US007623988B2

(12) **United States Patent**
Bedard et al.

(10) **Patent No.: US 7,623,988 B2**
(45) **Date of Patent: Nov. 24, 2009**

(54) **METHOD AND APPARATUS FOR THE MONITORING OF CLINICAL STATES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 756 days.

(21) Appl. No.: **11/165,003**

(22) Filed: **Jun. 23, 2005**

(65) **Prior Publication Data**

US 2006/0004270 A1 Jan. 5, 2006

Related U.S. Application Data

(60) Provisional application No. 60/581,727, filed on Jun. 23, 2004.

(51) **Int. Cl.**
G06F 15/00 (2006.01)
A61B 5/00 (2006.01)

(52) **U.S. Cl.** **702/189**; 600/316

(58) **Field of Classification Search** 702/182, 702/189; 600/310, 316, 317; 435/14
See application file for complete search history.

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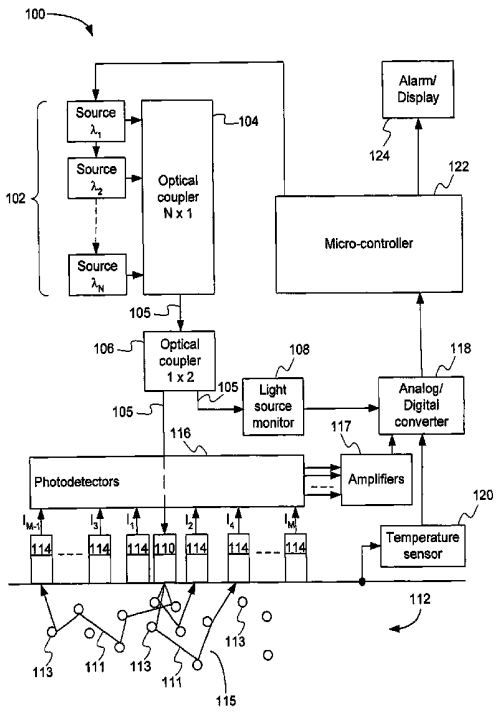
(57) **ABSTRACT**

A method and apparatus to monitor clinical states, for example hypoglycaemia, hyperglycaemia or an ischemic state, and to detect if a user if affected by such a state. In one embodiment, the method and apparatus use a correlation between one or more non-invasive physical measurements of the body of the subject and a reference value of blood-glucose of the subject to compute an estimation parameter value, and comparing that estimation parameter value with a critical parameter value indicative of the presence of a clinical state, for example hypoglycaemia, hyperglycaemia. In another embodiment, the algorithm estimates chromophore concentrations and the scattering coefficient in order to compute a level of oxygen saturation and detect the presence of an ischemic state.

30 Claims, 7 Drawing Sheets



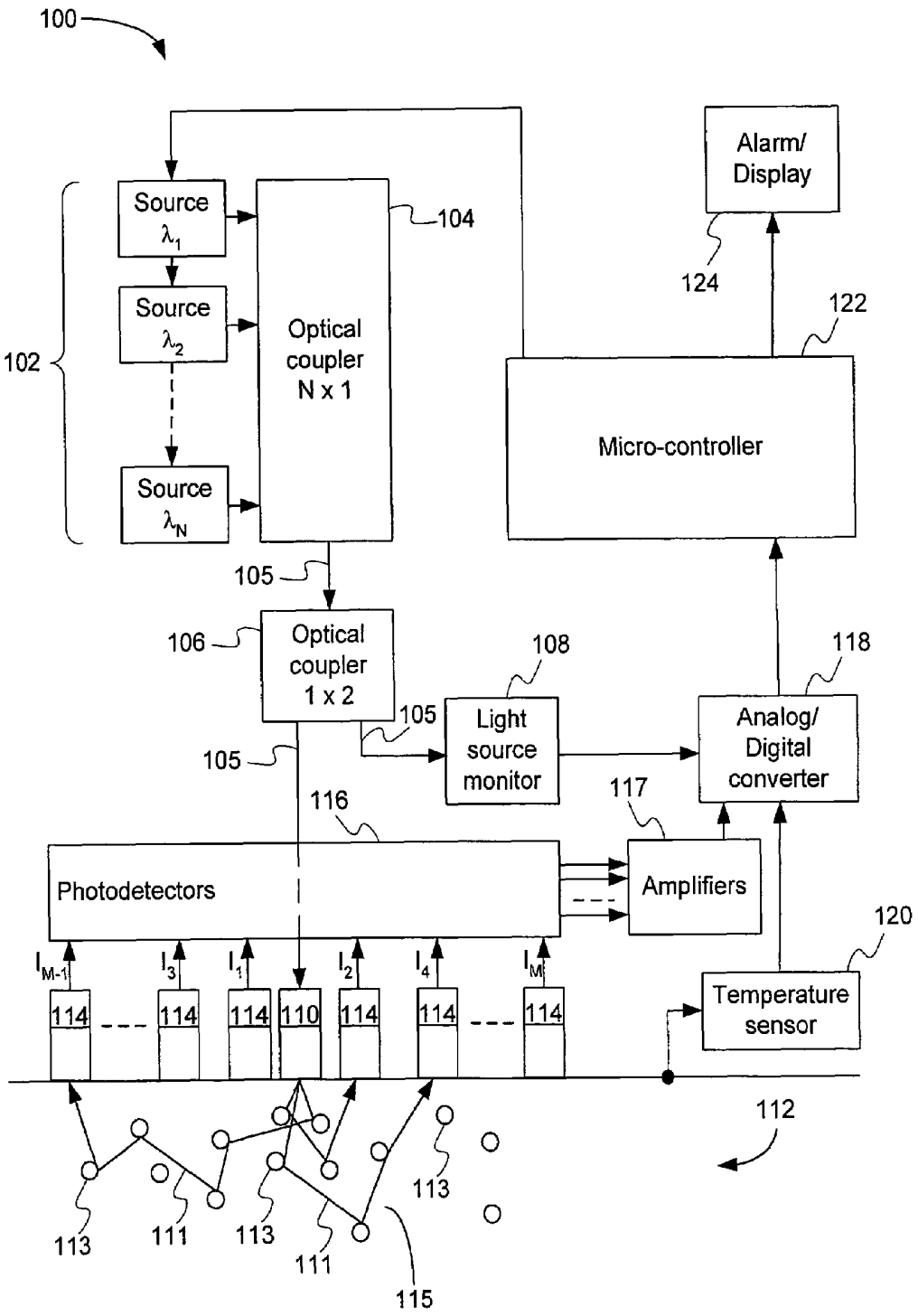

100
Source λ_1
Source λ_2
Source λ_N
102
Optical coupler N x 1
104
105
Optical coupler 1 x 2
106
105
105
Light source monitor
108
Alarm/ Display
124
122
Micro-controller
118
Analog/ Digital converter
117
116
Photodetectors
Amplifiers
120
Temperature sensor
I_{M-1}
I_3
I_1
I_2
I_4
I_M
114
110
112
113
111
115

