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Dick

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(54) **NON-INVASIVE MEASUREMENT OF SKIN BILIRUBIN LEVEL**

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(52) **U.S. Cl.** **356/39; 600/306; 600/315**

(58) **Field of Search** 356/39, 394; 600/315, 600/306, 310, 317, 320–323

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(57) **ABSTRACT**

The invention concerns a method and a device for non-invasive measurement of a tissue and in particular of the skin bilirubin level. The inventive device is characterized in that it comprises: a reading head (1) capable of sending several flashes of various specific wavelengths towards the tissue (2) to be examined and of receiving and measuring in return the reflected light; a calculator, such as a microprocessor, capable of calculating for each wavelength the amount of reflected light and bring it to a value calculated proportionally to a reference value identical for a predetermined wavelength; and a comparator for comparing the calculated value to a table of reference values.
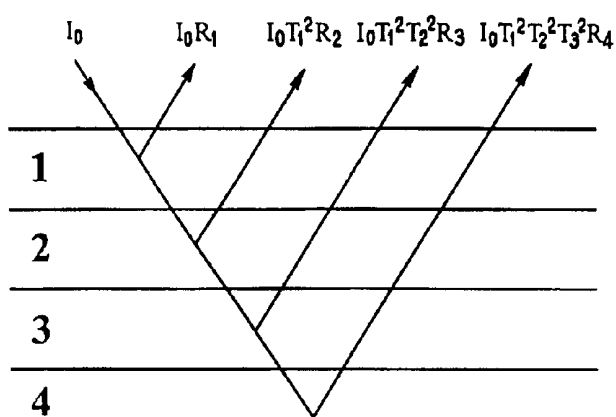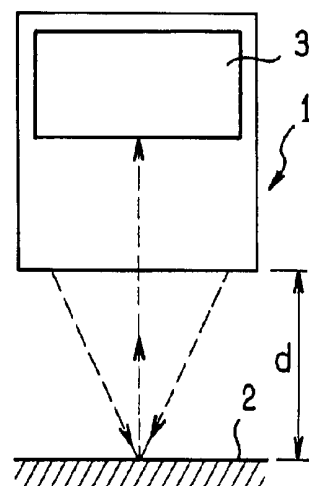
12 Claims, 3 Drawing Sheets

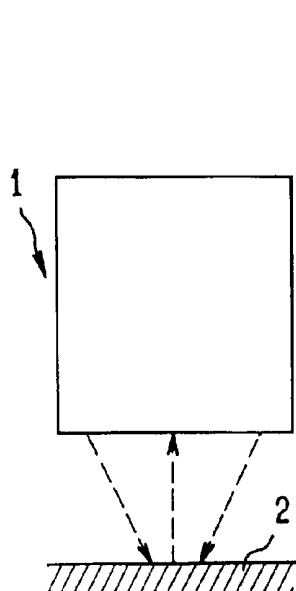I_0 I_0R_1 $I_0T_1^2R_2$ $I_0T_1^2T_2^2R_3$ $I_0T_1^2T_2^2T_3^2R_4$

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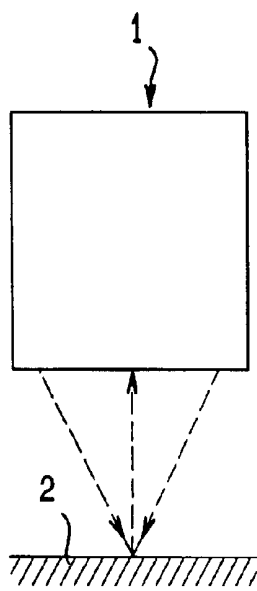
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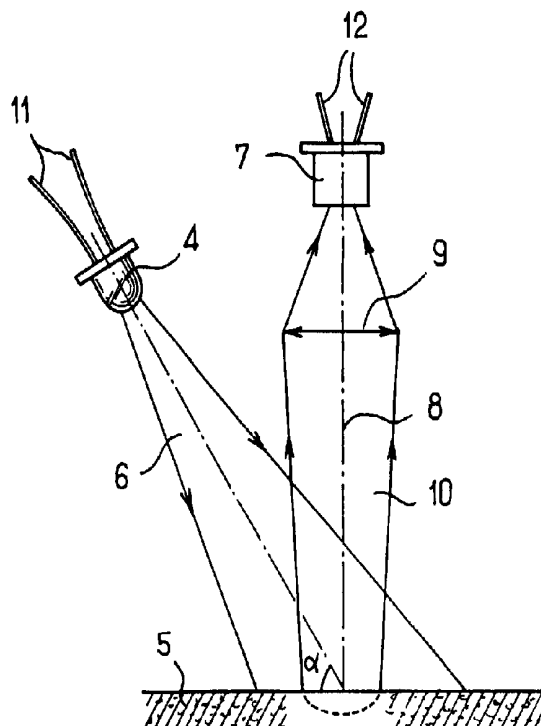
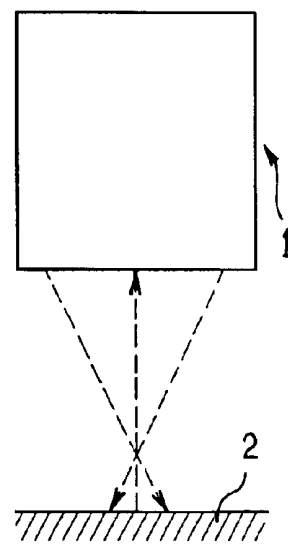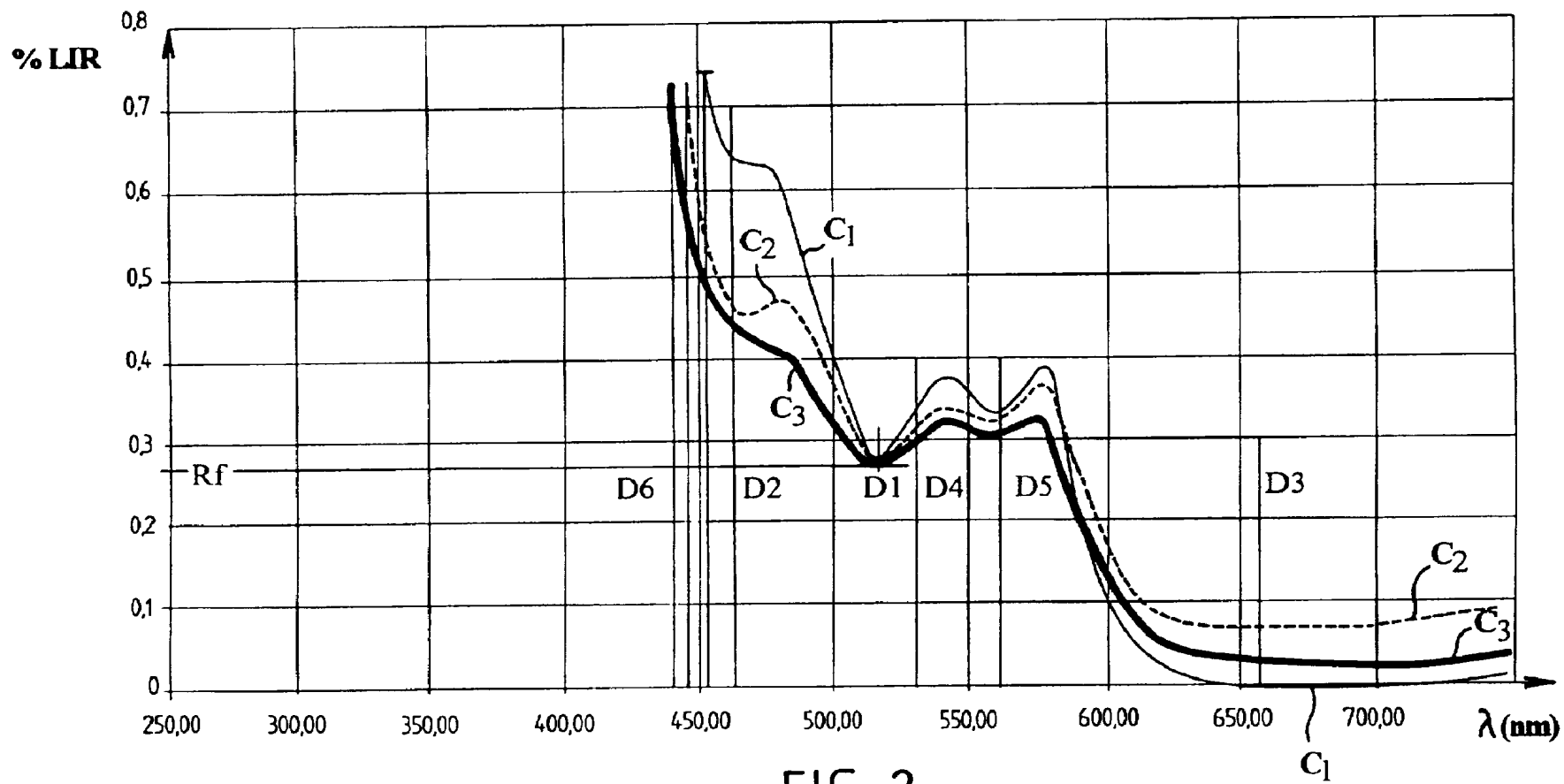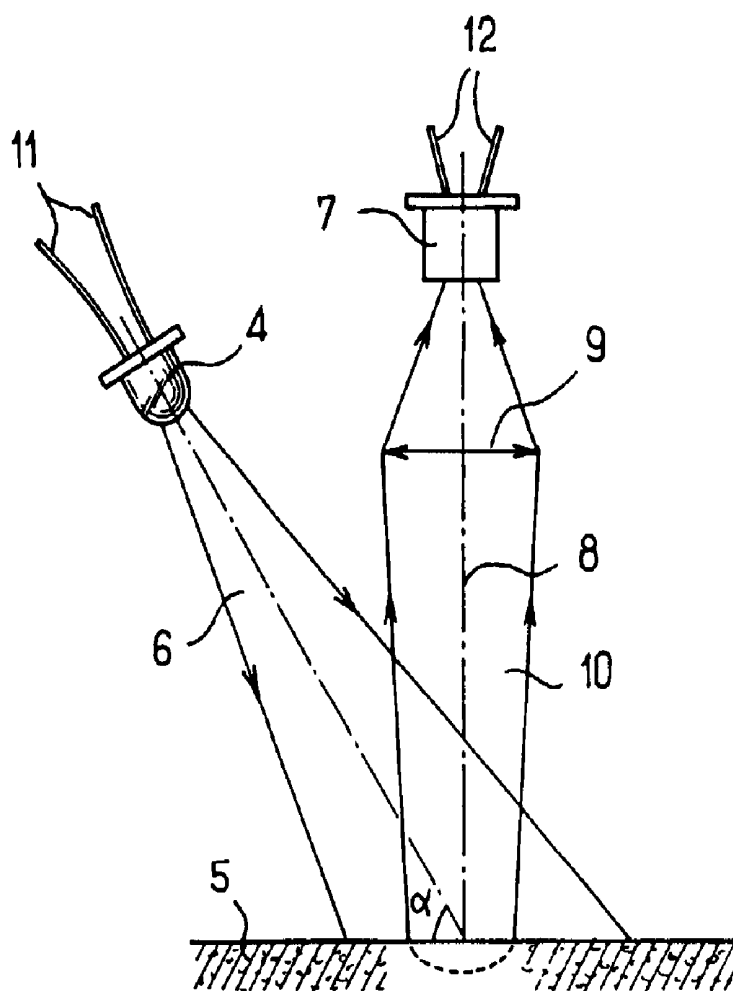**FIG.1**

