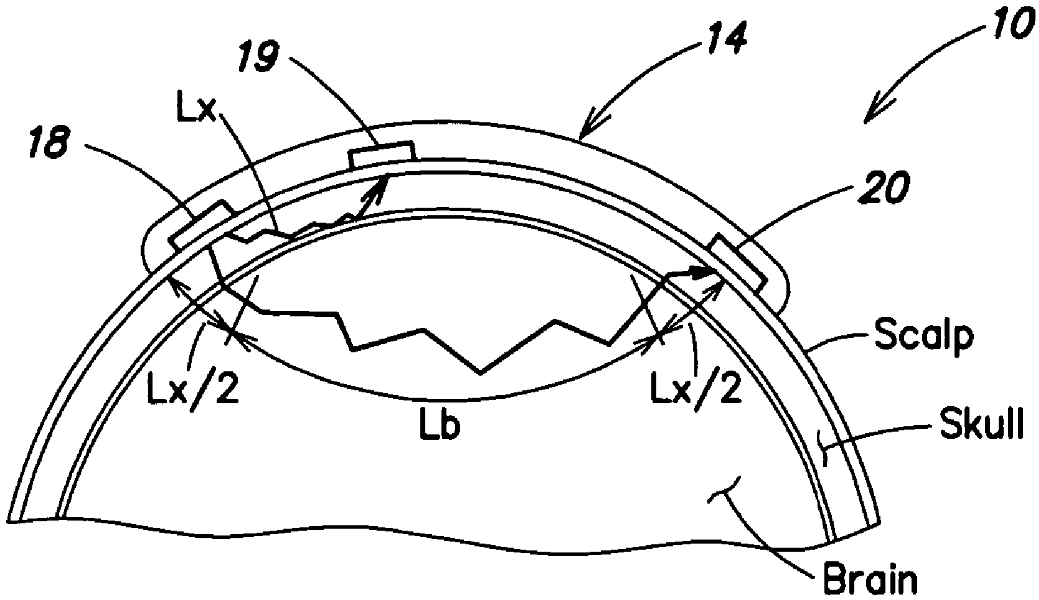
(57) **ABSTRACT**

A method and apparatus for non-invasively determining the blood oxygenation within a subject's tissue is provided that utilizes a near infrared spectrophotometric (NIRS) sensor capable of transmitting a light signal into the tissue of a subject and sensing the light signal once it has passed through the tissue via transmittance or reflectance.