Figure 1

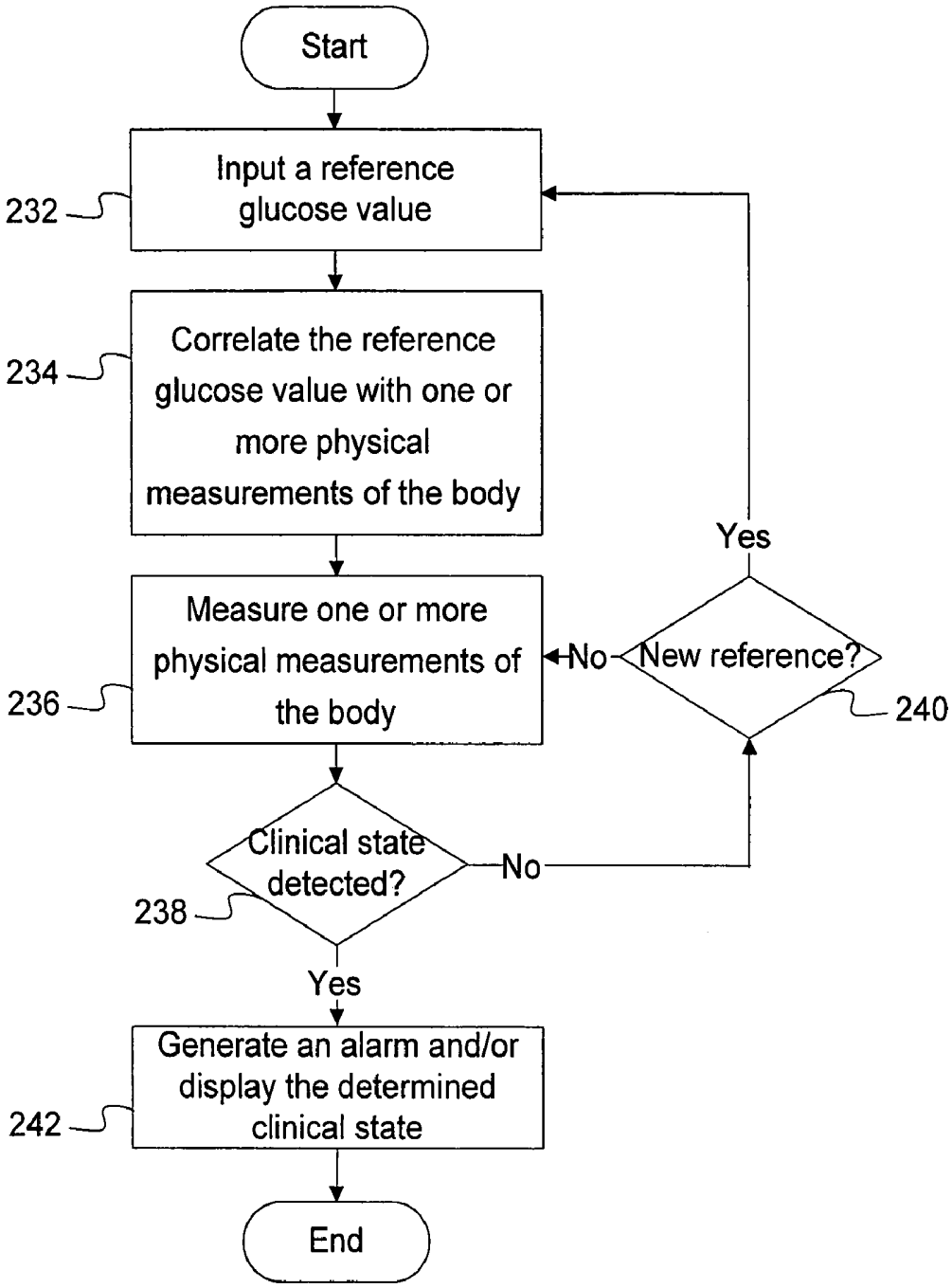

Start
Input a reference glucose value
232
Correlate the reference glucose value with one or more physical measurements of the body
234
Measure one or more physical measurements of the body
236
New reference?
240
Yes
No
Clinical state detected?
238
No
Yes
Generate an alarm and/or display the determined clinical state
242
End

Figure 2

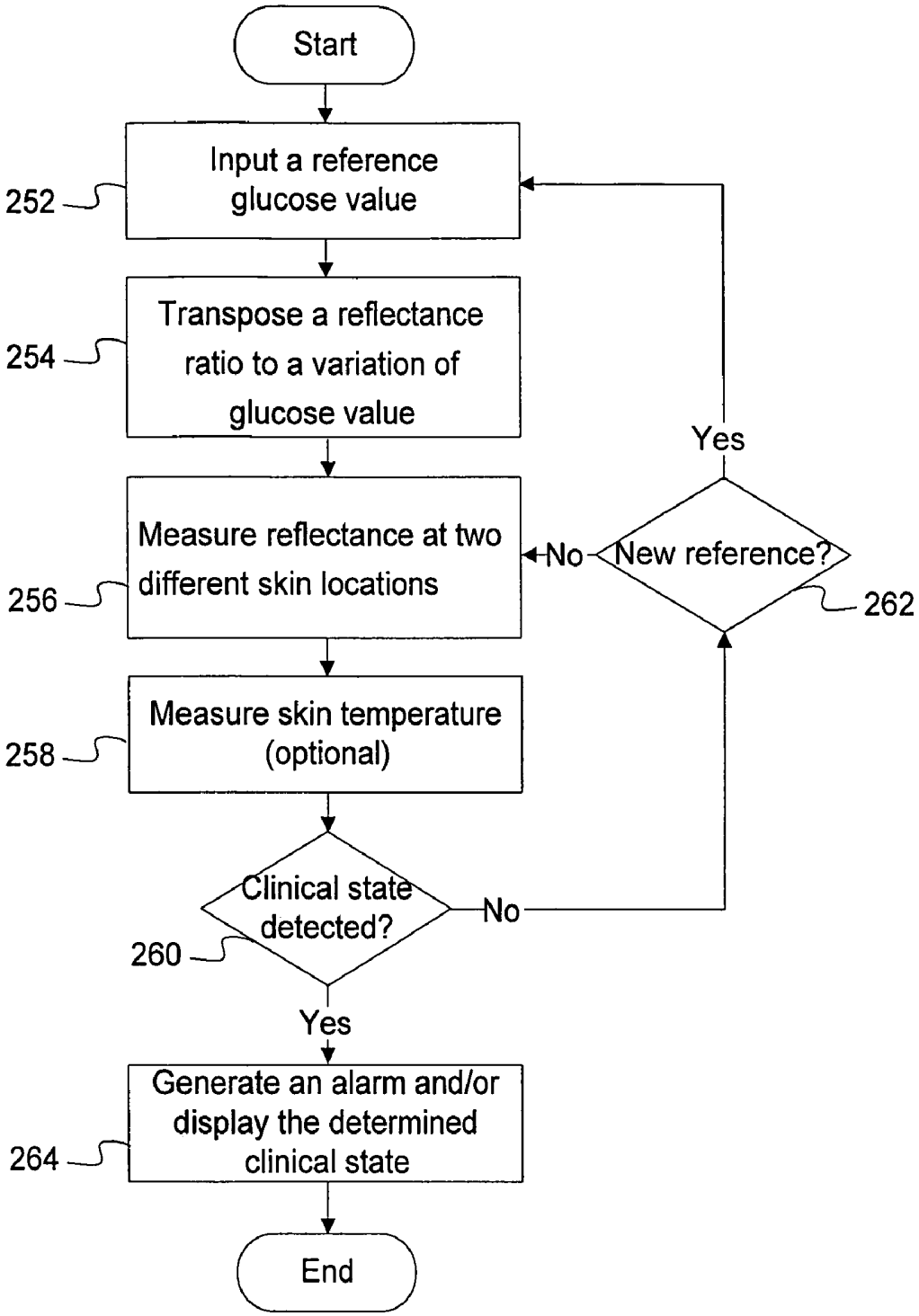

Start
Input a reference glucose value
252
Transpose a reflectance ratio to a variation of glucose value
254
Measure reflectance at two different skin locations
256
Measure skin temperature (optional)
258
Clinical state detected?
260
No
Yes
New reference?
262
No
Yes
Generate an alarm and/or display the determined clinical state
264
End