FIG.3

FIG.4   **FIG.5**   **FIG.6**

FIG_2

FIG_7

NON-INVASIVE MEASUREMENT OF SKIN BILIRUBIN LEVEL

This invention relates to a process and to a device for the non-invasive analysis of a tissue, such as the skin for instance.

Many works have shown that it was possible, by sending white light on a tissue such as the skin or a plant tissue and analyzing the reflected light, to obtain some information concerning the nature of the tissue and particularly the concentration of its various constituents. The general principle is that the constituents of the various wavelengths that form the white light are reflected differently depending on the constituents encountered by the light. A fine and continuous analysis of the reflected light should thus enable to obtain a fairly precise non-invasive analysis of the tissue being examined.

The devices already known that operate according to this principle require nonetheless a costly optical analysis equipment such as spectrographs and powerful calculators to analyze the collected data, as well as a delicate calibration of the various instruments.

This invention offers a process and a measuring device that overcome these difficulties of implementation.

To this effect, the process of this invention for the measurement of a skin constituent level, particularly that of the bilirubin level in the skin, is characterized in that are performed a first measurement of the reflection of the light with a first given wavelength representative of the measurement to be performed, and at least the measurement of a second reflection of the light of a predetermined wavelength used as reference for which is determined a reflection reference unit value by calculating the ratio k between the reflection measured on the tissue for this second wavelength and the reflection measured on a standard for this same second wavelength; and in that the level of the constituent to be evaluated is deduced by measuring the reflection of the first given wavelength according to a table of predetermined known values for this first wavelength, after correction by the factor k previously measured said reflection measurement so as to obtain the value to be compared with the table of reference values.

A device according to this invention is itself characterized in that it consists of:

a reading head that can send successively several flashes with various defined wavelengths toward the tissue to be examined, and receive and measure in return the reflected light,

a calculator such as a microprocessor, that can calculate for each wavelength the quantity of reflected light and bring it to a value calculated proportionally to a reference value identical for a given predetermined reference wavelength,

a comparator enabling to compare the value so calculated to a table of reference values.

Advantageously, this device uses electro-luminescent diodes for sending sequential flashes of determined wavelengths.

The invention and its implementation will become more apparent from the following description, together with the accompanying drawings.

In the drawings:

FIG. 1 shows the principle underlying the optical reflection of the light by the skin.

FIG. 2 shows three LIR curves recorded for three subjects, said curves having been subjected to a mathematical treatment so as to level them for a given wavelength threshold.

FIG. 3 is a diagram of the principle of a device according to this invention.

FIGS. 4, 5 and 6 show the principle underlying the practical use of said device.

FIG. 7 is a diagram of a variation in the implementation of a measuring device according to this invention.

FIG. 1 is a reminder of the principle concerning the propagation of light and of its reflection by the skin. This principle is explicited, in particular, in the publication of Dawson, Barker and al.: "a theoretical and experimental study of the in vivo absorption and diffusion of light by the skin" (Phys. Med. Biol. 1980, vol. 25, n°4, pages 695–709).

Considering successively that the layer 1 is the stratum corneum, that the layer 2 corresponds to the epidermis, that the layer 3 corresponds to the derm and the layer 4 to the hypodermis, if we reference respectively as R1, R2, R3 and R4 the reflection factors of the successive layers and as T1, T2, T3 and T4 the transmission factors of these same layers, the reflected light is globally such as:

$$I = I_o R_1 + I_o T_1^2 R_2 + I_o T_1^2 T_2^2 R_3 + I_o T_1^2 T_2^2 T_3^2 R_4 \ldots$$

If the skin is not too dry, the reflection factors R1, R2 and R3 are notably inferior to R4, while the global reflection is reduced to:

$$R = (I/I_o) \# T_1^2 T_2^2 T_3^2 R_4 \ldots$$

Taking the Neperian logarithm (LN) of the inverse of the reflection, LIR, leads to:

$$LIR = -LN(T_1^2) - LN(T_2^2) - LN(T_3^2) - LN(R_4) \ldots$$

This LIR, represented for all the wavelengths, enables to display all the skin characteristics. It becomes thus possible to draw curves and to deduce from them the skin qualities by analyzing the correspondent absorption bands that characterize the various constituents of the skin, and to deduce for instance the bilirubin, hemoglobin, melanin, etc., levels.

As already mentioned, the practical application of this theory comes up against considerable equipment and calibration difficulties, since the curves vary greatly from one subject to another, depending in particular on the subject's own pigmentation.

With this invention, it becomes nonetheless possible to overcome these difficulties, related to the very different skin reactions from one subject to another, by "tuning" all the curves to the level of a reference threshold for a specific predetermined wavelength λ_f used as a reference, which enables to perform a qualitative and quantitative analysis without having to draw the curves (thus avoiding the need for a spectrograph), just by recording a few measurement points for precise and relevant wavelengths, after a simple calculation of threshold setting.

Referring now to FIG. 2, in which were shown three curves with, in ordinate the absorption measured in LIR % as a function of the wavelength of the light received by the skin of three different subjects. Yet, these curves were treated mathematically, in order to standardize them and to show the operation of the device and the process of this invention.

To obtain the curves in FIG. 2, four successive steps are taken.

First step. A calibration is carried out by measuring the reflection on a "gray" or "white" "standard" (e.g. a compacted powder of barium sulfate). For good results, and in particular to eliminate possible drifts in the diodes, as time goes on and/or in response to the room temperature, said calibration/standardization is performed before each measurement on the "gray" or "white" chosen standard.

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In the illustrated example, it was assumed that six successive measurements were performed respectively for the wavelengths: 520 nm, 460 nm, 660 nm, 545 nm, 575 nm, and 430 nm. These specific wavelengths can actually be emitted by electro-luminescent diodes DEL of suitable quality.

FIG. 3 shows a diagram of the measuring device. Here the device 1 comprises electro-luminescent diodes DEL that send a light beam, for example slightly conical and convergent (as shown by the arrows), on the skin 2 of the subject to be examined. The reflected light, essentially perpendicular to the subject's skin, is received by a detector 3 that analyzes the intensity of the radiance received. The use of a conical beam is advantageous on several accounts: it allows for the elimination of most of the specular reflection and also for a precise determination of an optimum distance d between the position of the device 1 and the skin, by measuring the reflection when the light output is essentially reduced to a point on the skin 2. The cone angle is advantageously comprised between 30° and 50°, e.g. around 45°.

The detector of the measuring device records an intensity of the reflection factor:

I_{OD1} for the diode D1,

I_{OD2} for the diode D2, . . .

I_{OD6} for the diode D6.

Second step. An operation is performed to measure the reflection on the skin to be tested.

During the measuring process on the skin of a child "x," the detector of the measuring device records an intensity of the reflection factor:

I_{xD1} for the diode D1,

I_{xD2} for the diode D2, . . .

I_{xD6} for the diode D6.

Third step. Now takes place the mathematical "standardization" treatment so that, for a given reference wavelength, in this case that of the first diode D1 at 520 nm, all the curves go through the same absorption level point, or reflection factor, measured in ordinate.

The calculator, advantageoulsy a microprocessor, performs the following standardization calculations:

$$(I_{xD1}/I_{OD1})=R_{x1} \text{ for the diode D1}$$

$$(I_{xD2}/I_{OD2})=R_{x2} \text{ for the diode D2}$$

$$. . .$$

$$(I_{xD6}/I_{OD6})=R_{x6} \text{ for the diode D6}$$

Then the operation is such that, for the reference wavelength selected as relevant λ_{f}, all the reflection factors R_{x1f} are equal to a reference value Rf.

$$R_{x1f}=R_{0f} \quad 4 \quad k=R_{0f}/R_{x1f}$$

The various reflection factors R_{xn} are then multiplied by the corresponding factor k to obtain the standardized factors R_{xnf}.

$$R_{x2f}=k \ R_{x2}$$

$$R_{x6f}=k \ R_{x6}$$

By bringing, for this reference wavelength, all the reflection levels to the same threshold level Rf, it becomes possible to operate a direct reading of the level under examination, for instance the bilirubin level, by simple reading of the corresponding standardized LIR.

Fourth step. From the standardized reflection factors, the microprocessor computes the LIRs:

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$$LIR_{x1}=Log (1/R_{x1f})=Log (1/R_{f})=Constant$$

$$LIR_{x2}=Log (1/R_{x2f})$$

$$. . .$$

$$LIR_{x6}=Log (1/R_{x6f})$$

The LIRs so established enable a comparison with the spectral curves, i.e in the illustrated example three curves corresponding to the various reflection factors of three subjects under examination. In the example of the illustrated curves, the whole curves were actually obtained from a spectrograph analyzing continuously the wavelengths within a range from 430 nm to 750 nm, in order to have a more accurate representation of the path of these curves, though they are not actually necessary for the analysis measurements of the various constituents of the skin, as will be explained in detail thereafter, in reference to the three given examples of measurement.