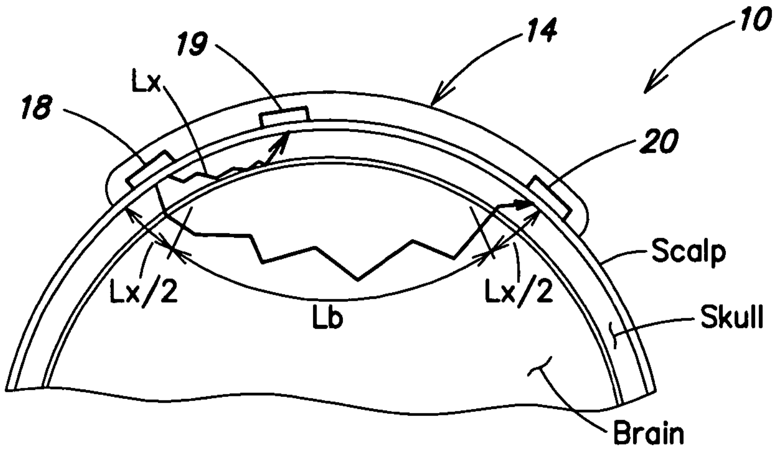


FIG. 1

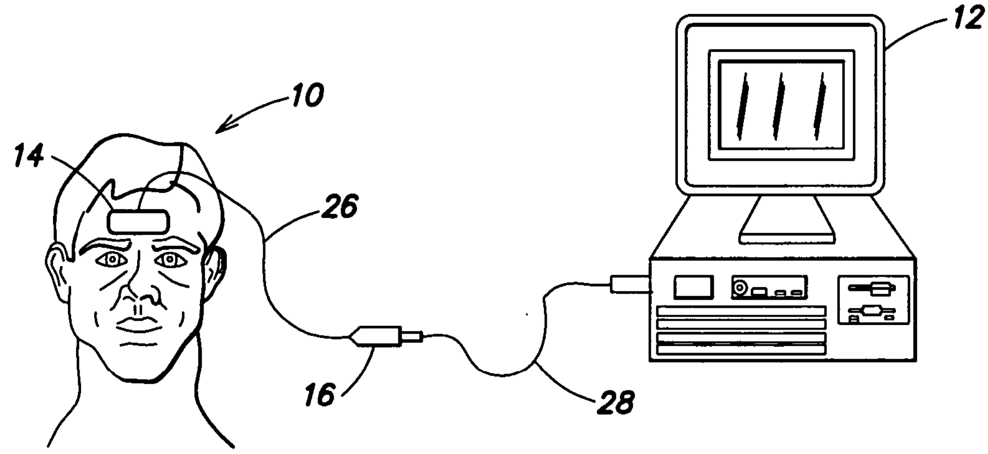


FIG. 2

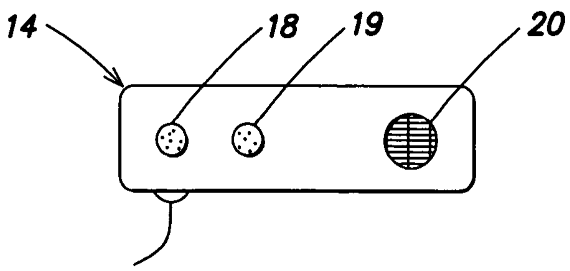


FIG. 3

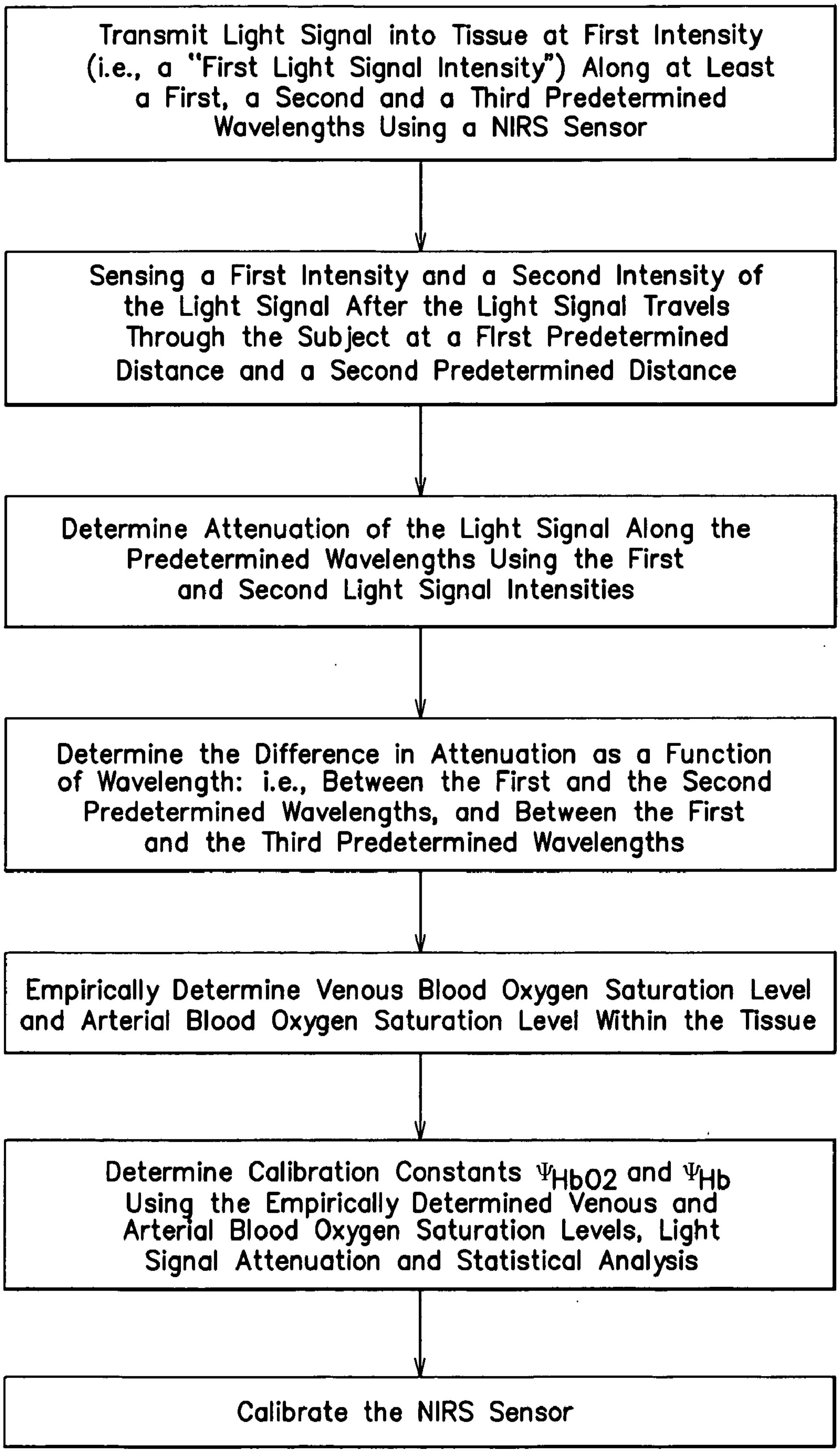

Transmit Light Signal into Tissue at First Intensity (i.e., a "First Light Signal Intensity") Along at Least a First, a Second and a Third Predetermined Wavelengths Using a NIRS Sensor
Sensing a First Intensity and a Second Intensity of the Light Signal After the Light Signal Travels Through the Subject at a First Predetermined Distance and a Second Predetermined Distance
Determine Attenuation of the Light Signal Along the Predetermined Wavelengths Using the First and Second Light Signal Intensities
Determine the Difference in Attenuation as a Function of Wavelength: i.e., Between the First and the Second Predetermined Wavelengths, and Between the First and the Third Predetermined Wavelengths
Empirically Determine Venous Blood Oxygen Saturation Level and Arterial Blood Oxygen Saturation Level Within the Tissue
Determine Calibration Constants Ψ_{Hb02} and Ψ_{Hb} Using the Empirically Determined Venous and Arterial Blood Oxygen Saturation Levels, Light Signal Attenuation and Statistical Analysis
Calibrate the NIRS Sensor

FIG. 4

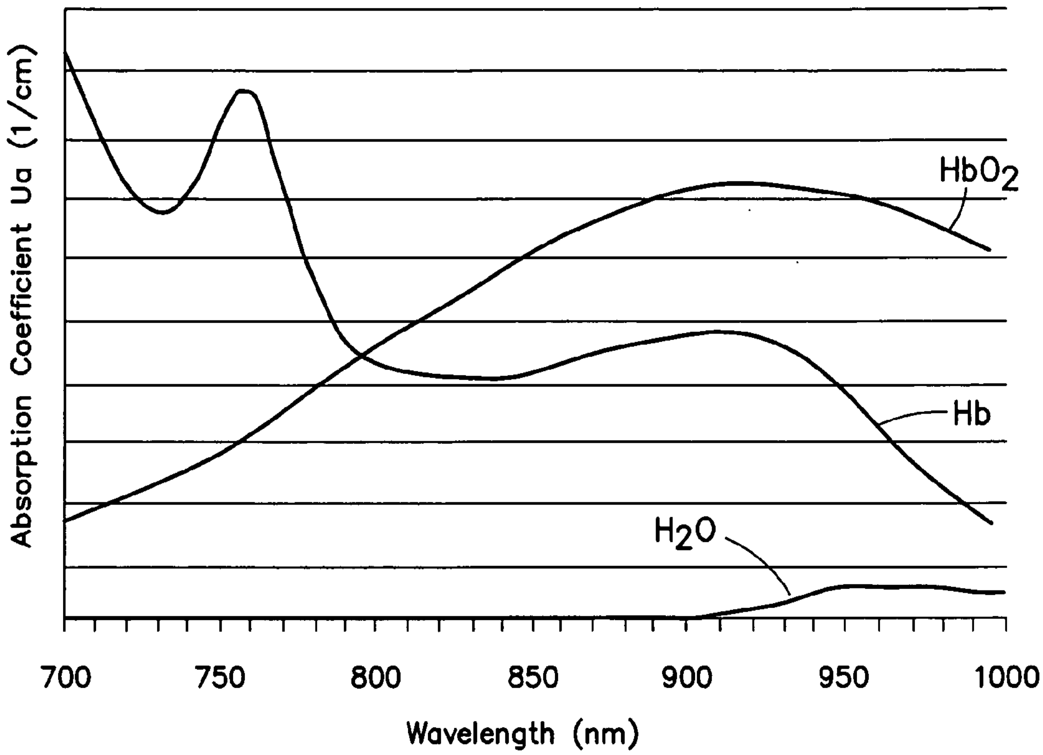

Absorption Coefficient Ua (1/cm)
HbO2
Hb
H2O
700
750
800
850
900
950
1000
Wavelength (nm)

FIG. 5

METHOD FOR SPECTROPHOTOMETRIC BLOOD OXYGENATION MONITORING

[0001] This application claims the benefit of the filing date of U.S. Provisional Applications 60/398,937, filed Jul. 26, 2002, and 60/407,277 filed Aug. 30, 2002. This application is a continuation of U.S. Patent Application No. 10/628,068, filed Jul. 24, 2003.

[0002] This invention was made with Government support under Contract No. IR43NS045488-01 awarded by the Department of Health & Human Services. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] 1. Technical Field.