Figure 3

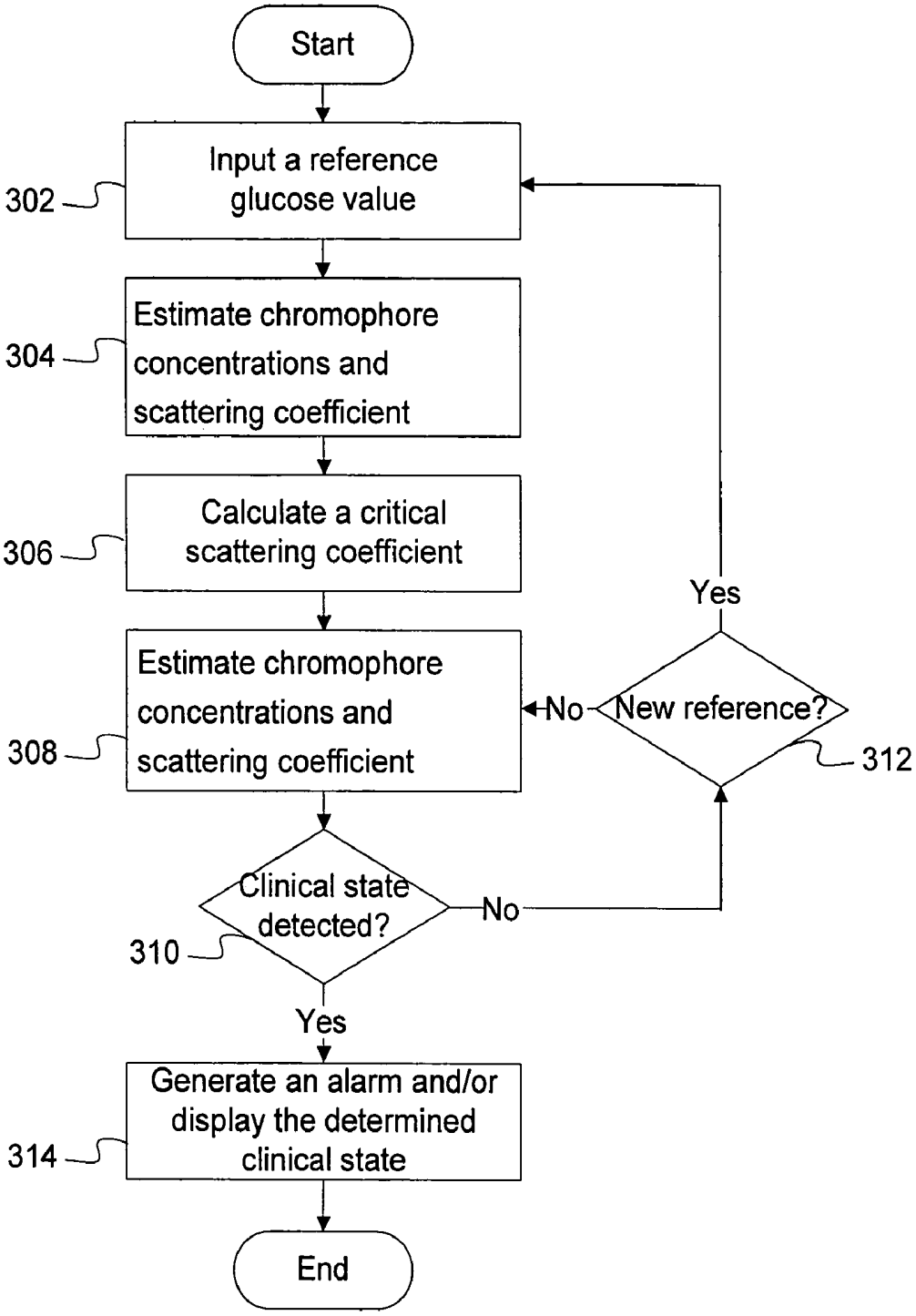

Start
Input a reference glucose value
302
Estimate chromophore concentrations and scattering coefficient
304
Calculate a critical scattering coefficient
306
Estimate chromophore concentrations and scattering coefficient
308
Clinical state detected?
310
No
Yes
New reference?
312
No
Yes
Generate an alarm and/or display the determined clinical state
314
End

Figure 4

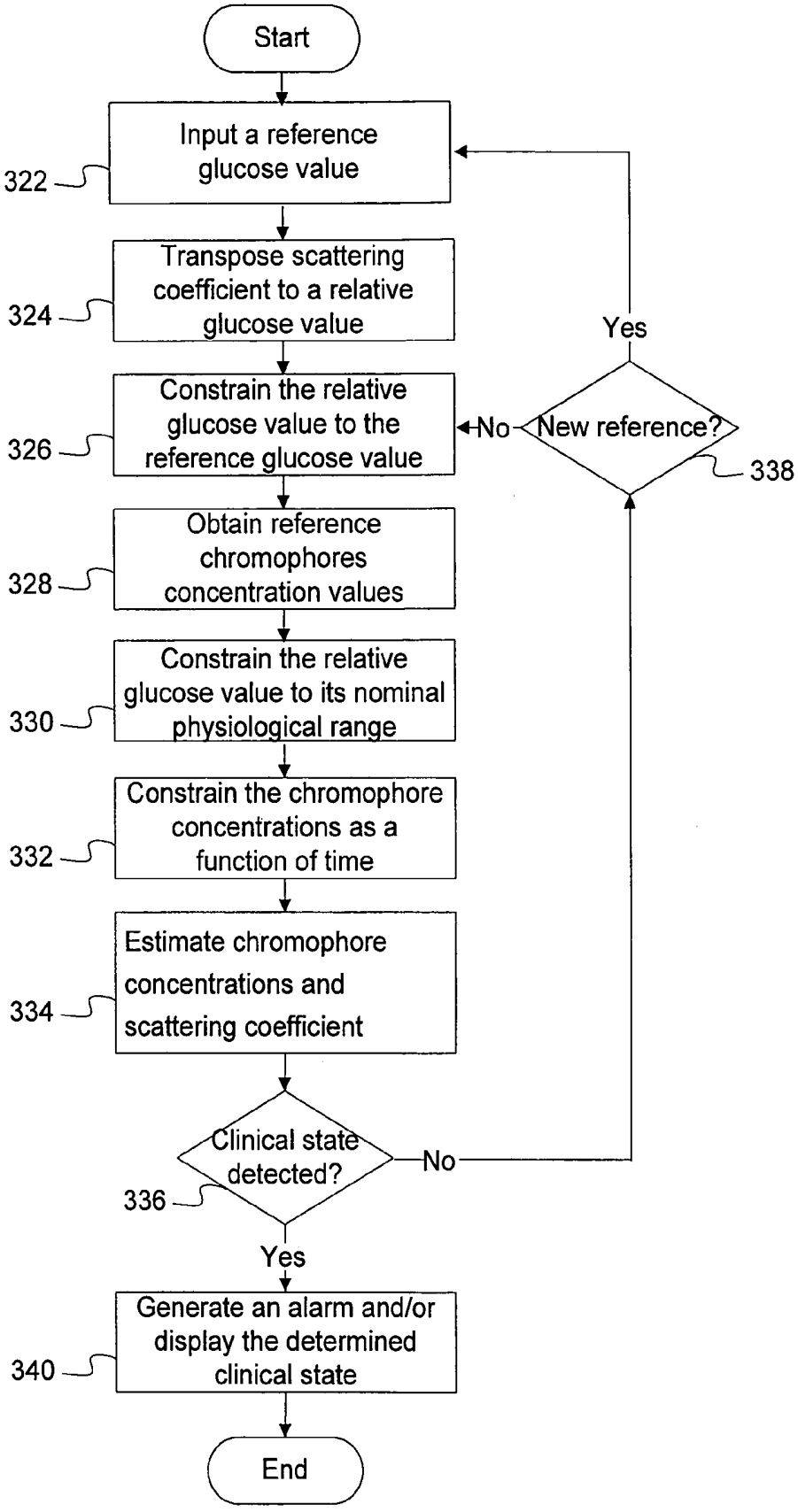

Start
Input a reference glucose value
322
Transpose scattering coefficient to a relative glucose value
324
Constrain the relative glucose value to the reference glucose value
326
Obtain reference chromophores concentration values
328
Constrain the relative glucose value to its nominal physiological range
330
Constrain the chromophore concentrations as a function of time
332
Estimate chromophore concentrations and scattering coefficient
334
Clinical state detected?
336
No
Yes
Generate an alarm and/or display the determined clinical state
340
End
New reference?
338
No
Yes