Back to FIG. 2, for a wavelength of 460 nm, can be found on the three curves respectively C1, C2, C3, corresponding absorption rates of about 0.75, 0.55 and 0.5 measured in % standardized LIR. The simple measurement of said absorption level enables, as can be noted, to deduce that for the subject of the curve C2, the bilirubin level is normal while for the subject of the curve C1, the bilirubin level is high and for the subject of the curve C3, the bilirubin level is too low. These data (these percentages of LIR) can be simply recorded in a table of reference values already tested and known.

Likewise, it is possible to evaluate the hemoglobin content from the reflection rate of the light emitted by the diodes D4 at 545 nm or 550 nm and D5 at 575 nm. Measurements of the reflection level in the emission area of the diode D6 at around 430 nm would add further precision to the results.

The skin pigmentation can be evaluated through the level of the reflection rates vis-à-vis the light emitted by the diode D3 at around 660 nm (within a range from 620 to 780 nm). Actually, it is observed that beyond this, the LIR curve is essentially a straight line, so that the determination on this curve of two points distant enough from this wavelength, e.g. about 620 nm and 780 nm, will enable to determine precisely the corresponding pigmentation characteristic: African, European, Asian, etc. type.

With the process of this invention, it is not necessary to trace the whole curves as it is possible to just resort to limited measurements for wavelengths that are precise and well-defined. This is because the temporary fluctuations and colors or pigmentations specific of the various skins are overcome by the "standardization" process already described.

Moreover, since no mechanical pressure is applied to the tissue to be examined, the measurement is not distorted, as would be the case if the measuring of a skin hemoglobin level were done through a pressure applied to the skin that would drive the blood away from the measurement area.

Thus, when one wants to measure the bilirubin level of the light skin of a quiet baby, this bilirubin level is evaluated directly from the LIR_{x2} measured with the diode D2, by carrying out the operation $LIR_{x2}-LIR_{x1}$.

If the bilirubin level is measured on a colored skin [non-European ethnic group] and/or a restless baby [blood rush in the skin area], the indications for the LIR_{x2} are automatically corrected in the same way because of the subtraction $LIR_{x2}-LIR_{x1}$, and because the value LIR_{x1} was standardized by the operation previously described (same standardized reflection threshold Rf for the diode D1, standardized for each measurement).

In reference to FIG. 4 to 6 is shown how, because of the use of a conical light beam, it was immediately possible, as shown in FIG. 5, to determine the right measurement distance d between the device and the subject's skin. When the device is too close, as shown in FIG. 4, the skin does not display the pinpoint as in FIG. 5, and neither does it if the device is too far, as shown in FIG. 6.

The device can thus be designed so that, when it is directed toward the skin, the lighting is only triggered when the device is at the right distance, i.e. when the light beam converges essentially into a pinpoint on the skin.

According to the variation of this embodiment shown in FIG. 7, the electro-luminescent diodes DEL with the reading head shown in the diagram 4, light the skin surface shown in 5, from an angle alpha (α), advantageouly comprised between 30° and 60°, for instance 45°; the light beam 6 is reflected on the skin; by setting the sensor 7 of the device reading head in the axis 8 perpendicular to the surface 5 of the lit area of the skin, only the part of the light coming from the electro-luminescent diode 4 that is diffused by the skin is detected by the sensor 7, and not the light reflected on the skin surface, which depends on the brightness of the skin. It is thus possible to obtain more reliable data concerning the characteristic to be measured: bilirubin level, hemoglobin level, etc.

In FIG. 7, a lens 9 was brought in the path of the beam 10 of the light diffused by the skin in order to increase the light power detected by the sensor 7. 11 and 12 represent respectively the power wires of the electro-luminescent diodes 4 and of the light output coming from the sensor 7.

Advantageously, if five or six electro-luminescent diodes DEL are used that emit suitable wavelengths such as previously defined, the diodes will preferably be powered successively so that the sensor may successively perform the measurements of the reflection levels needed for the analysis of the results. Prior to each measurement performed on a tissue to be analyzed, the device will have been calibrated, as previously mentioned, upon a "gray" or "standard white", which will allow to calculate the coefficient k such as previously mentioned.

Although the invention was described more precisely for the analysis of the bilirubin level contained in the skin, or other skin constituents such as pigmentation, hemoglobin, etc., the principle of this invention can be extended to the analysis of any tissue, provided that will be determined the precise wavelength(s) for which the reflection level must be recorded to obtain a relevant measurement, and the wavelength on which to tune all the curves so as to obtain the standardization of said curves.

What is claimed is:

1. Process for the measurement of the level of a tissue constituent, characterized in that is/are measured a first light reflection with a first given wavelength that is representative of the measurement to be performed and at least a second measurement of the light reflection for another second predetermined wavelength that will serve as a reference unit value Rf, by calculating the coefficient k between the reflection measured on the tissue for this second wavelength and the reflection measured on a standard for this same second wavelength, and in that the level of the constituent to be evaluated is deduced from the measurement of the reflection of the first wavelength according to a table of predetermined values known for this same first wavelength, after correction by the factor k previously measured of said reflection measurement, so as to obtain the value to be compared to the table reference values, said unit value and said second wavelength determining a point through which will go all the LIR curves after standardization.

2. Process according to claim 1, characterized in that, for an individual's skin, the second wavelength selected is λ=520 nm.

3. Process according to claim 2, characterized in that, for the measurement of the skin bilirubin level, the wavelength selected is λ=460 nm.

4. Device for the measurement of the level of a tissue constituent, characterized in that it comprises:

a reading head capable of sending successively several flashes of various predefined wavelengths toward the tissue to be examined as a conical beam having a cone angle between 30° and 50° and of receiving and mea-suring in return the reflected light,

a calculator, capable of calculating for each wavelength the amount of reflected light and of bringing it to a value calculated proportionally to a reference value identical for a predetermined wavelength,

a comparator for comparing the calculated value to a table of reference values.

5. Device according to claim 4, characterized in that it comprises electro-luminescent diodes as elements to send successive flashes of various specific wavelengths.

6. Device according to claim 4, characterized in that the light wavelength used to measure the reference value is about 520 nm.

7. Device according to claim 6, characterized in that the light wavelength used to measure the bilirubin level is about 460 nm.

8. Device according to claim 6, characterized in that the light wavelength used to measure the skin pigmentation is comprised between 620 and 780 nm.

9. Device according to claim 6, characterized in that the light wavelength used to measure the skin hemoglobin are two wavelengths or about 545 and 575 nm.

10. Device according to claim 6, characterized in that the light wavelength used to measure the skin hemoglobin is a wavelength of about 550 nm.

11. Device according to claim 6, characterized in that the light wavelength used to measure the skin hemoglobin is a wavelength of about 430 nm.

12. Device according to claim 6, characterized in that the light wavelengths used to measure the skin hemoglobin are two wavelengths of about 550 nm and 430 nm.
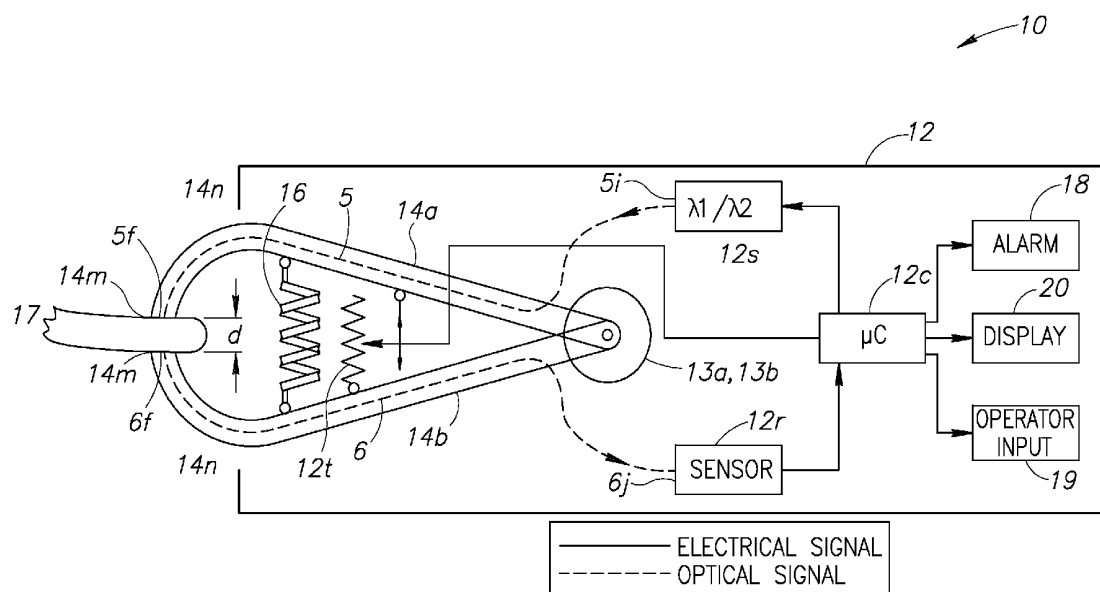
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(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2013/0023742 A1**

MOLCHO et al. (43) **Pub. Date: Jan. 24, 2013**

(54) **NON-INVASIVE DEVICE AND METHOD FOR MEASURING BILIRUBIN LEVELS**

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Publication Classification

(51) **Int. Cl.**
$A61B\ 5/1455$ (2006.01)
(52) **U.S. Cl.** **600/315**

(57) **ABSTRACT**

A transcutaneous non-invasive device and method for measuring bilirubin levels is provided. The device and method utilize optical, electrical, and mechanical means in communication with processing means to calculate the serum bilirubin concentration. Blanching pressure is applied to the tissue, whose thickness is measured. The level of bilirubin is calculated from the thickness of the tissue and the detected and measured values of radiation transmitted through the living tissue.