[0004] This invention relates to methods for non-invasively determining biological tissue oxygenation in general, and to non-invasive methods utilizing near-infrared spectroscopy (NIRS) techniques in particular.

[0005] 2. Background Information.

[0006] The molecule that carries the oxygen in the blood is hemoglobin. Oxygenated hemoglobin is called oxyhemoglobin (HbO_2) and deoxygenated hemoglobin is deoxyhemoglobin (Hb). Total hemoglobin is the summation of the two states of hemoglobin (Total $Hb=HbO_2+Hb$), and is proportional to relative blood volume changes, provided that the hematocrit or hemoglobin concentration of the blood is unchanged. The mammalian cardiovascular system consists of a blood pumping mechanism (the heart), a blood transportation system (blood vessels), and a blood oxygenation system (the lungs). Blood oxygenated by the lungs passes through the heart and is pumped into the arterial vascular system. Under normal conditions, oxygenated arterial blood consists predominately of HbO_2. Large arterial blood vessels branch off into smaller branches called arterioles, which profuse throughout biological tissue. The arterioles branch off into capillaries, the smallest blood vessels. In the capillaries, oxygen carried by hemoglobin is transported to the cells in the tissue, resulting in the release of oxygen molecules ($HbO_2 \Rightarrow Hb$). Under normal conditions, only a fraction of the HbO_2 molecules give up oxygen to the tissue, depending on the cellular metabolic need. The capillaries then combine together into venuoles, the beginning of the venous circulatory system. Venuoles then combine into larger blood vessels called veins. The veins further combine and return to the heart, and then venous blood is pumped to the lungs. In the lungs, deoxygenated hemoglobin Hb collects oxygen becoming HbO_2 again and the circulatory process is repeated.

[0007] Oxygen saturation is defined as:

$$O_2 \text{ saturation } \% = \frac{HbO_2}{(HbO_2 + Hb)} * 100\% \quad \text{(Eqn. 1)}$$

In the arterial circulatory system under normal conditions, there is a high proportion of HbO_2 to Hb, resulting in an arterial oxygen saturation (defined as SaO_2 %) of 95-100%. After delivery of oxygen to tissue via the capillaries, the proportion of HbO_2 to Hb decreases. Therefore, the measured oxygen saturation of venous blood (defined as SvO_2%) is lower and may be about 70%.

[0008] One spectrophotometric method, called pulse oximetry, determines arterial oxygen saturation (SaO_2) of peripheral tissue (i.e., finger, ear, nose) by monitoring pulsatile optical attenuation changes of detected light induced by pulsatile arterial blood volume changes in the arteriolar vascular system. The method of pulse oximetry requires pulsatile blood volume changes in order to make a measurement. Since venous blood is not pulsatile, pulse oximetry cannot provide any information about venous blood.

[0009] Near-infrared spectroscopy (NIRS) is an optical spectrophotometric method of continually monitoring tissue oxygenation that does not require pulsatile blood volume to calculate parameters of clinical value. The NIRS method is based on the principle that light in the near-infrared range (700 to 1,000 nm) can pass easily through skin, bone and other tissues where it encounters hemoglobin located mainly within micro-circulation passages (e.g., capillaries, arterioles, and venuoles). Hemoglobin exposed to light in the near infra-red range has specific absorption spectra that varies depending on its oxidation state (i.e., oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) each act as a distinct chromophore). By using light sources that transmit near-infrared light at specific different wavelengths, and measuring changes in transmitted or reflected light attenuation, concentration changes of the oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) can be monitored. The ability to continually monitor cerebral oxygenation levels is particularly valuable for those patients subject to a condition in which oxygenation levels in the brain may be compromised, leading to brain damage or death.

[0010] The apparatus used in NIRS analysis typically includes a plurality of light sources, one or more light detectors for detecting reflected or transmitted light, and a processor for processing signals that represent the light emanating from the light source and the light detected by the light detector. Light sources such as light emitting diodes (LEDs) or laser diodes that produce light emissions in the wavelength range of 700-1000 nm at an intensity below that which would damage the biological tissue being examined are typically used. A photodiode or other light source detector is used to detect light reflected from or passed through the tissue being examined. The processor takes the signals from the light sources and the light detector and analyzes those signals in terms of their intensity and wave properties.

[0011] It is known that relative changes of the concentrations of HbO_2 and Hb can be evaluated using apparatus similar to that described above, including a processor programmed to utilize a variant of the Beer-Lambert Law, which accounts for optical attenuation in a highly scattering medium like biological tissue. The modified Beer-Lambert Law can be expressed as:

$$A_\lambda = -\log(I/I_o)_\lambda = \alpha_\lambda * C * d * B_\lambda + G \quad \text{(Eqn. 2)}$$

wherein "A_λ" represents the optical attenuation in tissue at a particular wavelength λ (units: optical density or OD); "I_o" represents the incident light intensity (units: W/cm^2); "I" represents the detected light intensity; "α_λ" represents the wavelength dependent absorption coefficient of the chromophore (units: $OD*cm^{-1}*\mu M^{-1}$); "C" represents the concentration of chromophore (units: μM); "d" represents the light source to detector (optode) separation distance (units: cm); "B_λ" represents the wavelength dependent light scattering differential pathlength factor (unitless); and "G" represents light attenuation due to scattering within tissue (units: OD). The product of "$d*B_\lambda$" represents the effective pathlength of photon traveling through the tissue.

[0012] Absolute measurement of chromophore concentration (C) is very difficult because G is unknown or difficult to ascertain. However, over a reasonable measuring period of several hours to days, G can be considered to remain constant, thereby allowing for the measurement of relative changes of chromophore from a zero reference baseline. Thus, if time t_1 marks the start of an optical measurement (i.e., a base line) and time t_2 is an arbitrary point in time after t_1, a change in attenuation (ΔA) between t_1 and t_2 can be calculated, and variables G and 1_o, will cancel out providing that they remain constant.

[0013] The change in chromophore concentration ($\Delta C = C(t_2)-C(t_1)$) can be determined from the change in attenuation ΔA, for example using the following equation derived from the modified Beer-Lambert Law:

$$\Delta A=-\log(I_{t2}/I_{t1})_\lambda=\alpha_\lambda*\Delta C*d*B_\lambda \qquad \text{(Eqn. 3)}$$

Presently known NIRS algorithms that are designed to calculate the relative change in concentration of more than one chromophore use a multivariate form of Equation 2 or 3. To distinguish between, and to compute relative concentration changes in, oxyhemoglobin (ΔHbO_2) and deoxyhemoglobin (ΔHb), a minimum of two different wavelengths are typically used. The concentration of the HbO_2 and Hb within the examined tissue is determined in gmoles per liter of tissue (μM).

[0014] The above-described NIRS approach to determine oxygenation levels is useful, but it is limited in that it only provides information regarding a change in the level of oxygenation within the tissue. It does not provide a means for determining the absolute value of oxygen saturation within the biological tissue.