Figure 5

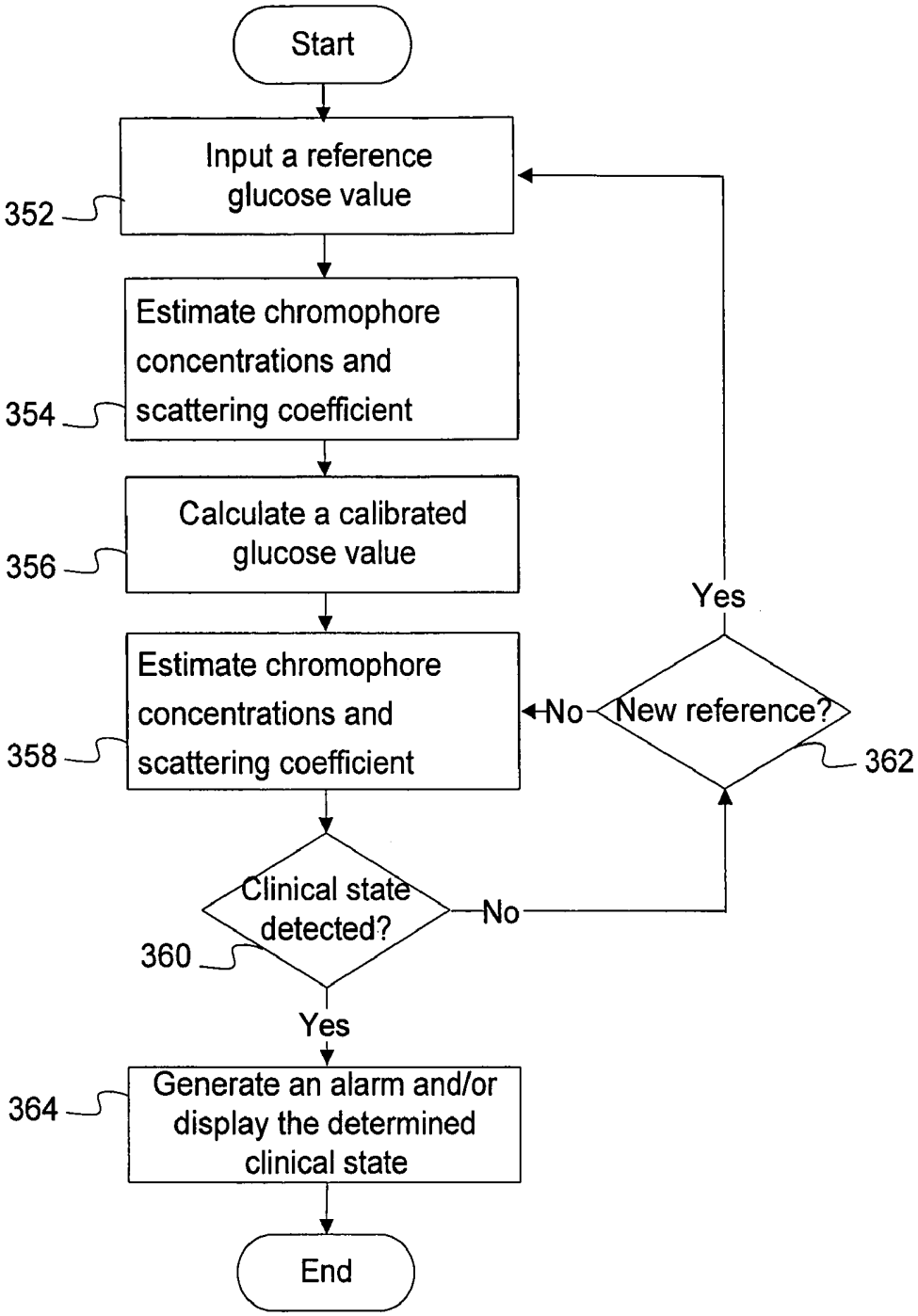

Start
Input a reference glucose value
352
Estimate chromophore concentrations and scattering coefficient
354
Calculate a calibrated glucose value
356
Estimate chromophore concentrations and scattering coefficient
358
New reference?
362
Yes
No
Clinical state detected?
360
No
Yes
Generate an alarm and/or display the determined clinical state
364
End