FIG.1

GAUGE DEVICE /21

↓

PLACE TESTED TISSUE
BETWEEN DEVICE ARMS /22

↓

MEASURE TISSUE
THICKNESS /23

↓

APPLY 520nm AND 470nm
LIGHT SIGNALS AND MEASURE
THE SIGNALS TRANSMITTED
THROUGH THE TISSUE RESPECTIVELY /24

↓

APPLY CALIBRATION CONSTANTS
TO THE MEASURED SIGNALS TO
CALCULATE THE d,
T(520), AND T(570) /25

↓

ESTIMATE AND DISPLAY
BILIRUBIN LEVEL $\widehat{BR}$ /26

↓

$\widehat{BR} > THR$ /27

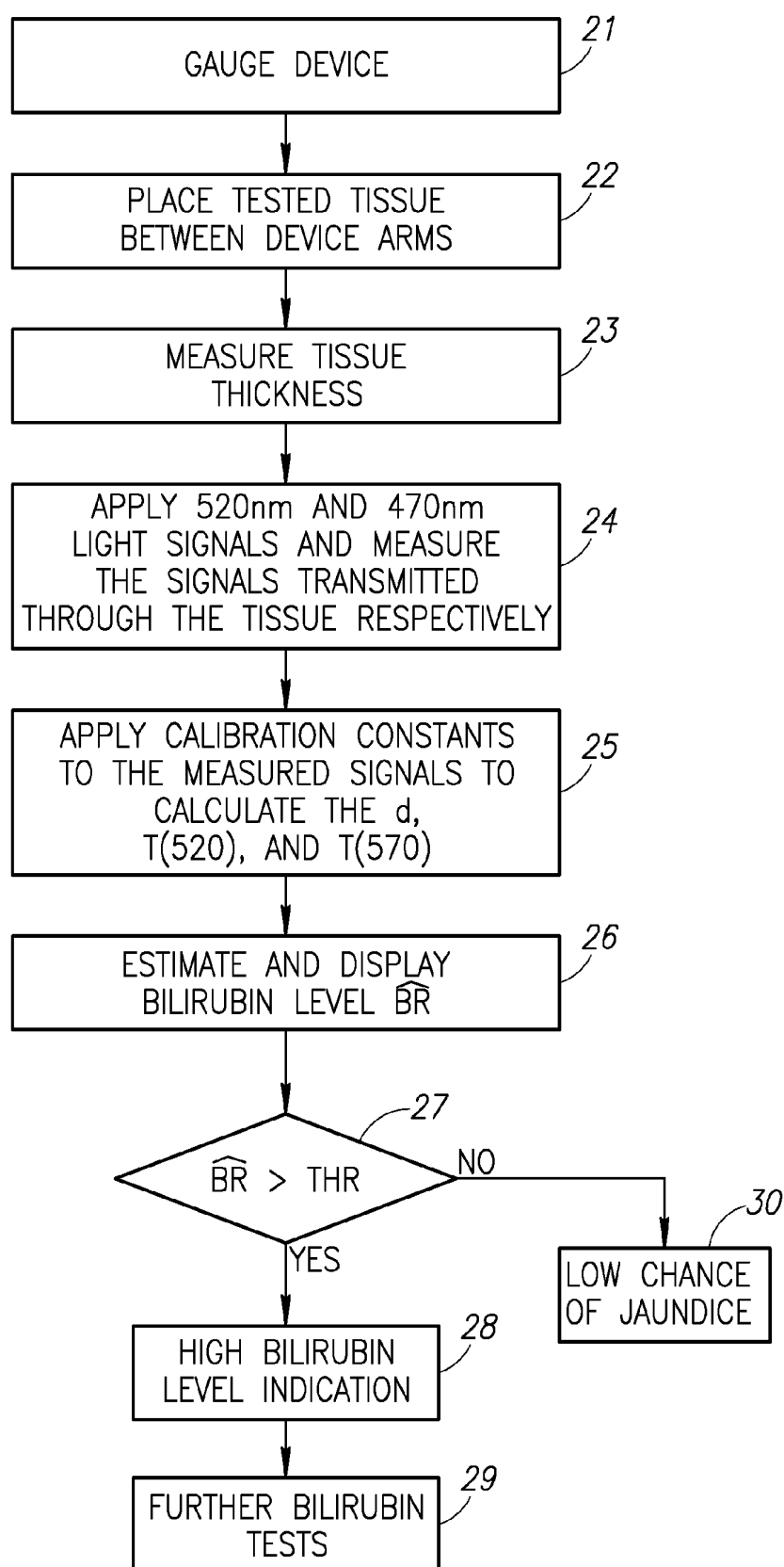NO → LOW CHANCE
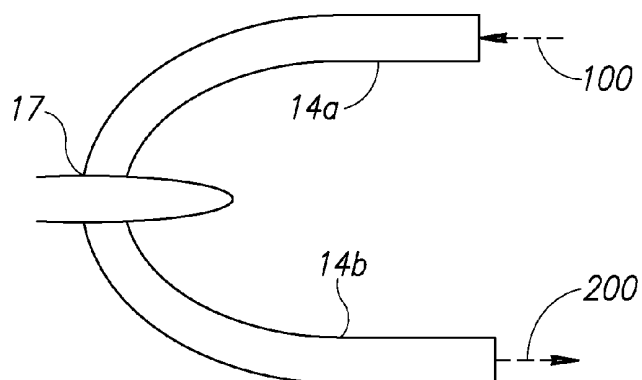OF JAUNDICE /30

YES

↓

HIGH BILIRUBIN
LEVEL INDICATION /28

↓

FURTHER BILIRUBIN
TESTS /29

FIG.2

FIG.3A
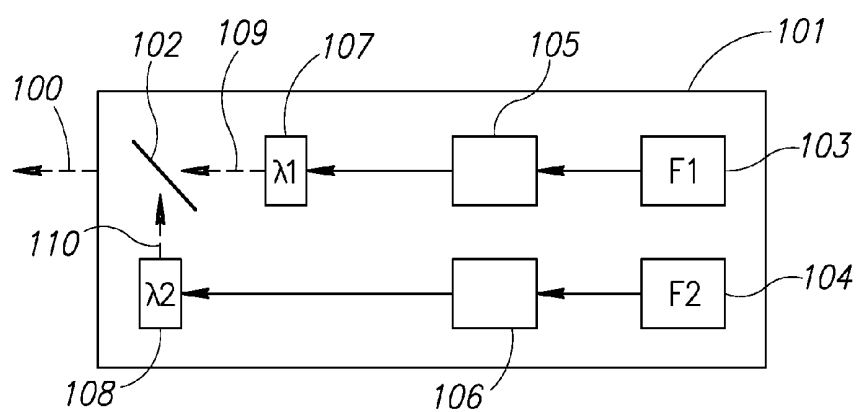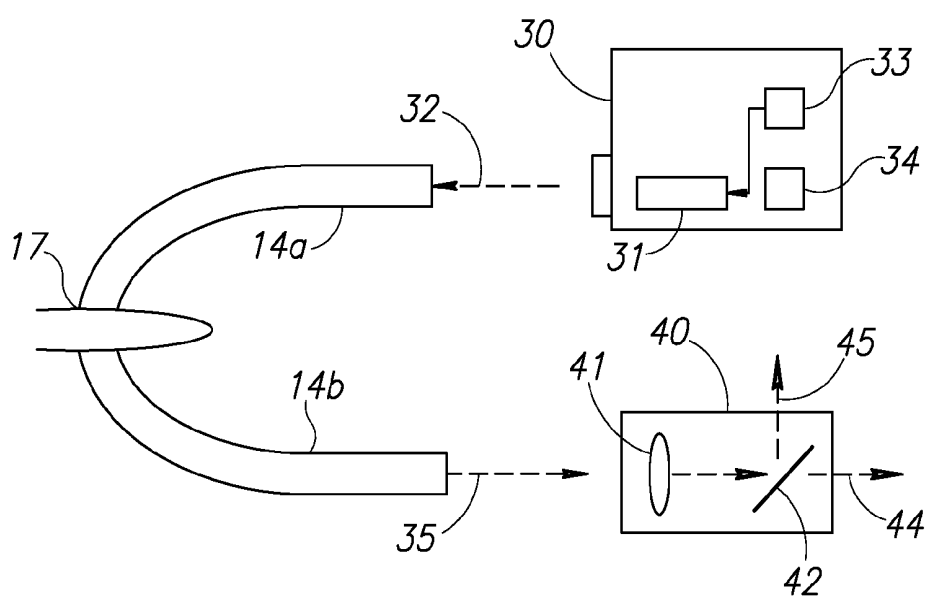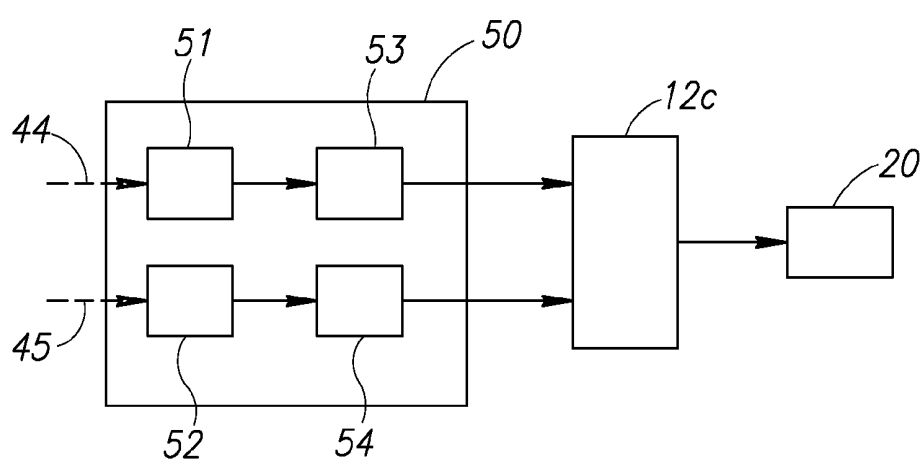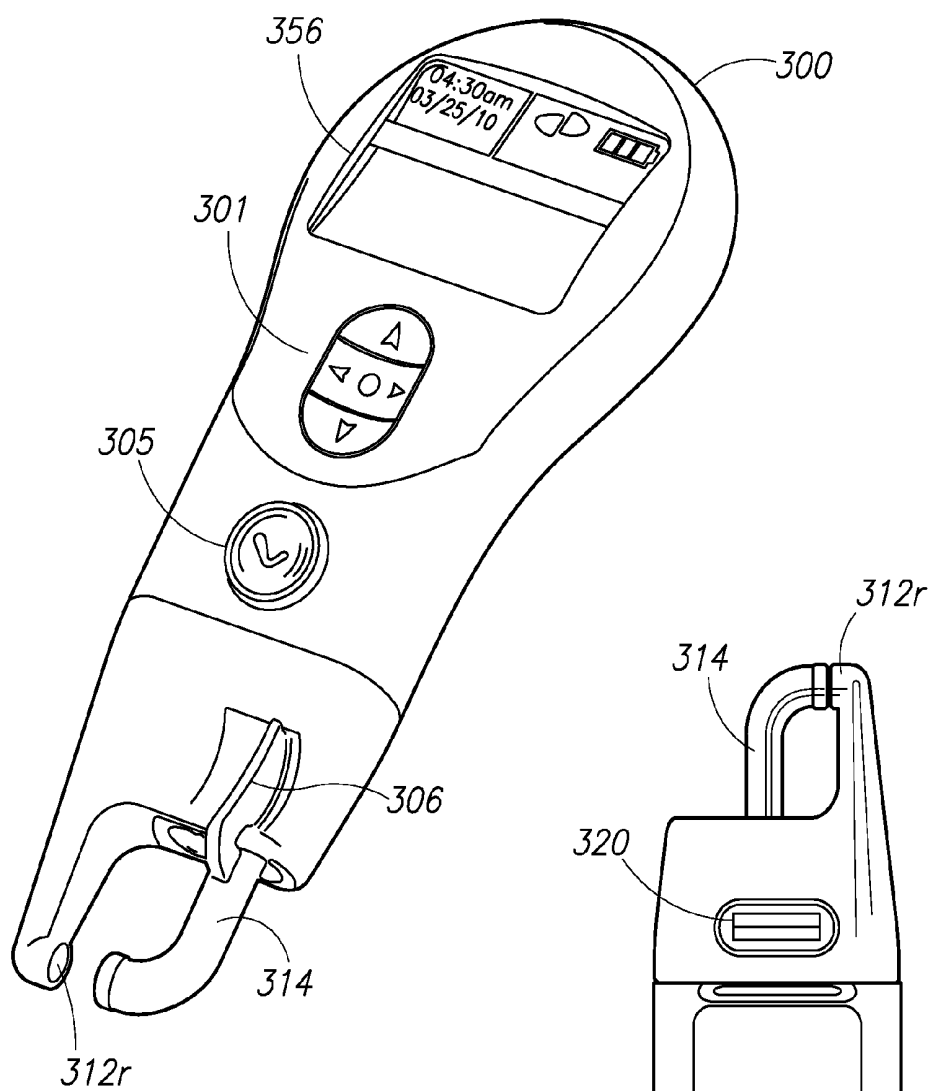
FIG.3B