[0015] At present, information regarding the relative contributions of venous and arterial blood within tissue examined by NIRS is either arbitrarily chosen or is determined by invasive sampling of the blood as a process independent from the NIRS examination. For example, it has been estimated that NIRS examined brain tissue comprising about 60 to 80% venous blood and about 20 to 40% arterial blood. Blood samples from catheters placed in venous drainage sites such as the internal jugular vein, jugular bulb, or sagittal sinus have been used to evaluate NIRS measurements. Results from animal studies have shown that NIRS interrogated tissue consists of a mixed vascular bed with a venous-to-arterial ratio of about 2:1 as determined from multiple linear regression analysis of sagittal sinus oxygen saturation ($SssO_2$) and arterial oxygen saturation (SaO_2). An expression representing the mixed venous/arterial oxygen saturation ($SmvO_2$) in NIRS examined tissue is shown by the equation:

$$SmvO_2=Kv*SvO_2+Ka*SaO_2 \qquad \text{(Eqn. 4)}$$

where "SvO_2" represents venous oxygen saturation; "SaO_2" represents arterial oxygen saturation; and Kv and Ka are the weighted venous and arterial contributions respectively, with Kv+Ka=1. The parameters Kv and Ka may have constant values, or they may be a function of SvO_2 and SaO_2. Determined oxygen saturation from the internal jugular vein ($SijvO_2$), jugular bulb ($SjbO_2$), or sagittal sinus ($SssO_2$) can be used to represent SvO_2. Therefore, the value of each term in Equation 4 is empirically determined, typically by discretely sampling or continuously monitoring and subsequently evaluating patient arterial and venous blood from tissue that the NIRS sensor is examining, and using regression analysis to determine the relative contributions of venous and arterial blood independent of the NIRS examination.

[0016] To non-invasively determine oxygen saturation within tissue at certain depth, it is necessary to limit the influence from the superficial tissues. For example, to determine brain oxygen saturation of adult human with NIRS technology, the contamination from extracraninal tissue (scalp and skull) must be eliminated or limited.

[0017] What is needed, therefore, is a method for non-invasively determining the level of oxygen saturation within biological tissue that can determine the absolute oxygen saturation value rather than a change in level; a method that provides calibration means to account for energy losses (i.e., light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability; and a method that can non-invasively determine oxygen saturation within tissue at certain depth by limiting the influence from the superficial tissues.

DISCLOSURE OF THE INVENTION

[0018] It is, therefore, an object of the present invention to provide a method for non-invasively determining the absolute oxygen saturation value within biological tissue.

[0019] It is a further object of the present invention to provide a method that provides calibration means to account for energy losses due to scattering as well as other background absorption from biological compounds.

[0020] It is a still further object of the present invention to provide a method that can non-invasively determine oxygen saturation within tissue at certain depth that limits the influence from the superficial tissues.

[0021] According to the present invention, a method and apparatus for non-invasively determining the blood oxygen saturation level within a subject's tissue is provided that utilizes a near infrared spectrophotometric (NIRS) sensor capable of transmitting a light signal into the tissue of a subject and sensing the light signal once it has passed through the tissue via transmittance or reflectance. The method includes the steps of: (1) transmitting a light signal into the subject's tissue, wherein the transmitted light signal includes a first wavelength, a second wavelength, and a third wavelength; (2) sensing a first intensity and a second intensity of the light signal, along the first, second, and third wavelengths after the light signal travels through the subject at a first and second predetermined distance; (3) determining an attenuation of the light signal for each of the first, second, and third wavelengths using the sensed first intensity and sensed second intensity of the first, second, and third wavelengths; (4) determining a difference in attenuation of the light signal between the first wavelength and the second wavelength, and between the first wavelength and the third wavelength; and (5) determining the blood oxygen saturation level within the subject's tissue using the difference in attenuation between the first wavelength and the second wavelength, and the difference in attenuation between the first wavelength and the third wavelength.

[0022] The present method makes it possible to account for energy losses (i.e., light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability. By determining differential attenuation as a function of wavelength, the energy losses due to scattering as well as other background absorption from biological compounds are cancelled out or minimized relative to the attenuation attributable to deoxyhemoglobin, and attenuation attributable to oxyhemoglobin.

[0023] In order to account for the resulting minimized differential attenuation attributable to tissue light scattering characteristics, fixed light absorbing components, and measuring apparatus characteristics, each of the parameters must be measured or calibrated out. Since direct measurement is difficult, calibration to empirically determined data combined with data developed using the NIRS sensor is performed by using regression techniques. The empirically determined data is collected at or about the same time the data is developed with the NIRS sensor. Once the calibration parameters associated with attenuation attributable to tissue light scattering characteristics, fixed light absorbing components, and measuring apparatus characteristics have been determined, the NIRS sensor can be calibrated.

[0024] The calibrated sensor can then be used to accurately and non-invasively determine the total oxygen saturation level in the original subject tissue or other subject tissue. In addition, if the effective pathlength of photon traveling through the tissue is known, for example, the separation distance ("d") between the light source to the light detector is known or is determinable, and the value of "B_λ", which represents the wavelength dependent light scattering differential pathlength factor is known or is determinable, then the total amount of concentrations of deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2) within the examined tissue can be determined using the present method and apparatus.

[0025] The calibrated sensor can be used subsequently to calibrate similar sensors without having to invasively produce a blood sample. Hence, the present method and apparatus enables a non-invasive determination of the blood oxygen saturation level within tissue. For example, an operator can create reference values by sensing a light signal or other reference medium using the calibrated sensor. The operator can then calibrate an uncalibrated sensor by sensing the same light signal or reference medium, and subsequently adjusting the uncalibrated sensor into agreement with the calibrated sensor. Hence, once a reference sensor is created, other similar sensors can be calibrated without the need for invasive procedure.

[0026] There are, therefore, several advantages provided by the present method and apparatus. Those advantages include: 1) a practical non-invasive method and apparatus for determining oxygen saturation within tissue that can be used to determine the total blood oxygen saturation within tissue as opposed to a change in blood oxygen saturation; 2) a calibration method that accounts for energy losses (e.g., light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability; 3) a practical non-invasive method and apparatus for determining oxygen saturation within tissue that can distinguish between the contribution of oxygen saturation attributable to venous blood and that saturation attributable to arterial blood; and 4) a practical non-invasive method and apparatus for determining oxygen saturation within tissue at certain depth that limits the influence from the superficial tissues.

[0027] In an alternative embodiment, aspects of the above-described methodology are combined with pulse oximetry techniques to provide a non-invasive method of distinguishing between blood oxygen saturation within tissue that is attributable to venous blood and that which is attributable to arterial blood. Pulse oximetry is used to determine arterial oxygen saturation, and the arterial oxygen saturation is, in turn, used to determine the venous oxygen saturation.