Figure 6

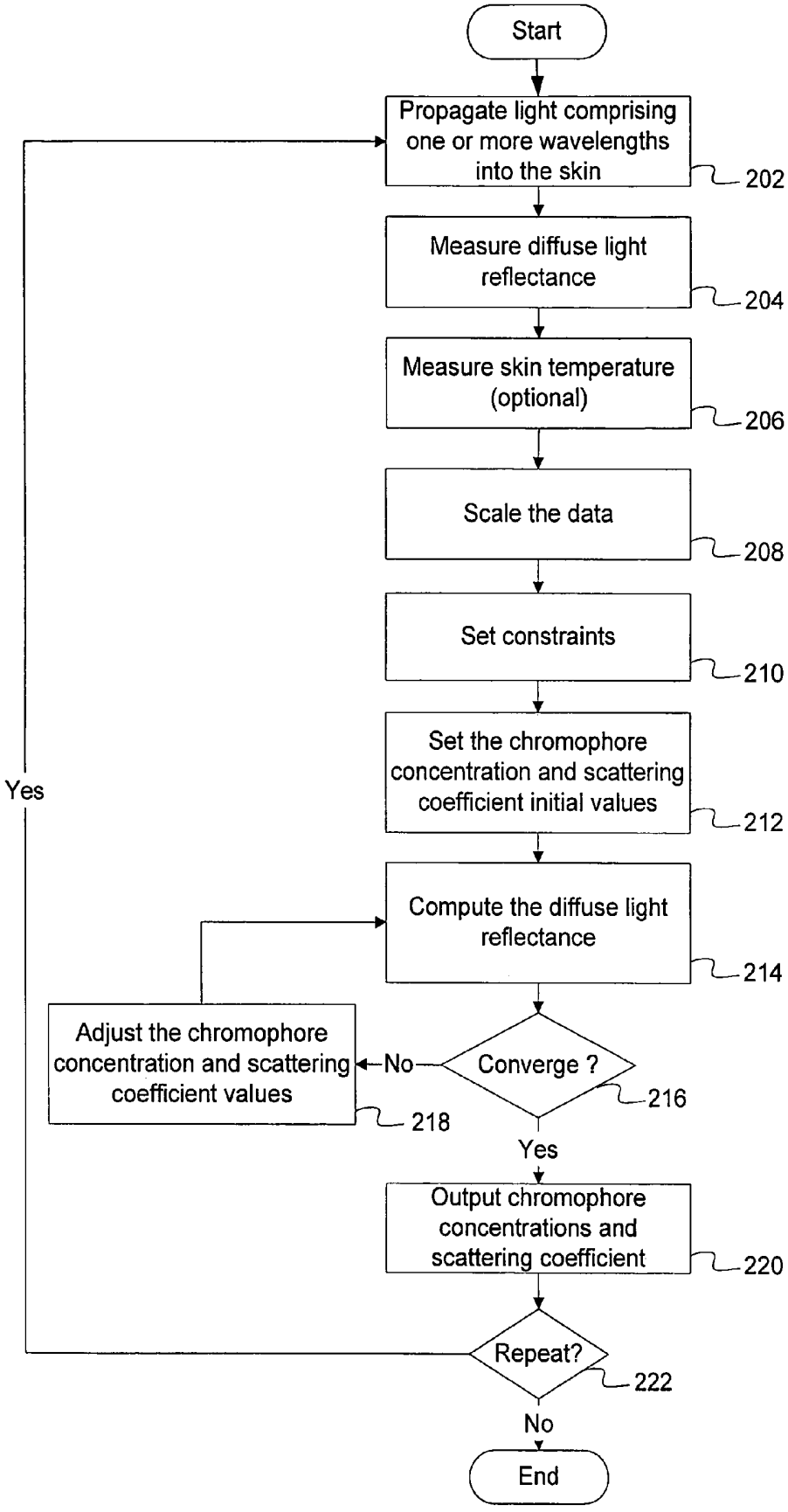

Start
Propagate light comprising one or more wavelengths into the skin
202
Measure diffuse light reflectance
204
Measure skin temperature (optional)
206
Scale the data
208
Set constraints
210
Set the chromophore concentration and scattering coefficient initial values
212
Compute the diffuse light reflectance
214
Converge ?
216
No
Adjust the chromophore concentration and scattering coefficient values
218
Yes
Output chromophore concentrations and scattering coefficient
220
Repeat?
222
Yes
No
End

Figure 7

METHOD AND APPARATUS FOR THE MONITORING OF CLINICAL STATES

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefits of U.S. provisional patent applications No. 60/581,727 filed Jun. 23, 2004; which is hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to a method and apparatus for the monitoring of clinical states. The present invention further relates to a method and apparatus for the estimation of chromophore concentrations and scattering coefficient.

BACKGROUND

Hypoglycemia is an important glucose related complication of diabetes. A common blood glucose monitoring method is an invasive method which periodically measures the blood glucose of a patient by obtaining a blood sample from an individual by a variety of methods, such as by needle or lance. The individual inserts a plastic strip carrying chemistry into a blood glucose meter and then applies a blood sample onto the strip for the measurement of blood glucose concentration by determination of change in reflectance or electric signal of a biosensor. This method produces measurements that, while very accurate, are too infrequent to detect hypoglycemic episodes. Frequently, in order to avoid hypoglycemia, diabetics maintain abnormally high blood glucose levels to prevent low blood glucose levels in between blood glucose measurements. This constant high blood glucose level often causes long-term complications, namely, retinopathy, neuropathy, nephropathy, and cardiovascular disease. In effect, the present blood glucose monitoring methods are forcing many diabetics to pay for a lower rate of acute complications with a higher rate of chronic complications later in life.

Thus, the most important factor for reducing diabetes-associated complications is the maintenance of an appropriate level of blood glucose. The maintenance of the appropriate level of blood glucose may prevent and even reverse many of the effects of diabetes.

Recently, new non-invasive approaches of measuring the level of blood glucose have been pursued. For example, U.S. Pat. No. 4,509,531 discloses a physiological monitor that continuously monitors changes in galvanic skin resistance and/or temperature of the wearer in order to detect the onset of a hypoglycaemic state. Similarly U.S. Pat. No. 4,365,637 discloses a device that senses the buildup of perspiration on the skin of the wearer in order to detect the onset of insulin shock. The main problem with these approaches is that they monitor symptoms of hypoglycaemia or insulin shock and are not necessarily correlated with the level blood glucose. Thus, these approaches are not suited for commercial use as they generate an unacceptable level of false alarms.

U.S. Pat. No. 5,676,143 and U.S. Pat. No. 5,551,422 disclose a method and apparatus for analytical determination of glucose in a biological matrix by measuring the relative intensity of scattered light in a tissue boundary and deriving a blood glucose concentration value. The main problem with this approach is long term drift errors in the estimation of blood glucose values because the initial calibration is not specific to the individual wearing the device and there is no periodic recalibration using an external reference blood glucose meter. Thus it is subject to many interfering parameters that may affect the measurement with time.

U.S. Pat. No. 6,882,940 discloses methods and devices for prediction of hypoglycemic events by obtaining a series of glucose measurement values, performed using a near-IR spectrometer, and skin conductance and/or temperature values. Once again, the main problem with this approach is long term drift errors in the estimation of blood glucose values because the initial calibration is not specific to the individual wearing the device and there is no periodic recalibration using an external reference blood glucose meter. Thus it is subject to many interfering parameters that may affect the measurement with time.

U.S. Pat. No. 6,066,847 discloses a procedure for verifying the accuracy of a non-invasive blood glucose measurement instrument by electrically connecting the instrument to a reference blood glucose meter. In the case there is too much discrepancy between the two measurements, the procedure prevents the individual from continuing to use the non-invasive blood glucose measurement instrument. The problem with such an approach is that once a discrepancy has been detected the non-invasive blood glucose measurement instrument is no longer usable until it is recalibrated.

SUMMARY

The present invention relates to a method for detecting a clinical state in a subject, comprising acquiring a reference value of blood-glucose of the subject, correlating one or more non-invasive physical measurements of the body of the subject with the reference value of blood-glucose of the subject, measuring the one or more non-invasive physical measurements of the body of the subject, computing an estimation parameter value representative of a variation in glucose value using the measured one or more non-invasive physical measurements and the correlation between the one or more non-invasive physical measurements of the body of the subject with the reference value of blood-glucose of the subject, comparing the estimation parameter value with a critical parameter value, wherein the critical parameter value is indicative of a clinical state, and indicating that a clinical state is detected if the estimation parameter value has reached the critical parameter value.

The present invention further relates to the above mentioned method for detecting a clinical state in a subject wherein the one or more non-invasive physical measurements of the body of the subject is the reflectance of light in the skin of the subject and wherein measuring the one or more non-invasive physical measurements of the body of the subject includes propagating at least one probing light beam into the skin of the subject and measuring reflectance values of the at least one probing light beam from at least two distances from the propagation point.

Furthermore, the present invention relates to a method for detecting a clinical state in a subject, comprising acquiring a reference value of blood-glucose of the subject, correlating at least two parameters of skin of the body of the subject with the reference value of blood-glucose of the subject, propagating at least two probing light beams into the skin from at least one propagation point, measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point, estimating values representative of the at least two parameters of skin of the body of the subject using the measured reflectance values and a mathematical skin parameter estimation model, computing an estimation parameter value representative of a variation in glucose value using the estimated values of the at least two

parameters of skin of the body of the subject and the correlation between the at least two parameters of skin of the body of the subject with the reference value of blood-glucose of the subject, comparing the estimation parameter value with a critical parameter value, wherein the critical parameter value is indicative of a clinical state and indicating that a clinical state is detected if the estimation parameter value has reached the critical parameter value.

The present invention also relates to a method for computing an estimate of a value representative of at least one parameter of skin selected from a group including chromophore concentrations and a scattering coefficient, comprising, propagating at least two probing light beams into the skin from at least one propagation point, measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point, computing estimates of the at least one parameter of skin of the body of the subject using a reflectance mathematical model and outputting the estimate of the value representative of the at least one selected parameters of skin.

As well, the present invention relates to an apparatus implementing the above mentioned methods.

BRIEF DESCRIPTION OF THE FIGURES

A non-limitative embodiment of the invention will now be described by way of example only with reference to the accompanying drawings, in which:

FIG. **1** is a block diagram showing an apparatus for the monitoring of glucose related clinical states and estimation of chromophore concentrations and scattering coefficient, according to a non-limitative embodiment of the present invention;

FIG. **2** is a flow diagram of a general algorithm for the monitoring of glucose related clinical states, according to a non-limitative embodiment of the present invention;

FIG. **3** is a flow diagram of a first example of a specific embodiment of the algorithm illustrated in FIG. **2**;

FIG. **4** is a flow diagram of a second example of a specific embodiment of the algorithm illustrated in FIG. **2**;

FIG. **5** is a flow diagram of a third example of a specific embodiment of the algorithm illustrated in FIG. **2**;

FIG. **6** is a flow diagram of a fourth example of a specific embodiment of the algorithm illustrated in FIG. **2**; and

FIG. **7** is a flow diagram of an algorithm for the estimation of chromophore concentrations and scattering coefficient.