FIG.3C

FIG.4A

FIG.4B

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03/25/10

FIG.5A
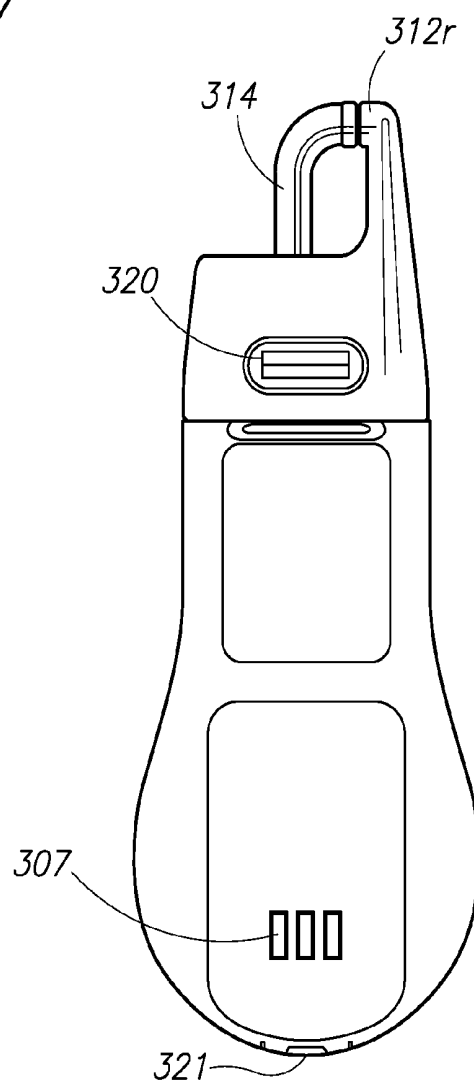
FIG.5B

NON-INVASIVE DEVICE AND METHOD FOR MEASURING BILIRUBIN LEVELS

FIELD OF THE INVENTION

[0001] The present invention relates to medical devices for measuring bilirubin levels in a living tissue. More particularly, the present invention relates to a non-invasive device and method for estimating bilirubin levels in a newborn subject for diagnosing jaundice.

BACKGROUND OF THE INVENTION

[0002] Jaundice is fairly common among newborn infants, and is presumably a consequence of metabolic and physiological adjustments after birth. Often, the jaundice disappears within a fairly short period of time. In many cases the jaundice is detected early and treated effectively thus curing the infant within a fairly short period of time. When an infant is jaundiced the serum bilirubin normally rises to a high level. In extreme cases, a brain-damaging condition known as kernicterus can occur, leading to significant lifelong disability. In other extreme cases the jaundice can progress severely and even lead to death. Jaundice is usually diagnosed by an invasive blood test in which blood sample is usually taken from the heel. While this blood test is considered to be safe, obtaining the blood sample is an uncomfortable invasive procedure for a newborn infant.

[0003] U.S. Pat. No. 4,267,844 by Yamanishi relates to an electro-optical medical instrument provided for measuring non-invasively the presence of bilirubin in skin tissue. The instrument in this publication utilizes a source of flash light and optical means to provide a beam of light to illuminate the skin tissue. A portion of the reflected light is collected and separated by optical means to two components: One, having a central wavelength of 455 nm, which is known as being highly absorbed by bilirubin in skin tissue; And another having a wavelength greater than 500 nm, which absorption by the bilirubin in the skin tissue is low. These optical signals are measured by photoelectric transducers, the electrical output of which is amplified, and then used to compute a bilirubin indication by means of a logarithmic converter. User obtained calibration is called upon to convert the bilirubin indication to serum bilirubin concentration.

[0004] U.S. Pat. No. 6,064,898 by Aldrich relates to a non-invasive blood component analyzer using spectrophotometry. The analyzer in this publication utilizes measurements of transmitted light having various wavelengths selected in accordance with the blood components of interest. The parameters used to derive the blood components are each given by the difference between the systolic and diastolic values of the relevant measured signal. The visible wavelengths mentioned are 420 nm, 548 nm, 506 nm, 521 nm, 569 nm, and 586 nm. The first two are proposed for the measurement of bilirubin concentration in skin tissue.

[0005] Another non-invasive bilirubin measuring instrument is described in U.S. Pat. No. 5,792,049, by Eppstein, in which the reflectance of skin tissue is measured at several visible and near infra-red wavelengths. The measured values of reflectance are utilized to arrive at an estimate of the serum bilirubin concentration. For calibrating the instrument, the reflectance of a calibration target is measured at these same wavelengths

[0006] It is an object of the present invention to provide a method and means for applying non-invasive measurements for detecting the bilirubin level in a subject. It is a further object of the present invention to provide a method and means for applying non-invasive measurements for detecting the bilirubin level in a subject in a fast and simple manner.

[0007] Other objects and advantages of the present invention will become apparent as the description proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The present invention is illustrated by way of example in the accompanying drawings, in which similar references consistently indicate similar elements and in which:

[0009] FIG. 1 schematically illustrates a device for measuring bilirubin levels according to one general embodiment of the present invention;

[0010] FIG. 2 is a flowchart illustrating a method for operating the device illustrated in FIG. 1;

[0011] FIGS. 3A to 3C schematically illustrate one embodiment of the invention for operating the device of the invention utilizing a synchronous detection approach, wherein FIG. 3A shows an illustration of the measurement setup, FIG. 3B shows an illustration of an embodiment of a radiation source, and FIG. 3C shows an illustration of an embodiment of a synchronous detector;

[0012] FIGS. 4A and 4B schematically illustrate another embodiment of the invention utilizing flashtube as a light source, wherein FIG. 4A shows a possible measurement setup and FIG. 4B shows a possible embodiment of a detection unit; and

[0013] FIGS. 5A and 5B schematically illustrate a device for measuring bilirubin levels according to yet another embodiment of the invention, wherein FIG. 5A shows a perspective view of the device and FIG. 5B shows a rear view of the device.

[0014] It is noted that the embodiments exemplified in the figures are not intended to be in scale and are in diagram form to facilitate ease of understanding and description.

SUMMARY OF THE INVENTION

[0015] The present invention presents a system and device for non-invasive measurement of bilirubin levels by transmitting radiation through a subject's living tissue. Blanching pressure is applied to the tissue and the thickness of the tissue is also measured.

[0016] In an embodiment of the present invention, there is provided a non-invasive device for measuring the bilirubin level of a subject. The device includes at least one radiation source for radiating a subject's living tissue, at least one detector for detecting rays transmitted through the tissue, means for applying blanching pressure to the portion of the subject's living tissue; means for measuring the thickness of the portion of the subject's living tissue through which radiation is being transmitted and processing means connected to the radiation source, the detector and the thickness measuring means. The radiation source is configured to emit radiation in at least two wavelengths. The processing means are configured to calculate the bilirubin level of the subject using data obtained from the detector and from the thickness measuring means.

[0017] Furthermore in accordance with an embodiment of the invention, the means for applying blanching pressure comprise one of group of devices including a pair of rotatable arms, a single moving or rotating arm and a clip or pincer device, configured to be attached to the tissue being measured.

[0018] Furthermore in accordance with an embodiment of the invention, the wavelengths may comprise a first wavelength ($\lambda 1$) within a range 520 nm±5 nm and a second wavelength ($\lambda 2$) within a range 470 nm±10 nm.

[0019] Furthermore in accordance with an embodiment of the invention, the radiation source includes one of a group including at least two laser diodes, at least two light emitting diodes (LEDs), and at least one laser diode together with at least one LED. Alternatively, the radiation source may include a white light emitter and two filters for filtering the emitted white light.

[0020] Furthermore in accordance with an embodiment of the invention, the device further includes optical means configured to direct beams of light emitted from the at least one radiation source towards the subject's living tissue.