[0028] These and other objects, features, and advantages of the present invention method and apparatus will become apparent in light of the detailed description of the invention provided below and the accompanying drawings. The methodology and apparatus described below constitute a preferred embodiment of the underlying invention and do not, therefore, constitute all aspects of the invention that will or may become apparent by one of skill in the art after consideration of the invention disclosed overall herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] **FIG. 1** is a diagrammatic representation of a NIRS sensor.

[0030] **FIG. 2** is a diagrammatic representation of a NIRS sensor placed on a subject's head.

[0031] **FIG. 3** is a diagrammatic view of a NIRS sensor.

[0032] **FIG. 4** is a block diagram of the present methodology for calibrating a NIRS sensor.

[0033] **FIG. 5** is a graph showing an exemplary plot of absorption coefficient vs. wavelength.

DETAILED DESCRIPTION THE INVENTION

[0034] The present method of and apparatus for non-invasively determining the blood oxygen saturation level within a subject's tissue is provided that utilizes a near infrared spectrophotometric (NIRS) sensor that includes a transducer capable of transmitting a light signal into the tissue of a subject and sensing the light signal once it has passed through the tissue via transmittance or reflectance. The present method and apparatus can be used with a variety of NIRS sensors. The present method is not limited to use with this preferred NIRS sensor, however.

[0035] Referring to **FIGS. 1-5**, the preferred NIRS sensor includes a transducer portion **10** and processor portion **12**. The transducer portion **10** includes an assembly housing **14** and a connector housing **16**. The assembly housing **14**, which is a flexible structure that can be attached directly to a subject's body, includes one or more light sources **18** and light detectors **19**, **20**. A disposable adhesive envelope or pad is used for mounting the assembly housing **14** easily and securely to the subject's skin. Light signals of known but different wavelengths from the light sources **18** emit through a prism assembly. The light sources **18** are preferably laser diodes that emit light at a narrow spectral bandwidth at predetermined wavelengths. In one embodiment, the laser diodes are mounted within the connector housing **16**. The laser diodes are optically interfaced with a fiber optic light guide to the prism assembly that is disposed within the assembly housing **14**. In a second embodiment, the light sources **18** are mounted within the assembly housing **14**. A first connector cable **26** connects the assembly housing **14** to the connector housing **16** and a second connector cable **28** connects the connector housing **16** to the processor portion **12**. The light detector **20** includes one or more photodiodes. The photodiodes are also operably connected to the processor portion **12** via the first and second connector cables **26**, **28**. The processor portion **12** includes a processor for processing light intensity signals from the light sources **18** and the light detectors **19**, **20**.

[0036] The processor utilizes an algorithm that characterizes a change in attenuation as a function of the difference in attenuation between different wavelengths. The present method advantageously accounts for but minimizes the effects of pathlength and parameter "E", which represents energy losses (i.e., light attenuation) due to light scattering within tissue (G), other background absorption losses from biological compounds (F), and other unknown losses including measuring apparatus variability (N). E=G+F+N.

[0037] Referring to **FIG. 1**, the absorption $A_{b\lambda}$ detected from the deep light detector **20** comprises attenuation and energy loss from both the deep and shallow tissue, while the absorption $A_{x\lambda}$ detected from the shallow light detector **19** comprises attenuation and energy loss from shallow tissue only. Absorptions A_λ and $A_{x\lambda}$ can be expressed in the form of Equation 5 and Equation 6 below which is a modified version of Equation 2 that accounts for energy losses due to "E":

$$A_{b\lambda}=-\log(I_b/I_o)_\lambda=\alpha_\lambda*C_b*L_b+\alpha_\lambda*C_x*L_x+E_\lambda \quad \text{(Eqn. 5)}$$

$$A_{x\lambda}=-\log(I_x/I_o)_\lambda=\alpha_\lambda*C_x*L_x+E_{x\lambda} \quad \text{(Eqn. 6)}$$

Substituting Equation 6, into Equation 5 yields A'_λ, which represents attenuation and energy loss from deep tissue only:

$$A'_\lambda = A_{b\lambda} - A_{x\lambda} = \alpha_\lambda * C_b * L_b + (E_\lambda - E_{x\lambda}) = -\log\left(\frac{I_b}{I_x}\right)_\lambda \quad \text{(Eqn. 7)}$$

Where L is the effective pathlength of the photon traveling through the deep tissue and A'_1 and A'_2 are the absorptions of two different wavelengths. Let $E'_\lambda=E_\lambda-E_{x\lambda}$, therefore:

$$A'_1-A'_2=\Delta A'_{12} \quad \text{(Eqn. 8)}$$

Substituting Equation 7 into Equation 8 for A'_1 and A'_2, $_{\Delta A'12}$ can be expressed as:

$$\Delta A'_{12}=A\alpha_{\lambda 12}*C_b*L_b+\Delta E'_{12} \quad \text{(Eqn. 9)}$$

and rewritten Equation 9 in expanded form:

$$\Delta A'_{12}=<(\alpha_{r1}-\alpha_{r2})[Hb]_b+(\alpha_{o1}-\alpha_{o2})[HbO_2]_b>L_b+(E'_1-E'_2)=(\Delta\alpha_{r12}*[Hb]_b*L_b)+(\Delta\alpha_{o12}*[HbO_2]_b*L_b)+\Delta E'_{12} \quad \text{(Eqn. 10)}$$

where:

$(\Delta\alpha_{r12}*[Hb]_b*L_b)$ represents the attenuation attributable to Hb;

$(\Delta\alpha_{o12}*[Hbo_2]_b* L_b)$ represents the attenuation attributable to HbO_2; and

$\Delta E'_{12}$ represents energy losses (i.e. light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability.

[0038] The multivariate form of Equation 10 is used to determine $[HbO_2]_b$ and [Hb]b with three different wavelengths:

$$\begin{bmatrix} \Delta A'_{12} - \Delta E'_{12} \\ \Delta A'_{13} - \Delta E'_{13} \end{bmatrix} (L_b)^{-1} = \begin{bmatrix} \Delta\alpha_{r12} & \Delta\alpha_{o12} \\ \Delta\alpha_{r13} & \Delta\alpha_{o13} \end{bmatrix} \begin{bmatrix} [Hb]_b \\ [HbO_2]_b \end{bmatrix} \quad \text{(Eqn. 11)}$$

Rearranging and solving for $[HbO_2]_b$ and $[Hb]_b$, simplifying the $\Delta\alpha$ matrix into $[\Delta\alpha']$:

$$\begin{bmatrix} \Delta A'_{12} \\ \Delta A'_{13} \end{bmatrix} [\Delta\alpha']^{-1} (L_b)^{-1} - \begin{bmatrix} \Delta E'_{12} \\ \Delta E'_{13} \end{bmatrix} [\Delta\alpha']^{-1} (L_b)^{-1} = \begin{bmatrix} [Hb]_b \\ [HbO_2]_b \end{bmatrix} \quad \text{(Eqn. 12)}$$