DETAILED DESCRIPTION

Generally stated, an apparatus according to an embodiment of the present invention monitors glucose related clinical states, for example hypoglycaemia, hyperglycaemia or ischemic state, and detects if a user if affected by such a state. The apparatus may also be used to estimate the concentration of chromophores and the scattering coefficient. In order detect a glucose related clinical state, estimate the concentration of chromophores or estimate the scattering coefficient, the apparatus generates a probing light beam and analyses the back scattered light, as will be described hereinbelow.

Referring to FIG. **1**, the monitoring apparatus **100** uses N light sources (or emitters) **102**, each generating a probing light at respective predetermined wavelengths λ_1 to λ_N, coupled to a N×1 optical coupler **104** in order to generate a probing light beam **105** comprising all of the N wavelengths of the N individual light sources **102**. The number of light sources **102**, and thus wavelengths, as well as their power levels, may vary depending on the application.

The probing light beam **105** then goes through a 1×2 optical coupler **106** that provides the probing light beam **105** to both a light source monitor **108** and to an emitter collimating optic **110**. The emitter collimating optic **110**, preferably in direct contact with the skin, propagates the probing light beam **105** into the dermis **112** of the skin. The probing light beam **105** is then attenuated and scattered into a number of reflected beams **111** by various scatterers **113** and chromophores **115**, which are present in the dermis. The attenuated and reflected beams **111** are then received by receiver collimating optics **114**, providing optical signals I_1 to I_M to photodetectors **116**. Each of the receiver collimating optics **114** is positioned at a distance away from the emitter collimating optic **110** that is different from that of the other receiver collimating optics **114**. The number of receiver collimating optics **114** may vary according to the application. A temperature sensor **120** provides a signal indicative of the temperature of the skin.

At least one Analog to Digital Converter (ADC) **118** then converts the analog signals from the light source monitor **108**, the photodetectors **116**, as amplified by amplifiers **117**, and the temperature sensor **120** into digital signals which are provided to a micro-controller **122**. The micro-controller **122** includes an algorithm that controls the operations of the apparatus and performs the monitoring of certain clinical states, and may also perform estimations of certain biological parameters such as, for example, chromophore concentrations and scattering coefficient, which will be further described below. The results of the monitoring and estimations are then given to the wearer of the monitoring apparatus **100** by either setting a visual, audio and/or mechanical alarm, when a certain clinical state is detected, of displaying the result via alarm/display **124**. The micro-controller **122** is also connected to an input/output **126** through which data such as, for example, a reference blood glucose level may be provided to the monitoring apparatus **100** or through which data such as, for example, chromophore concentrations and scattering coefficient may be provided from the monitoring apparatus **100** to other devices. It is to be understood that the input/output **126** may be any type of interface such as, for example, an electrical, infrared (IR) or a radio frequency (RF) interface.

In an alternate embodiment, the N×1 optical coupler **104** and the 1×2 optical coupler **106** may be replaced by a single N×2 coupler or they may be omitted altogether, the N light sources **102** being independently propagated into the dermis **112**, and one, or more, of the receiver collimating optics **114** may be used to replace the light source monitor **108**.

As mentioned previously, the micro-controller **122** includes an algorithm that controls the operations of the apparatus and is also configured so as to monitor glucose related clinical states, for example hypoglycaemia and hyperglycaemia, or other clinical states, for example an ischemic state, and detects if a user if affected by such a state. The general monitoring and detection algorithm is depicted by the flow chart shown in FIG. **2**. The steps composing the algorithm are indicated by blocks **232** to **242**.

At block **232**, the algorithm starts by receiving, as an input, a reference glucose value g_{ref} provided by, for example, a reference meter such as a conventional blood-glucose monitor. Then, at block **234**, one or more non-invasive physical measurements of the body are correlated with the reference glucose value g_{ref} using a predetermined relation.

At block **236**, the algorithm measures the non-invasive physical measurements selected at block **234** on the body of the user and then determines, at block **238**, if a clinical state exists by verifying if the non-invasive physical measurements taken at block **238** have reached a critical threshold value

using the correlation relation. If a clinical state is determined then, at block **242**, the algorithm generates an alarm and/or displays the determined clinical state. If not, the algorithm goes to block **240** where it verifies if a new reference glucose value is available, if yes it proceeds to block **232** where the new reference glucose value is inputted, if not, it then proceeds back to block **236** for the next iteration.

It is to be understood that for better performances, a new reference glucose value should be inputted at either periodic time intervals or a certain number of times per given period of use.

EXAMPLES

A first example of a specific embodiment of the general monitoring and detection algorithm illustrated in FIG. **2** is depicted by the flow chart shown in FIG. **3**. The steps composing the algorithm are indicated by blocks **252** to **264**.

At block **252**, the algorithm starts by receiving, as an input, a reference glucose value g_{ref} provided by, for example, a reference meter such as a conventional blood-glucose monitor. Then, at block **254**, the algorithm transposes a reflectance ratio into a variation of glucose value using a predetermined relation, for example:

$$\Delta g = C_{cal} \cdot \mathrm{Ratio}_{ref_t} \qquad \text{Equation 1}$$

where

Δg is the variation in glucose value;

C_{cal} is a calibration constant providing a best fit between the variation in glucose and the variation of the reflectance ratio;

$$Ratio_{ref_t} = \left[\frac{\left(\left(\frac{R_{mes}^{\langle 2 \rangle}}{R_{mes}^{\langle 1 \rangle}} \right) \right)_t}{\left(\left(\frac{R_{mes}^{\langle 2 \rangle}}{R_{mes}^{\langle 1 \rangle}} \right) \right)_0} - 1 \right] \qquad \text{Equation 2}$$

where

$R_{mes}^{\langle i \rangle}$ is the measured reflectance value at receiver i;

$$\left(\left(\frac{R_{mes}^{\langle 2 \rangle}}{R_{mes}^{\langle 1 \rangle}} \right) \right)_t$$

is the ratio of the measured reflectance values at time t.

Optionally, the Equation 1 may take into account a factor for the effect of varying skin temperature, resulting in:

$$\Delta g = C_{cal} \cdot \mathrm{Ratio}_{ref_t} + \mathrm{Temp}_{corr} \cdot T_{drift} \qquad \text{Equation 3}$$

where

Temp_{corr} is correction factor accounting for the drift in skin temperature;

T_{drift} is the difference in temperature between time t and time t=0.

Thus the relative glucose value g will be determined by:

$$g = g_{ref} + \Delta g \qquad \text{Equation 4}$$

At block **256**, the algorithm propagates a probing light beam at a wavelength of 870 nm and measures two reflectance values, $R_{mes}^{\langle i \rangle}$ and $R_{mes}^{\langle 2 \rangle}$, at 2.1 mm and 6.9 mm distance, respectively, from the probing light beam **105**. Optionally, at block **258**, the algorithm measures the skin temperature of the user.

The algorithm then determines, at block **260**, if a clinical state exists, e.g. in the case of a hypoglycaemia state, by verifying if the relative glucose value has gone below the critical glucose value ($g \leqq g_c$), for example 5 mmol/L, or in the case of a hyperglycaemia state, by verifying if the estimated relative glucose value has gone above the critical glucose value ($g \geqq g_c$), for example 11 mmol/L. In this specific example, values of C_{cal}=0.85 and Temp_{corr}=1.65 may be used in Equation 1 and Equation 3 for the purpose of computing the relative glucose value g. If a clinical state is determined then, at block **264**, the algorithm generates an alarm and/or displays the determined clinical state. If not, the algorithm goes to block **262** where it verifies if a new reference glucose value is available, if yes it proceeds to block **252** where the new reference glucose value is inputted, if not, it then proceeds back to block **256** for the next iteration.