[0021] Furthermore in accordance with an embodiment of the invention, the device further includes light guiding means and optical coupling means, where the optical coupling means configured to direct beams of light received from the light guiding means to the detector.

[0022] Furthermore in accordance with an embodiment of the invention, the light beams are transmitted through the tissue at different times.

[0023] Furthermore in accordance with an embodiment of the invention, the radiation source includes means for emitting a synchronous signal. The synchronous signal may include first and second oscillators, configured to generate first and second electrical signals having first and second frequencies, respectively; first and second driver units electrically coupled to the first and second oscillators; first and second light emitting elements adapted to generate first and second light signals. The first and second light emitting elements may be electrically coupled to the first and second driver units.

[0024] Furthermore in accordance with an embodiment of the invention, the device further includes a dichroic beam-combiner, which may be configured to combine the first and second light signals into a single beam. The beam may include components of the first and second light wavelengths ($\lambda 1$ and $\lambda 2$) of the first and second modulation frequencies (F1 and F2), respectively.

[0025] Furthermore in accordance with an embodiment of the invention, the device further includes a reference detector configured to receive and measure a portion of the light incident on the dichroic beam-combiner.

[0026] Furthermore in accordance with an embodiment of the invention, the device further includes a detector-amplifier unit having light sensing means adapted to produce electric signals corresponding to the first and second light signals received by the detector-amplifier unit and to amplify the resulting electric signals; first and second synchronous detectors configured to receive the first and second signals and to extract the magnitude of the transmitted signal in wavelength $\lambda 1$ and frequency F1 and wavelength $\lambda 2$ and frequency F2 respectively, from the resulting electric signals.

[0027] Furthermore in accordance with an embodiment of the invention, the means for measuring the thickness includes one of a group of devices including a potentiometer, an opti-

cal measuring device, Rotary Variable Differential Transformer (RVDT) and a Linear Variable Differential Transformer (LVDT).

[0028] Furthermore in accordance with an embodiment of the invention, the device further includes gauging means for testing the device. The gauging means may include a testing jig composed of a transmissive material having known optical properties and thickness.

[0029] Furthermore in accordance with an embodiment of the invention, the device further includes means to eliminate external interference in the measured transmittance signals.

[0030] In addition, there is provided a method for measuring the bilirubin level of a subject. The method includes the steps of:

[0031] applying blanching pressure to the subject's living tissue;

[0032] determining the thickness of the subject's blanched tissue;

[0033] transmitting at least two different wavelengths through a subject's blanched tissue;

[0034] detecting and recording the signals transmitted through the tissue having blanching pressure applied thereto; and

[0035] calculating the bilirubin level in the subject using data obtained from the recorded signals and the thickness.

[0036] Furthermore in accordance with an embodiment of the invention, the method further comprises the step of gauging a device configured to measure the bilirubin level. Furthermore in accordance with an embodiment of the invention, the method further comprises the step of calculating first (λ_0) and second (λ_1) calibration constants.

[0037] Furthermore in accordance with an embodiment of the invention, the step of transmitting includes the step of configuring at least one radiation source for radiating the subject's living tissue.

[0038] Furthermore in accordance with an embodiment of the invention, the method further includes a gauging step, which includes the steps of:

[0039] transmitting at least two different wavelengths through a transmissive material having known optical properties and thickness;

[0040] detecting and recording the signals transmitted through the transmissive material and the signal of the thickness measuring means;

[0041] calculating the tissue transmittance at each wavelength, T (λ), according to the equation:

$$T(\lambda) = JT(\lambda) \frac{UT(\lambda))}{UJ(\lambda)}$$

wherein:

[0042] JT (λ) is the known transmittance of the transmissive material in a testing jig, at wavelength λ;

[0043] UT (λ) is the recorded detector signal in response to the light at wavelength λ transmitted through the tissue; and

[0044] UJ (λ) is recorded detector signal in response to the light at wavelength λ transmitted through the transmissive material; and

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[0045] calculating the tissue thickness d, according to the equation:

$$d = Jd \frac{Ud}{UJd}$$

[0046] Wherein Jd is the known thickness of the transmissive material;

[0047] Ud is recorded signal of the thickness measuring means when the tissue is being measured; and

[0048] UJd is the recorded signal of the thickness measuring means when the testing jig is being measured.

[0049] Furthermore in accordance with an embodiment of the invention, the bilirubin level is calculated according to the equation:

$$B\hat{R} = A_0 + A_1 \frac{1}{d} \log_e \frac{T(\lambda 1)}{T(\lambda 2)}$$

wherein:

[0050] B$\hat{R}$—calculated serum bilirubin level indication in mg/dl or μmol/L

[0051] A_0—First calibration constant;

[0052] A_1—Second calibration constant;

[0053] d—The thickness of the measured tissue (e.g., in millimeters);

[0054] T(λ)—The calculated transmittance of tissue for light of wavelength (λ).

[0055] Furthermore in accordance with an embodiment of the invention, the step of detecting the optical signals includes the step of removing ambient noise and interference from the received signal.

DESCRIPTION OF THE INVENTION

[0056] The present inventors have discovered that serum bilirubin levels in a living subject may be inferred from transcutaneous non-invasive measurements performed on the living tissue of a patient, by employing optical, electrical, and mechanical means in communication with processing means. Radiation is transmitted through the living tissue and measured by a detector or sensor. The thickness of the tissue is also measured. The processing means may be configured to calculate the serum bilirubin concentration based on the measured and detected values.

[0057] FIG. 1 illustrates a device 10 for measuring bilirubin levels according to one general preferred embodiment of the present invention. Device 10 comprises a housing 12 comprising processing means 12c in communication with a radiation source 12s, optical sensor means 12r, alert means 18 (optional), input means 19 for use by a human operator, and a display means 20. Radiation source 12s may be implemented by means of a white light emitter followed by two optical bandpass filters, two laser diodes, or two light emitting diodes, for example, capable of emitting radiation in two different wavelengths λ1 and λ2.

[0058] By experimentation, it was found that the wavelengths giving the best results were 520 nm±5 nm and 470 nm±10 nm. However, persons knowledgeable in the art will

appreciate that wavelengths outside these ranges may also be used to measure and achieve an indication of the bilirubin level.

[0059] Thus, the device may also comprise optical means (not shown) configured to direct beams of light emitted by light emitters from the radiation source 12s. Sensor 12r may also comprise optical coupling means (not shown) configured to direct beams of light to optical detectors comprised (not shown) therein.

[0060] In an alternative embodiment, the device may directly transmit and receive light without the need for light guiding means.

[0061] In an embodiment of the invention, device 10 may comprise tissue thickness measurement means, such as device comprising a pair of rotatable arms 14a and 14b, for example. The pair of rotatable arms 14a and 14b may comprise an elongated portion attached at one end to housing 12 by means of respective hinges 13a and 13b, and respective curved portions 14n at their free ends which are configured to define two contact surfaces 14m at the extremities of rotatable arms 14a and 14b, wherein contact surfaces 14m are facing each other in opposing relationship. Rotatable arms 14a and 14b are thus rotatable about their respective hinges 13a and 13b, and they further comprise respective light guiding means 5 and 6 passing along their lengths and along their curved portions 14n.

[0062] In another embodiment of the invention, the tissue thickness measurement means may comprise a clip or pincer device configured to be attached to the tissue being measured.

[0063] Light guiding means 5 may be adapted to deliver light emitted from radiation source 12s to an object 17 placed between the free extremities of rotatable arms 14a and 14b. Object 17 is either the tissue under test, or a test jig (not shown). The tissue being tested may be any tissue, such as the top of ear or ear lobe, for example, where the thickness of the tissue may be measured.

[0064] Light guiding means 6 may be adapted to collect light transmitted through the object 17 and deliver it to sensor means 12r. A first end 5i of light guiding means 5 emerging from the hinged end of movable arm 14a is adapted to receive light radiation emitted from radiation source 12s and deliver it to its other end 5f, which is aligned with contact surface 14m of rotatable arm 14a for emitting the light passed through it to the object 17. Light guiding means 6 may be adapted to collect light transmitted through the object 17 by a corresponding end 6f aligned with contact surface 14m of rotatable arm 14b such that light transmitted through the object is collected and passed therethrough and emitted via its other end 6j to optical detector means in sensor 12r. Light guiding means 5 and 6 may be implemented by means of any suitable fiber optics means, for example. The light radiation source may also be connected via other optical means to 14m and the sensor may also be connected via other optical means to the contact surface 14m.

[0065] In an alternative embodiment, the sensor may also be located close to the ear, without any need for transferring light.

[0066] Device 10 comprises input means 19 for operating the device. These input means may comprise buttons, switches and the like so that the operator can select the desired operating mode of the device and initiate its operation. The device may comprise two main modes: The "Gauging" mode and the "Measurement" mode.

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[0067] In the measurement mode, processing means 12c, after receiving an appropriate activation command from the input means 19, sends a signal to the radiation source 12s to generate light in a first wavelength λ1 (520 nm for example). The emitted light passes through light guiding means 5, which may be embedded in, or attached to the rotatable arm 14a. The light transferred through light guiding means 5 may be emitted at its distal end 5f, which may be aligned with contact surface 14m of rotatable arm 14a, and passes through object 17 (such as the top part of the ear, for example).

[0068] Light transmitted through 17 may be collected by light guiding means 6 aligned with surface 14m of rotatable arm 14b. The collected light is delivered through light guiding means 6 and emitted through its 6j to sensor means 12r, which measures the magnitude of light transmitted through tissue 17. The resulting signal may be sampled by the processing means and stored in its memory. The operation proceeds as processing means 12c sends another signal to the radiation source 12s to emit light radiation in a second wavelength λ2 (470 nm, for example). The emitted light travels in the same path through light guiding means 5 to tissue 17 and to light guiding means 6, which collects light transmitted through tissue 17, and to sensor means 12r which measures the magnitude of light transmitted through tissue 17. The resulting signal may be sampled by the processing means and stored in its memory.

[0069] Additionally, the processing means may read and store the output of the thickness measuring means 12t (explained hereinafter).

[0070] In gauging mode, the same sequence occurs however, in this case object 17 is a test jig instead of tissue 17. The test jig may contain a transmissive material of known optical properties and thickness such as Neutral Density Filter, P63-385 (Edmund Optics).