Then combined matrices $[\Delta A'][\Delta\alpha']^{-1}=[A_c]$ and $[\Delta E][\Delta\alpha']^{-1}=[\Psi_c]$:

$$\begin{bmatrix} A_{Hb} \\ A_{HbO_2} \end{bmatrix} (L_b)^{-1} - \begin{bmatrix} \Psi_{Hb} \\ \Psi_{HbO_2} \end{bmatrix} (L_b)^{-1} = \begin{bmatrix} [Hb]_b \\ [HbO_2]_b \end{bmatrix} \quad \text{(Eqn. 13)}$$

The parameters A_{Hb} and A_{HbO2} represent the product of the matrices $[\Delta A_\lambda]$ and $[\Delta\alpha']^{-1}$ and the parameters ΨHb and ΨHbO2 represent the product of the matrices $[\Delta E'_\lambda]$ and $[\Delta']^{-1}$. To determine the level of cerebral blood oxygen saturation (SnO_2), Equation 13 is rearranged using the form of Equation 1 and is expressed as follows:

$$SnO_2\% = \frac{(A_{HbO_2} - \Psi_{HbO_2})}{(A_{HbO_2} - \Psi_{HbO_2} + A_{Hb} - \Psi_{Hb})} * 100\% \quad \text{(Eqn. 14)}$$

Note that the effective pathlength Lb cancels out in the manipulation from Equation 13 to Equation 14.

[0039] The value for SnO_2 is initially determined from $SmvO_2$ using Equation 4 and the empirically determined values for SvO_2 and SaO_2. The empirically determined values for SvO_2 and SaO_2 are based on data developed by discrete sampling or continuous monitoring of the subject's blood performed at or about the same time as the sensing of the tissue with the sensor. The temporal and physical proximity of the NIRS sensing and the development of the empirical data helps assure accuracy. The initial values for Kv and Ka within Equation 4 are clinically reasonable values for the circumstances at hand. The values for A_{HbO2} and A_{Hb} are determined mathematically using the values for $I_{b\lambda}$ and $I_{x\lambda}$ for each wavelength sensed with the NIRS sensor (e.g., using Equation 5 and 6). The calibration parameters Ψ_{Hb} and Ψ_{HbO2}, which account for energy losses due to scattering as well as other background absorption from biological compounds, are then determined using Equation 14 and non-linear regression techniques by correlation to different weighted values of SvO_2 and SaO_2 (i.e., different values of Ka and Kv). Statistically acceptable values of Kv and Ka and Ψ_{Hb} and Ψ_{HbO2} are converged upon using the non-linear regression techniques. Experimental findings show that after proper selection of Ka and Kv, the calibration parameters Ψ_{Hb} and Ψ_{HbO2} are constant within a statistically acceptable margin of error for an individual NIRS sensor used to monitor brain oxygenation on different human subjects. In other words, once the sensor is calibrated it can be used on various human subjects and produce accurate information for each human subject. The same is true for animal subjects.

[0040] In an alternative method of determining the absolute oxygen saturation value Equation 7 is rewritten:

$$A'_\lambda - E'_\lambda = -\log\ (I_b/I_x)_\lambda - E'_\lambda = \alpha_\lambda * C * L_b = (\alpha_{r\lambda}[Hb]_b + \alpha_{o\lambda}[HbO_2]_b)L_b \quad \text{(Eqn. 15)}$$

For a two wavelength system, let "R" be a calibration index parameter:

$$R = \frac{A'_1 - E'_1}{A'_2 - E'_2} = \frac{(\alpha_{r1}[Hb]_b + \alpha_{o1}[HbO_2]_b)L_b}{(\alpha_{r2}[Hb]_b + \alpha_{o2}[HbO_2]_b)L_b} \quad \text{(Eqn. 16)}$$

$$= \frac{\alpha_{r1} + \alpha_{o1}\frac{[HbO_2]_b}{[Hb]_b}}{\alpha_{r2} + \alpha_{o2}\frac{[HbO_2]_b}{[Hb]_b}}$$

$$= \frac{\alpha_{r1} + \alpha_{o1}\frac{SnO_2}{1 - SnO_2}}{\alpha_{r2} + \alpha_{o2}\frac{SnO_2}{1 - SnO_2}}$$

Canceling out L_b and substituting:

$$\frac{[HbO_2]_b}{[Hb]_b} = \frac{SnO_2}{1 - SnO_2} \text{ from } SnO_2 = \frac{[HbO_2]_b}{[HbO_2]_b + [Hb]_b}$$

the following expression for SnO_2 is obtained:

$$SnO_2 = \frac{\alpha_{r1} - \alpha_{r2}R}{(\alpha_{r1} - \alpha_{o1}) + (\alpha_{o2} - \alpha_{r2})R} \quad \text{(Eqn. 17)}$$

[0041] The value of A_1' and A_2' are determined by measuring I_b and I_x for each wavelength. The parameters E'_1 and E'_2 can be considered as empirically determined calibration coefficients derived from the "best-fit" combinations of the weighted ratios of venous and arterial blood-oxygen saturation of the brain. By using non-linear regression techniques, the values of E'_1 and E'_2 are determined by correlating to different combinations of venous and arterial oxygen saturation weighted values to find the "best-fit" relationship of "R" as a function of A_1', A_2', E'_1 and E'_2 (Equation 17) to a specific ratio of venous and arterial saturation weighted values.

[0042] In the determination of the SnO_2 percentage, the effective photon pathlength L_b cancels out. If, however, the photon pathlength is known or estimated, then the determination of the total value of Hb and/or HbO_2 is possible. For example, if a value for pathlength L_b is input into Equation 13 along with the calibration values Ψ_{Hb} and Ψ_{HbO2}, then the total value of Hib and/or HbO_2 can be calculated. According to Equation 2, pathlength L can be estimated from the product of "B*d". The light source to detector separation (optode) distance parameter "d" in the pathlength calculation is a measurable value and can be made constant by setting a fixed distance between light source to detector in the NIRS sensor design. Alternatively, the parameter "d" can be measured once the optodes are placed on the subject by use of calipers, ruler, or other distance measurement means. The pathlength differential factor "B" is more difficult to measure and requires more sophisticated equipment. From a large data set of measured neonatal and adult head differential pathlength factor values, an estimation of the value of "B" can be determined within a statistically acceptable margin of error. Substitution of these predetermined values of "B" into Equation 13 results in the determination of the total values of Hb and HbO_2.