It is to be understood that other wavelengths, advantageously wavelengths between 500 nm and 1000 nm, a plurality of wavelengths and a plurality of receivers, with their associated receiver distances and reflectance values, may be used, along with appropriate values of C_{cal} and Temp_{corr}.

A second example of a specific embodiment of the general monitoring and detection algorithm illustrated in FIG. **2** is depicted by the flow chart shown in FIG. **4**. The steps composing the algorithm are indicated by blocks **302** to **314**.

At block **302**, the algorithm starts by receiving, as an input, a reference glucose value g_{ref} provided by, for example, a reference meter such as a conventional blood-glucose monitor. Then, at block **304**, the scattering coefficient is estimated (an example of a method for the estimation of the scattering coefficient will be further described below), the algorithm estimates the relative scattering coefficient $\delta_{\mu' sref}$ associated with the reference glucose value g_{ref} and, at block **306**, calculates a critical scattering coefficient using a predetermined relation between the scattering coefficient, the reference glucose value g_{ref} and a critical glucose value. For example, the predetermined relation may be:

$$\delta_{\mu' sc} = +0.3\% \cdot (g_{ref} - g_c) + \delta_{\mu' sref} \qquad \text{Equation 5}$$

where

$\delta_{\mu' sc}$ is the critical scattering coefficient; and

g_c is the critical glucose value, for example 5 mmol/L.

At block **308** the algorithm estimates the scattering coefficient and then determines, at block **310**, if a clinical state exists, e.g. in the case of a hypoglycaemia state, by verifying if the estimated scattering coefficient has gone below the critical scattering coefficient ($\delta_{\mu' s} \leqq \delta_{\mu' sc}$) or in the case of a hyperglycaemia state, by verifying if the estimated scattering coefficient has gone above the critical scattering coefficient ($\delta_{\mu' s} \geqq \delta_{\mu' sc}$). If a clinical state is determined then, at block **314**, the algorithm generates an alarm and/or displays the determined clinical state. If not, the algorithm goes to block **312** where it verifies if a new reference glucose value is available, if yes it proceeds to block **302** where the new reference glucose value is inputted, if not, it then proceeds back to block **308** for the next iteration.

A third embodiment of an algorithm for the detection of a clinical state is depicted by the flow chart shown in FIG. **5**. The steps composing the algorithm are indicated by blocks **322** to **340**.

At block **322**, the algorithm starts by receiving, as an input, a reference glucose value g_{ref} provided by, for example, a reference meter such as a conventional blood-glucose moni-

tor. Then, at block **324**, the algorithm transposes the scattering coefficient $\delta\mu'_s$ into a relative glucose value using a predetermined relation, for example:

$$\delta\mu'_s=-0.3\%\cdot g \quad \text{Equation 6}$$

where

g is the relative glucose value.

At block **326**, the relative glucose value is constrained to the reference glucose value obtained at block **322**, e.g. $g=g_{ref}$, and, at block **326**, the reference chromophore concentration values associated with the reference glucose value, w_{ref}, b_{ref}, S_{ref}, are estimated (an example of a method for the estimation of the chromophore concentration will be further described below) taking into account the constraint of block **326**.

At block **330**, the relative glucose value is constrained to its nominal physiological range, for example:

$$2\ \text{mmol/L}\leqq g\leqq 20\ \text{mmol/L}. \quad \text{Equation 7}$$

At block **332**, the chromophore concentrations are constrained to their respective reference chromophore concentrations, obtained at block **328**, plus a tolerance which varies as a function of the elapsed time since the last reference glucose value was inputted. For example, the following constraints may be used:

$$w_{ref}-1\%/\text{hr}\cdot t\leqq w\leqq w_{ref}+1\%/\text{hr}\cdot t; \quad \text{Equation 8}$$

$$b_{ref}-0.01\%/\text{hr}\cdot t\leqq b\leqq b_{ref}+0.01\%/\text{hr}\cdot t; \quad \text{Equation 9}$$

$$S_{ref}-1\%/\text{hr}\cdot t\leqq S\leqq S_{ref}+1\%/\text{hr}\cdot t; \quad \text{Equation 10}$$

where

t is the elapsed time since the last reference glucose value input.

Then, at block **334**, estimates of the chromophore concentrations and scattering coefficient are estimated (an example of a method for the estimation of the chromophore concentration and scattering coefficient will be further described below), taking into account the constraints of blocks **330** and **332** represented by Equations 7, 8, 9 and 10, are used to estimate the relative glucose value g using Equation 6.

The algorithm then determines, at block **336**, if a clinical state exists, e.g. in the case of a hypoglycaemia state, by verifying if the estimated relative glucose value has gone below the critical glucose value ($g\leqq g_c$), for example 5 mmol/L, or in the case of a hyperglycaemia state, by verifying if the estimated relative glucose value has gone above the critical glucose value ($g\geqq g_c$), for example 11 mmol/L. If a clinical state is determined then, at block **340**, the algorithm generates an alarm and/or displays the determined clinical state. If not, the algorithm goes to block **338** where it verifies if a new reference glucose value is available, if yes it proceeds to block **322** where the new reference glucose value is inputted, if not, it then proceeds back to block **326** for the next iteration.

A fourth embodiment of an algorithm for the detection of a clinical state is depicted by the flow chart shown in FIG. **6**. The steps composing the algorithm are indicated by the blocks **352** to **364**.

At block **352**, the algorithm starts by receiving, as an input, a reference glucose value g_{ref} provided by, for example, a reference meter such as a conventional blood-glucose monitor. Then, at block **354**, using estimates of chromophore concentrations and of the scattering coefficient (an example of a method for the estimation of the chromophore concentration and scattering coefficient will be further described below), the algorithm estimates the relative scattering coefficient $\delta_{\mu'sref}$ associated with the reference glucose value g_{ref} and, at block **356**, it calculates the coefficients of a dynamic calibration relation between the last two measured reference glucose values and their associated scattering coefficients. For example, the following dynamic calibration relation may be used:

$$g=g_{refi}+(\delta_{\mu's}-\delta_{\mu'srefi})\cdot(g_{refi}-g_{refi-1})/(\delta_{\mu'srefi}-\delta_{\mu'srefi-1}). \quad \text{Equation 11}$$

At block **358**, using estimates of chromophore concentrations and of the scattering coefficient (an example of a method for the estimation of the chromophore concentration and scattering coefficient will be further described below), the algorithm estimates the relative scattering coefficient $\delta_{\mu's}$.

The algorithm then determines, at block **360**, if a clinical state exists, e.g. in the case of a hypoglycaemia state, by verifying if the estimated relative glucose value has gone below the critical glucose value ($g\leqq g_c$), for example 5 mmol/L, or in the case of a hyperglycaemia state, by verifying if the estimated relative glucose value has gone above the critical glucose value ($g\geqq g_c$), for example 11 mmol/L, using Equation 16 to transpose the estimated scattering coefficient $\delta_{\mu's}$ into a glucose value g. If a clinical state is determined then, at block **364**, the algorithm generates an alarm and/or displays the determined clinical state. If not, the algorithm goes to block **362** where it verifies if a new reference glucose value is available, if yes it proceeds to block **352** where the new reference glucose value is inputted, if not, it then proceeds back to block **358** for the next iteration.

Of course, other similar relationships between non-invasive physical measurements, a reference glucose value and a critical glucose value may be used to detect a hypoglycaemia or hyperglycaemia state.

Estimation of Chromophore Concentrations and Scattering Coefficient

An algorithm that may be used for the estimation of chromophore concentrations and scattering coefficient is depicted by the flow chart shown in FIG. **7**. The steps composing the algorithm are indicated by blocks **202** to **222**.