[0071] The tissue transmittance at each wavelength, T(λ), is calculated by the processing means as the product of the known jig transmittance JT(λ) and the ratio of the tissue transmitted signal UT(λ) and jig transmitted signal UJ(λ), as shown in the following equation

$$T(\lambda) = JT(\lambda)\frac{UT(\lambda))}{UJ(\lambda)} \qquad (1)$$

[0072] The tissue thickness d is calculated by the processing means as the product of the known jig thickness, Jd, and the ratio of tissue net thickness signal Ud and the jig net thickness signal UJd in the following equation

$$d = Jd\frac{Ud}{UJd} \qquad (2)$$

[0073] The net thickness signal is the difference between the real thickness signal and a bias signal. The later is adjusted such that a zero d will be registered when object 17 is removed and the arms come into contact.

[0074] After calculating the thickness and transmittance of the tissue at the λ1 and λ2 wavelengths, processing means 12c calculates an estimate of the serum bilirubin level, as explained in the description hereinbelow. If the bilirubin level calculated by processing means 12c indicates high bilirubin levels (e.g., a level greater than a threshold value e.g. 12

mg/dl), then a corresponding indication may be issued by processing means 12c by sending a signal to visual and/or audible alert means 18 (such as a speaker or a beeper, for example), for alerting that the measured results indicate high chances of jaundice conditions in the subject. Power supply means (e.g., rechargeable batteries—not shown) are preferably provided for powering the electronic elements of device 10.

[0075] In an embodiment of the present invention, after calculating the bilirubin level, the processing means may send a signal to a digital display means for displaying the calculated result for the bilirubin level.

[0076] As seen in FIG. 1, spring 16, or any other suitable elastic element, may be used for mechanically coupling between rotatable arm 14a and 14b. Spring 16 is adapted to apply pressure over the tissue 17 maintained between rotatable arms 14a and 14b during the tissue measurements. Spring 16 is preferably configured to bring rotatable arms 14a and 14b together and apply pressure over tissue 17 such that the force that they apply over tissue 17 overcomes the systolic pressure, such that light transmitted through tissue 17 provide an indication of light transmittance through a piece of tissue from which blood has been expelled. This applied pressure is referred to herein as 'blanching pressure'. The blanching pressure is preferably larger than the systolic pressure.

[0077] Thickness measurement means 12t are preferably also provided in housing 12 for measuring the distance d between tips 14m of rotatable arms 14a and 14b. As exemplified in FIG. 1, thickness measurement means 12t may be implemented by means of a potentiometer or a Linear Variable Differential Transformer (LVDT), adapted for measuring the thickness (or width) d of the tested tissue 17. Processing means 12c is adapted to obtain tissue thickness d readings obtained by means of thickness measurement means 12t, which are then used for calculating the bilirubin levels in the tested tissue.

[0078] It will be appreciated by persons knowledgeable in the art, that thickness measurement means 12t may be implemented by any suitable means, such as by optical means, a potentiometer, an optical measuring device, Rotary Variable Differential Transformer (RVDT) and a Linear Variable Differential Transformer (LVDT).

[0079] In the preferred embodiment shown in FIG. 1, two rotatable arms 14a and 14b are used. In one specific preferred embodiment of the invention only one arm is made rotatable, while the other arm is fixedly attached to housing 12. However, having both arms 14a and 14b rotatable is advantageous since with this configuration movements and vibrations induced by the operator's hands while operating device 10 are substantially eliminated since both arms 14a and 14b are free to move relative to housing 12.

[0080] The present invention furthermore provides a method for measuring the bilirubin levels in a living tissue. The method illustrated in block diagram shown in FIG. 2, is based on calculation of a bilirubin level indication by means of equation (3):

$$B\widehat{R} = A_0 + A_1\frac{1}{d}\log_e\frac{T(\lambda 1)}{T(\lambda 2)} \qquad (3)$$

[0081] Wherein:

[0082] BR̂—calculated serum bilirubin level indication in mg/dl or μmol/L

[0083] A_0—First calibration constant;

[0084] A_1—Second calibration constant;

[0085] d—The thickness of the measured tissue (e.g., in millimeters);

[0086] T(λ)—The transmittance of tissue for light of wavelength (λ), calculated according to equation (1).

[0087] Equation (3) was developed following thorough research carried out by the inventors in which light transmittance and tissue thickness were measured in newborns that were scheduled for bilirubin measurement by means of the standard blood test. The first and second normalization constants were derived such that the differences between the true bilirubin levels and the calculated levels according to equation (3) were minimized in least square sense.

[0088] Reference is now made to FIG. 2, which is a flow-chart illustrating a method for operating the device 10. The calibration constants A_0 and A_1 will have been stored in the device's memory in the factory during manufacture. The method may comprise a gauging step 21, performed at the manufacturing process or preferably on a regular basis, such as daily before commencing any measurements, for example. The gauging step comprises reading transmitted signals and thickness signal of the test jig and storing these in the memory of the processing means 12c for subsequent calculations.

[0089] In step 22, the tested tissue 17, such as the top part of the ear, for example, is placed between the device arms (14a and 14b). The arms are forced tightly as explained herein-above to apply blanching pressure on tissue 17. The thickness signal of the pressed tissue is then measured and recorded in step 23, and in step 24 light signals are emitted in the two wavelengths (λ1 and λ2, such as 520 nm and 470 nm, for example). The measurements of the respective transmitted signals are carried out and recorded.

[0090] In step 25, the calibration constants are applied to the measured variables to calculate the tissue thickness and transmittance in the 520 nm and 470 nm wavelengths. In step 26 the estimated bilirubin level is calculated according to equation (3) and transferred to the display means 20.

[0091] Optionally, in step 27, it is checked whether the bilirubin level indication calculated in step 26 is above a predetermined level (Thr). Then in step 28, device 10 indicates that a high bilirubin level was measured (risk for jaundice conditions) in the subject, which may require further test as indicated in step 29. If it is determined in step 27 that the bilirubin level is below the predetermined level, then in step 30, device 10 indicates that low or normal bilirubin levels were measured.

[0092] In another embodiment of the invention d, T(λ1), and T(λ2) in equation (3) may be replaced with the signals Ud, UT(λ1) and UT(λ2). In this case, different normalization constants will replace A_0 and A_1 to reflect the change of the variables in equation (3).

[0093] According to one embodiment of the present invention, the bilirubin measurement device 10 generates the light beams of 520 nm and 470 nm concurrently, for a short period of time. The transmitted signals arrive simultaneously at the optical detector means where they are separated according to their wavelength, measured and stored. The operation of this embodiment proceeds with the calculations, display and alert via alert means 18 as described above.

[0094] According to one embodiment of the present invention, the bilirubin measurement device is further adapted to eliminate external influences which may introduce noise and other such interferences in the measured transmittance signals (e.g., fluorescent light or any other such light source). FIGS. 3A to 3C illustrate one preferred embodiment for an implementation in which synchronous detection is used for substantially removing interfering light signals.

[0095] FIG. 3A provides a schematic illustration of light guiding arms 14a and 14b during transmittance measurements. A light beam 100 enters arm 14a, leaves arm 14a into the tested tissue 17. Transmitted light is collected by arm 14b and exit it as beam 200.

[0096] FIG. 3B is a block diagram showing one preferred embodiment of a radiation source 101 adapted for carrying out the synchronous detection technique of the invention. The radiation source 101 comprises two oscillators referenced at 103 and 104 which are configured to generate two different electrical signals having frequencies F1 and F2 respectively. Radiation source 101 further comprises two driver units 105 and 106 electrically coupled to oscillators 103 and 104, and two light emitting elements (such as light emitting diodes (LEDs), or laser diodes, for example) 107 and 108 adapted to generate light signals with center wavelengths λ1 and λ2 (such as, 520 nm and 470 nm, for example), which are electrically coupled to driver units 105 and 106. In this configuration, signals generated by oscillators 103 and 104 are used by driver units 105 and 106 as modulating signals for activating light emitting elements 107 and 108 such that they simultaneously produce light signals in the respective frequencies F1 and F2 produced by oscillators 103 and 104. Accordingly, in operation, light emitting elements 107 and 108 produce light signals 109 and 110 having F1 and F2 frequencies and λ1 and λ2 wavelengths, respectively.

[0097] As described above, in the present invention, the light beams to be transmitted through tissue 17 are in the 520 nm±5 nm and 470 nm±10 nm wavelength ranges and are modulated at frequencies F1 and F2 respectively. It should be noted that the F and F2 frequencies are predetermined frequencies. The emitted light signals 109 and 110 are coupled to a suitable beam combining means 102 (e.g., dichroic beam-combiner), which combines the light signals 109 and 110 into a single beam 100 comprising components of both light wavelengths (520 nm±5 nm and 470 nm±10 nm) and modulation frequencies (F1 and F2), respectively.

[0098] In an alternative embodiment, optional filters (not shown) may be inserted between the light emitting elements 107 and 108 and the beam combining means 102. In a further alternative embodiment, a reference detector (not shown) may be used to monitor the intensity of the beams generated by the light emitting elements 107 and 108. The reference detector receives a portion of the light incident on the beam combining means 102.

[0099] In an alternative embodiment, the light beams (for example blue and green) may be transmitted through tissue 17 at different times, instead of modulating the light beams by using different frequencies F1 and F2. In order to eliminate the ambient light, a measurement of the light is taken with the illuminating device switched off. The latter measured reading is taken after a pre-determined time period (after measuring the illuminated reading) and deducted from the illuminated reading to obtain the net illumination. The pre-determined time period may be determined by the nature of the ambient light.

[0100] With reference to FIG. 3C showing one embodiment of a detection unit 201, transmitted light beam 200 enters detection unit 201 wherein it is focused by optical means 202 (such as a lens, for example) and introduced into detector-amplifier unit 203. Detector-amplifier unit 203 comprises light sensing means adapted to produce electric signals corresponding to light signals received in detector/amplifier unit 203 and to amplify the resulting electric signals. The amplified signal e(t) produced by detector/amplifier unit 203 is fed into two synchronous detectors 205 and 206 which are also adapted to receive signals produced by oscillators 103 and 104 in the F1 and F2 frequencies, respectively. Synchronous detector 205 is adapted to extract from the electric signal e(t) the magnitude of the transmitted signal in wavelength λ1 and frequency F1. Synchronous detector 206 is adapted to extract from the electric signal e(t) the magnitude of the transmitted signal in wavelength λ2 and frequency F2. The output of the synchronous detectors 205 and 206 are then fed into processing means 12c.