[0043] An alternative method of determining total values of Hb and HbO_2 combines Equation 3 and Equation 13 together. The multivariate form of Equation 3 is shown below:

$$\begin{bmatrix} -\log(I_{t2}/I_{t1})_{\lambda 1}/L_{\lambda 1} \\ -\log(I_{t2}/I_{t1})_{\lambda 2}/L_{\lambda 2} \\ -\log(I_{t2}/I_{t1})_{\lambda 3}/L_{\lambda 3} \end{bmatrix} = \begin{bmatrix} \alpha_{Hb\lambda 1} & \alpha_{HbO_2\lambda 1} \\ \alpha_{Hb\lambda 2} & \alpha_{HbO_2\lambda 2} \\ \alpha_{Hb\lambda 3} & \alpha_{HbO_2\lambda 3} \end{bmatrix} * \begin{bmatrix} \Delta Hb \\ \Delta HbO_2 \end{bmatrix} \quad \text{(Eqn. 18)}$$

At time $t=t_1$, the values of ΔHb and ΔHbO_2 are zero. Applying Equation 13, and knowing the calibration values of Ψ_{Hb} and Ψ_{HbO2} at a predetermined differential pathlength factor "B" and optode separation "d", the total absolute values of Hb and HbO_2 are determined at time $t=t_1$, which are represented by $[Hb]_{t1}$ and $[HbO_2]_{t1}$ respectively. At time $t=t_2$, the values of ΔHb and ΔHbO_2 are then determined using Equation 18. The total values of Hb and HbO_2 are then determined at time $t=t_2$ using the following equations:

$$[Hb]_{t2} = \Delta Hb(t_2) + [Hb]_{t1} \quad \text{(Eqn. 19)}$$

$$[HbO_2]_{t2} = \Delta HbO_2(t_2) + [HbO_2]_{t1} \quad \text{(Eqn. 20)}$$

Equations 19 and 20 are valid only if all the shared parameters in Equations 13 and 18 are exact. Reduced to practice, the advantage of combining Equations 13 and 18 results in improved signal to noise ratio (SNR) in the calculation of the total values for Hb and HbO_2. Conversely, improved SNR in the calculation of SnO_2 is also obtained from the following expression:

$$SnO_2\,\% = \frac{HbO_2}{(HbO_2 + Hb)} * 100\% \quad \text{(Eqn. 21)}$$

[0044] After the calibration parameters Ψ_{Hb} and Ψ_{Hb02} are determined using the above-described methodology for an individual NIRS sensor, this particular sensor is said to be calibrated. A calibrated NIRS sensor affords accurate measurement of total tissue oxygen saturation, SnO_2, by non-invasive means. The calibrated sensor can be used thereafter on any human patient, including adults and neonates. The same is true for animal subject if the sensor was calibrated on animals. Although the present method is described above in terms of sensing blood oxygenation within cerebral tissue, the present method and apparatus are not limited to cerebral applications and can be used to determine blood oxygenation within tissue found elsewhere within the subject's body.

[0045] According to an additional aspect of the present invention, the above-described method can also be used to establish a calibrated "reference" sensor that can be used to calibrate similar sensors through the use of a phantom sample (also referred to as a "reference sample"). The phantom sample has optical characteristics that are similar to the tissue being examined by the NIRS sensor. The calibrated reference NIRS sensor is used to sense the phantom sample and produce reference values. Similar, but uncalibrated, NIRS sensors can thereafter be calibrated by sensing the same phantom sample and adjusting either the hardware of the uncalibrated sensor or the output of the uncalibrated sensor until the output of the uncalibrated sensor agrees with the reference values produced by the calibrated reference sensor. Therefore, the calibration parameters Ψ_{Hb} and Ψ_{HbO2} for the uncalibrated sensor would be determined from the phantom sample. This technique makes it unnecessary to calibrate each new sensor in the manner described above, and thereby provides a relatively quick and cost effective way to calibrate NIRS sensors.

[0046] Besides Hb and HbO_2, other biological constituents of interest (e.g., cytochrome aa_3, etc.) could be determined using the multivariate forms of equations 2, 3, 6 or 7. For each additional constituent to be determined, an additional measuring wavelength will be needed.

[0047] In an alternative embodiment, the above-described methodology can be combined with pulse oximetry techniques to provide an alternative non-invasive method of distinguishing between oxygen saturation attributable to venous blood and that attributable to arterial blood. As demonstrated by Equation 4, $SmvO_2$ is determined by the ratio of venous oxygen saturation SvO_2 and arterial oxygen saturation SaO_2. A calibrated NIRS sensor affords accurate measurement of total tissue oxygen saturation, SnO_2, by using regression techniques by correlation to mixed venous oxygen saturation $SmvO_2$. Therefore, the following expression will result:

$$SnO_2 = SmvO_2 = K_v * SvO_2 + Ka * SaO_2 \quad \text{(Eqn. 22)}$$

Non-invasive pulse oximetry techniques can be used to determine the arterial oxygen saturation (SaO_2) of peripheral tissue (i.e., finger, ear, nose) by monitoring pulsatile optical attenuation changes of detected light induced by pulsatile arterial blood volume changes in the arteriolar vascular system. Arterial blood oxygen saturation determined by pulse oximetry is clinically denoted as SpO_2. If NIRS monitoring and pulse oximetry monitoring are done simultaneously and SpO_2 is set equal to SaO_2 in Equation 23, then venous oxygen saturation can be determined from the following expression:

$$SvO_2 = \frac{SnO_2 - (Ka * SpO_2)}{Kv} \quad \text{(Eqn. 23)}$$

For the brain, venous oxygen saturation SvO_2 would be determined from internal jugular vein ($SijvO_2$), jugular bulb ($SjbO_2$), or sagittal sinus ($SssO_2$) and the parameters Ka and Kv would be empirically determined during the calibration of the NIRS sensor. Under most physiological conditions, SpO_2 is representative of brain arterial oxygen saturation SaO_2. Therefore, depending on which venous saturation parameter was used to calibrate the NIRS sensor, this clinically important parameter (i.e., $SijvO_2$, $SjbO_2$, or $SssO_2$) can be determined by Equation 24 by non-invasive means.

[0048] Since many changes and variations of the disclosed embodiment of the invention may be made without departing from the inventive concept, it is not intended to limit the invention otherwise than as required by the appended claims.

What is claimed is:

1. A method for determining blood oxygenation within a subject's tissue, said: method comprising the steps:

transmitting a light signal with a near infrared spectrophotometric sensor along a plurality of wavelengths into the subject's tissue;

receiving light energy with the sensor corresponding to the light signal after the light signal has passed through the subject's tissue;

processing the light energy received along the plurality of wavelengths, including using wavelength dependent sensor calibration constants representative of energy losses incurred by the light signal passing through the subject's tissue, to determine the blood oxygenation within the subject's tissue.

2. The method of claim 1, wherein the processing includes the determination of the blood oxygen saturation level within the subject's tissue.

3. The method of claim 1, wherein the processing step includes determining the wavelength dependent sensor calibration constants.

4. The method of claim 3, wherein the step of determining the wavelength dependent sensor calibration constants includes the use of empirical data or a reference sample.

5. The method of claim 1, wherein the energy losses are attributable to one or more of light scattering, absorption from background biological compounds, and apparatus variability.

6. The method of claim 1, wherein the calibration constants are operable to calibrate the sensor for use on a plurality of different subjects without recalibration.

7. The method of claim 1, wherein the processing step includes determining one or both of oxyhemoglobin concentration and deoxyhemoglobin concentration within the subject's tissue.

8. The method of claim 7, wherein the concentrations of one or both of oxyhemoglobin and deoxyhemoglobin are determined by determining values of oxyhemoglobin and deoxyhemoglobin at a first point in time, and the changes in oxyhemoglobin and deoxyhemoglobin at a second point in time later than the first point in time.

9. The method of claim 1, further comprising the step of determining the arterial oxygen saturation within the subject using a pulse oximeter, and processing the arterial oxygen saturation with the light energy received along the plurality of wavelengths, to determine the venous blood oxygen saturation level within the subject's tissue.

10. A method for determining blood oxygenation within a subject's tissue, said method comprising the steps:

transmitting a light signal with a near infrared spectrophotometric sensor along at least three wavelengths into the subject's tissue;

receiving light energy with the sensor corresponding to the light signal after the light signal has passed through the subject's tissue;

processing the light energy received along each of the at least three wavelengths, including compensating for energy losses attributable to absorption from biological compounds other than hemoglobin, to determine the blood oxygenation within the subject's tissue.

11. The method of claim 10, wherein the processing step includes determining wavelength dependent sensor calibration constants.

12. The method of claim 11, wherein the step of determining wavelength dependent sensor calibration constants includes the use of empirical data or a reference sample.

13. The method of claim 10, wherein the energy losses are also attributable to apparatus variability.

14. The method of claim 10, further comprising the step of determining one or both of oxyhemoglobin concentration and deoxyhemoglobin concentration within the subject's tissue.

15. The method of claim 10, wherein the processing includes the determination of the blood oxygen saturation level within the subject's tissue.

16. A method for determining blood oxygenation within a subject's tissue, said method comprising the steps:

transmitting a light signal with a near infrared spectrophotometric sensor along at least a first wavelength, a second wavelength, and a third wavelength, into the subject's tissue;

receiving light energy with the sensor corresponding to the light signal after the light signal has passed through the subject's tissue;

processing the light energy received along the first, second, and third wavelengths, including determining the difference in attenuation of the light signal between the first wavelength and second wavelength, and between the first wavelength and the third wavelength, and determining wavelength dependent sensor calibration constants to compensate for energy losses, to determine the blood oxygenation within the subject's tissue.

17. The method of claim 16, wherein the processing includes the determination of the blood oxygen saturation level within the subject's tissue.

18. The method of claim 16, wherein the wavelength dependent calibration constants are subject independent.

19. The method of claim 16, wherein the energy losses are attributable to one or more of light scattering, absorption from biological compounds, and apparatus variability.

20. The method of claim 18, wherein the step of receiving light energy includes receiving light energy with at least one first light signal detector spaced apart from a light signal transmitter by a first distance, and with at least one second light signal detector spaced apart from the light signal transmitter by a second distance, wherein the second distance is greater than the first distance.

21. The device of claim 20, wherein the step of processing the light energy received includes contrasting a signal detected at the first signal detector from a signal detected at the second light signal detectors for each discrete wavelength.

22. The method of claim 16, further comprising the step of determining one or both of an oxyhemoglobin concentration and a deoxyhemoglobin concentration within the subject's tissue.

23. The method of claim 16, further comprising the step of determining an arterial oxygen saturation within the subject's tissue using a pulse oximeter.

24. The method of claim 23, further comprising the step of determining a venous oxygen saturation within the subject's tissue using the arterial oxygen saturation determined using the pulse oximeter.

25. A spectrophotometric examination device, comprising:

a light signal transmitter operable to transmit at least one light signal along a plurality of discrete wavelengths;

at least one light signal detector operable to detect the light signal, and produce at least one detected signal corresponding to the light signal; and

a processor having an algorithm for determining the blood oxygenation in a subject's tissue, the algorithm being operable to process the detected signal along a plurality of discrete wavelengths, and the algorithm including a plurality of wavelength dependent calibration constants to compensate for energy losses incurred by the light signal passing through the subject's tissue.

26. The device of claim 25, wherein the algorithm is operable to determine the blood oxygen saturation level within the subject's tissue.

27. The device of claim 25, wherein the light signal transmitter is operable to transmit the light signal along at least three discrete wavelengths.

28. The device of claim 25, wherein the wavelength dependent calibration constants are subject independent.

29. The device of claim 25, wherein the energy losses are attributable at least in part to one or more of light scattering, absorption from biological compounds, and apparatus variability.

30. The device of claim 25, wherein the at least one light signal detector operable to detect the light signal, includes a first light signal detector spaced apart from the light signal transmitter by a first distance, and a second light signal detector spaced apart from the light signal transmitter by a second distance, wherein the second distance is greater than the first distance.

31. The device of claim 25, wherein the algorithm is operable to process the detected signal along each discrete wavelength, by contrasting a signal detected at the first signal detector from a signal detected at the second light signal detectors for each discrete wavelength.

32. The device of claim 25, wherein the algorithm is operable to determine the total concentration of one or both of oxyhemoglobin and deoxyhemoglobin.

33. The device of claim 25, further comprising a pulse oximeter operable to determine arterial oxygen saturation within the subject.

34. The device of claim 25, wherein the algorithm is operable to determine a venous oxygen saturation within the subject's tissue using the arterial oxygen saturation determined using the pulse oximeter.

35. The device of claim 25, wherein the wavelength dependent calibration constants are based on empirical data or a reference sample.

36. The device of claim 25, wherein the energy losses are selected from a group consisting of absorption from background biological compounds, and apparatus variability.

37. The device of claim 25, wherein the calibration constants are operable to calibrate the device for use on a plurality of different subjects without recalibration.

38. A spectrophotometric examination device, comprising:

a light signal transmitter operable to transmit at least one light signal along at least three discrete wavelengths;

at least one light signal detector operable to detect the light signal, and produce at least one detected signal corresponding to the light signal; and

a processor having an algorithm for determining the blood oxygenation in a subject's tissue, the algorithm being operable to process the light energy received along a plurality of wavelengths, and compensate for energy losses attributable to absorption from biological compounds other than hemoglobin, to determine the blood oxygenation within the subject's tissue.

39. The device of claim 38, wherein the algorithm is operable to determine the blood oxygen saturation level within the subject's tissue.

40. The device of claim 38, wherein the energy losses are at least partially attributable to one or more of light scattering, absorption from background biological compounds, and apparatus variability.

41. The device of claim 38, wherein the algorithm is operable to calibrate the device for use on a plurality of different subjects without recalibration.

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摘要(译)

提供一种用于非侵入性地确定受试者组织内的血液氧合的方法和装置，其利用近红外分光光度（NIRS）传感器，其能够将光信号传输到受试者的组织中并且一旦通过就感测光信号。组织通过透射率或反射率。