[0101] Processing means 12c is adapted to sample the electric signals received and calculate the bilirubin level in accordance with equation (3), and display the calculated result value in display means 20, and issue alert indications, if so needed.

[0102] According to yet another embodiment of the invention, a flashtube may be employed as a light source, as shown in FIGS. 4A and 4B. The flashtube typically produces a short pulse of light radiation comprising a wide spectrum of wavelengths. Flashtube enclosure 30 comprises a flashtube 31, a power supply 34 to power the flashtube and a trigger unit 33 for activating flashtube 31 following a command from processing means 12c.

[0103] The flashtube 31 produces a pulsed light beam 32, which travels through arm 14a (through light guiding means 5), transmitted through tissue 17, collected and conducted through arm 14b, and emerges as light beam 35.

[0104] Light beam 35 enters optical unit 40 wherein it is focused by an optical means 41 (lens), and thereafter passed through a beam splitting means 42 (e.g., Dichroic beam splitter) which splits the light beam into two component beams: a transmitted beam 44 which includes the tissue transmitted light at wavelength λ1 (approx. 520 nm±5 nm) and a reflected beam 45 which includes the tissue-transmitted light at wavelength λ2 (approx. 470 nm).

[0105] With reference to FIG. 4B, light beams 44 and 45 enter electro-optic unit 50, which comprises two band-pass filter/ detector units 51 and 52. The band-pass filter in unit 51 is adapted to pass the tissue-transmitted light at wavelength λ1 to the detector, while blocking all other spectral components of beam 44. The detector generates an electrical signal corresponding to the magnitude of tissue transmitted light at wavelength λ1. Likewise, the filter/detector unit 52 receives beam 45 and provides an electrical signal corresponding to the magnitude of tissue transmitted light at wavelength λ2. Peak detectors 53 and 54 sample and hold the peak values of the electrical signals generated by units 51 and 52. Processing means 12c converts these peak values to a digital format for the calculation of tissue transmittance at λ1 and λ2.

[0106] Processing means 12c calculates a bilirubin level indication according to equation (3) and provides the result value for display in display means 20.

[0107] FIGS. 5A and 5B illustrate yet another embodiment of the present invention, showing a front perspective view and a rear view of device 300. Device 300 comprises the main elements of the embodiments explained above, (but not shown in FIG. 5). Device 300 further comprises operation buttons 301 for inputting device operation commands and activating button 305 for activating the device 300. Buttons 301 and 305 are possible embodiments of the input means 19.

[0108] Device 300 comprises a stationary arm 312r and a movable arm 314, with a force element holding them flush against each other such as a spring (not shown). The operator of the device 300 can engage lever 306 to open a gap between arms 312r and 314 such that the tissue 17, or test jig, can be placed in the gap. When lever 306 is released, the spring will apply the blanching pressure to expel the blood from the tissue that is between the arms. One arm conveys the illuminating light to the tissue, while the other arm receives light transmitted through the tissue and delivers it to the detection unit

[0109] The thickness of the tissue d may be measured by means of a potentiometer or LVDT (not shown), or by any other thickness measuring element.

[0110] The processing means 12c (not shown) calculates a bilirubin level indication as explained hereinabove. A power source may be provided (not shown) for supplying power to all the elements in device 300. The power source is capable of being recharged by means of battery charging connectors 307. The display means 20 may be a display screen 356 provided for displaying the measured bilirubin level in a numerical format, or in a graphical format where the measured value is displayed as a point on nomogram, and for operation assistance.

[0111] Device 300 may comprise a barcode reader 320 for operation in a most efficient manner. Activation button 305 may activate the barcode reader 320 such that a patient's data is stored on board. After measuring the bilirubin level by device 300, the user can transfer the patient data along with the bilirubin level results to an external data processing system (e.g., personal computer, healthcare computer system, or the like) via data outlet 321. In this manner, a patient's bilirubin level can be measured and the results recorded on a central computer within a very short period of time. All this is performed in a non-invasive manner.

[0112] While some of the embodiments of the invention have been described by way of illustration, it will be apparent that the invention can be carried into practice with many modifications, variations and adaptations, and with the use of numerous equivalents or alternative solutions that are within the scope of a person skilled in the art, without departing from the spirit of the invention, or the scope of the claims.

1. A non-invasive device for measuring the bilirubin level of a subject comprising:

at least one radiation source for radiating a subject's living tissue, said at least one radiation source configured to emit radiation in at least first and second wavelengths;

at least one detector for detecting rays transmitted through said tissue;

means for applying blanching pressure to the portion of the subject's living tissue;

means for measuring the thickness of the portion of the subject's living tissue through which radiation is being transmitted; and

processing means in communication with said at least one radiation source, said at least one detector and said means for measuring thickness,

wherein said processing means are configured to calculate the bilirubin level of said subject using data obtained from said at least one detector and from said thickness measurement means.

2. The device according to claim **1**, wherein the means for applying blanching pressure comprise one of group of devices including a pair of rotatable arms, a single moving or rotating arm and a clip or pincer device, configured to be attached to the tissue being measured.

3. The device according to claim **1**, wherein said at least first and second wavelengths comprise a first wavelength ($\lambda 1$) within a range 520 nm±5 nm and a second wavelength ($\lambda 2$) within a range 470 nm±10 nm.

4. The device according to claim **1**, wherein said at least one radiation source comprises one of a group including at least two laser diodes, at least two light emitting diodes (or LEDs) and at least one laser diode together with at least one LED.

5. The device according to claim **1**, wherein said at least one radiation source comprises a white light emitter and at least two filters for filtering the emitted white light.

6. The device according to claim **4**, wherein the device further comprises optical means configured to direct beams of light emitted from the at least one radiation source towards the subject's living tissue.

7. The device according to claim **6**, wherein the light beams are transmitted through the tissue at different times.

8. The device according to claim **4**, wherein the device further comprises light guiding means and optical coupling means, said optical coupling means configured to direct beams of light received from the light guiding means to said at least one detector.

9. The device according to claim **1**, wherein said at least one radiation source comprises means for emitting a synchronous signal, said synchronous signal comprising:

first and second oscillators, configured to generate first and second electrical signals having first and second frequencies, respectively;

first and second driver units electrically coupled to said first and second oscillators;

first and second light emitting elements adapted to generate first and second light signals, said first and second light emitting elements electrically coupled to said first and second driver units.

10. The device according to claim **9**, wherein the device further comprises:

a dichroic beam-combiner, configured to combine said first and second light signals into a single beam, said beam comprising components of the first and second light wavelengths ($\lambda 1$ and $\lambda 2$) of the first and second modulation frequencies (F**1** and F**2**), respectively.

11. The device according to claim **1**, wherein the device further comprises:

a reference detector configured to receive and measure a portion of the light incident on the dichroic beam-combiner.

12. The device according to claim **9**, wherein the device further comprises:

a detector-amplifier unit comprising light sensing means adapted to produce electric signals corresponding to said first and second light signals received by the detector-amplifier unit and to amplify the resulting electric signals;

first and second synchronous detectors configured to receive said first and second signals and to extract the magnitude of the transmitted signal in wavelength $\lambda 1$ and frequency F**1** and wavelength $\lambda 2$ and frequency F**2** respectively, from the resulting electric signals.

13. The device according to claim **1**, wherein the means for measuring the tissue thickness comprises one of a group of devices including a potentiometer, an optical measuring device, Rotary Variable Differential Transformer (RVDT) and a Linear Variable Differential Transformer (LVDT).

14. The device according to claim **1**, further comprising gauging means for testing the device.

15. The device according to claim **14**, wherein the gauging means comprises a testing jig composed of a transmissive material having known optical properties and thickness.

16. The device according to claim **1**, further comprising means to eliminate external interference in the measured transmitted signals.

17. A method for measuring the bilirubin level of a subject comprising the steps of:

applying blanching pressure to the subject's living tissue;

determining the thickness of the subject's blanched tissue;

transmitting at least two different wavelengths through a subject's blanched tissue;

detecting and recording the signals transmitted through the tissue having blanching pressure applied thereto; and

calculating the bilirubin level in the subject using data obtained from said recorded signals and said thickness.

18. The method according to claim **17**, further comprising the steps of:

gauging a device configured to measure the bilirubin level; and

calculating first (A**0**) and second (A**1**) calibration constants.

19. The method according to claim **17**, wherein the step of transmitting comprises the step of:

configuring at least one radiation source for radiating the subject's living tissue.

20. The method according to claim **18**, further comprising a gauging step, said gauging step comprising the steps of:

transmitting at least two different wavelengths through a transmissive material having known optical properties and thickness;

detecting and recording the signals transmitted through the transmissive material and the signal of the thickness measuring means;

calculating the tissue transmittance at each wavelength, T(λ), according to the equation:

$$T(\lambda) = JT(\lambda) \frac{UT(\lambda))}{UJ(\lambda)}$$

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wherein:

JT(λ) is the known transmittance of the transmissive material in a testing jig, at wavelength λ;

UT(λ) is the recorded detector signal in response to the light at wavelength λ transmitted through the tissue; and

UJ(λ) is recorded detector signal in response to the light at wavelength λ transmitted through the transmissive material; and

calculating the tissue thickness d, according to the equation:

$$d = Jd\frac{Ud}{UJd}$$

Wherein, Jd is the known thickness of the transmissive material;

Ud is recorded signal of the thickness measuring means when the tissue is being measured; and

UJd is the recorded signal of the thickness measuring means when the testing jig is being measured.

21. The method according to claim 18, wherein the step of calculating the bilirubin level is calculated according to the equation:

$$B\hat{R} = A_0 + A_1\frac{1}{d}\log_e\frac{T(\lambda1)}{T(\lambda2)}$$

wherein:

B$\hat{R}$—calculated serum bilirubin level indication in mg/dl or μmol/L

A_0—First calibration constant;

A_1—Second calibration constant;

d—The thickness of the measured tissue (e.g., in millimeters);

T(λ)—The calculated transmittance of tissue for light of wavelength (λ).

22. The method according to claim 17, wherein said step of detecting comprises the step of

removing ambient noise and interference from the received signal noise and interference from the ambient light.

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