At block **202**, the algorithm starts by propagating probing light beam comprising two or more wavelengths into the skin, the wavelengths being selected according to the chromophores of interest such that variations in the concentrations of the various chromophores induce noticeable variations on light reflectance values at the input of the receiver collimating optics **114**. The number of selected wavelengths should be such that there is at least one more wavelength than there are variables, i.e. number of chromophores of interest plus, if present, the scattering coefficient, ensuring that the ensuing model comprises a number of equations greater than the number of variables.

At block **204**, the diffuse light reflectance is measured at two or more locations that are at different distances from the propagation point of the probing light beam of block **202**. The diffuse light reflectance measurements are preferably taken simultaneously for all locations, the longer the time interval between each measurement, the less precise the algorithm results may become. The distances, as well as their values, are selected according to the chromophores of interest and the application. The more locations are used, the more precise the diffuse light reflectance model becomes, but also the more computation intensive is becomes and more expensive becomes the associated estimation apparatus **100**.

At block **206**, optionally, the skin temperature is measured.

At block **208**, the algorithm scales the measured data provided to micro-controller **122** by the ADC **118**. for example using the value measured at the light source monitor **108** or the signal at the first receiver I_1, so that the algorithm may be executed independently of the characteristics of the physical

components used in the estimation apparatus **100** as well as power levels of the various light sources **102**.

At block **210**, fixed or dynamic constraints associated with each of the chromophores of interest, as well as with the scattering coefficient, are set. The constraints define a range of possible values for each of the chromophore concentrations, as well as the scattering coefficient, so as to prevent the algorithm from considering obviously erroneous values. In the case of dynamic constraints, the range of possible values for each of the chromophore concentrations and scattering coefficient takes the form of confidence interval whose center value is the last value of that chromophore concentration or of the scattering coefficient. The confidence interval is selected according to the maximum possible variation of each of the chromophore concentrations of interest, or of the scattering coefficient, in the time in between each execution of the algorithm.

Then, at block **212**, the algorithm sets initial values for the chromophore concentrations and scattering coefficient, these values may be previously computed values, user inputted values, predefined or random values within the range of possible values defined by the constraints set at block **210**.

The algorithm then computes, at block **214**, the diffuse light reflectance for each of the receiver collimating optics **114**, for each of the N wavelengths, as a function of the chromophore concentrations, the scattering coefficient and, optionally, the skin temperature obtained from temperature sensor **120**, using a mathematical model of the diffuse light reflectance, which will be further explained in an example below.

At block **216**, the algorithm verifies the convergence of the diffuse light reflectance values obtained at block **214** with the scaled measured data from block **208**. If there is convergence, the algorithm proceeds to block **220**, if not, it goes to block **218** where the chromophore concentrations and the scattering coefficient values are adjusted so as to minimize the error between the model values and the measured values using, for example, a curve fitting algorithm or any other suitable numerical optimization method. The algorithm then goes back to block **214** to compute a new set of diffuse light reflectance values using the adjusted chromophore concentrations and scattering coefficient values.

At block **220**, once the diffuse light reflectance values have converged towards the measured values, the current chromophore concentrations and scattering coefficient values are outputted. Then, at block **222**, the whole algorithm is repeated if continuous monitoring is desired, otherwise the algorithm ends.

Example

In a sample application, the chromophores of interest are water, oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb). The light attenuation coefficients in the dermis associated with these chromophores, for various wavelengths, are well known in the literature, such as, for example, in Jacques; *Skin Optics Summary, Oregon Medical Laser Center News:* (January 1998). As well, the light attenuation coefficient has an intrinsic value associated with the dermis itself which is also well known.

The following wavelengths provide noticeable variations in light reflectance values in relation to variations in the water, HbO2 and Hb concentrations:

$$\lambda=(505\ 660\ 805\ 870\ 950)^T\ \text{nm}$$

The light attenuation coefficients for each chromophore may be represented by the vectors $\mu_{a.raw.\lambda}$:

$$\begin{pmatrix}\text{"Intrinsic"}\\ \text{"Water"}\\ \text{"HbO2"}\\ \text{"Hb"}\end{pmatrix} \qquad \mu_{a.raw.505nm}=\begin{pmatrix}0.669\\ 0.025\\ 110\\ 110\end{pmatrix}\ \text{cm}^{-1}$$

$$\mu_{a.raw.660nm}=\begin{pmatrix}0.285\\ 0.14\\ 1.4\\ 20\end{pmatrix}\ \text{cm}^{-1} \qquad \mu_{a.raw.805nm}=\begin{pmatrix}0.249\\ 0.95\\ 5\\ 5\end{pmatrix}\ \text{cm}^{-1}$$

$$\mu_{a.raw.870nm}=\begin{pmatrix}0.246\\ 2.1\\ 7.2\\ 5\end{pmatrix}\ \text{cm}^{-1} \qquad \mu_{a.raw.950nm}=\begin{pmatrix}0.245\\ 12.5\\ 8\\ 4.3\end{pmatrix}\ \text{cm}^{-1}$$

The reduced scattering coefficients in the dermis associated with these chromophores, for various wavelengths, are also well known in the literature.

The light scattering coefficients of the dermis may be represented as a function of wavelength by the following equation:

$$\mu'_{s.dermis}(\lambda)=\left[2\cdot 10^5\cdot\left(\frac{\lambda}{\text{nm}}\right)^{-1.5}+2\cdot 10^{12}\cdot\left(\frac{\lambda}{\text{nm}}\right)^{-4}\right]\text{cm}^{-1} \qquad \text{Equation 12}$$

Which, for the selected wavelengths, results in the following values:

$\mu'_{s.dermis.505\ nm}=48.4\ \text{cm}^{-1}$ $\mu'_{s.dermis.660\ nm}=22.3\ \text{cm}^{-1}$
$\mu'_{s.dermis.805\ nm}=13.5\ \text{cm}^{-1}$ $\mu'_{s.dermis.870\ nm}=11.3\ \text{cm}^{-1}$
$\mu'_{s.dermis.950\ nm}=9.29\ \text{cm}^{-1}$

The compounded attenuation coefficients in the dermis for the selected chromophores may be modelized as a function of water (w), blood (b) and oxygen saturation (S). Blood (b) and oxygen saturation (S) are more convenient variables used to quantify oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb).

Oxyhemoglobin (HbO2) may be approximated by:

$$\text{HbO2}\sim S*b; \qquad \text{Equation 13}$$

and

Deoxyhemoglobin (Hb) by:

$$\text{Hb}\sim(1-S)*b \qquad \text{Equation 14}$$

Thus, $\mu_{a.raw.\lambda}$ may be converted using the following transformation:

$$\mu_a(w,b,S)=\mu_{a.raw}\times\begin{bmatrix}(1-b)\cdot(1-w)\\ (1-b)\cdot w\\ b\cdot S\\ b\cdot(1-S)\end{bmatrix}\begin{pmatrix}\text{"Intrinsic"}\\ \text{"Water"}\\ \text{"HbO2"}\\ \text{"Hb"}\end{pmatrix}$$

The reduced scattering coefficient in the dermis may be further modelized for variations due to temperature and scattering coefficient changes related to glucose and other interfering analytes.

Assuming a measured skin temperature nominal value of T=34.5° C., the variation in scattering coefficient due to temperature changes may be expressed as:

$$\mu'_s(\delta\mu_s,T)=[1+\delta T\mu'_s\cdot(T-34.5)]\cdot(1+\delta\mu'_s) \qquad \text{Equation 15}$$

where

$\delta T\mu'_s$=−0.4% is the nominal change in scattering coefficient due temperature; and

$\delta\mu'_s$ is the scattering coefficient change.

The change of scattering due to glucose may be roughly approximated to −0.3%/mmol/L, and may be precisely determined using prior experimental tests and/or calibration. The change of scattering due to temperature may also be precisely determined with prior experimental tests and/or calibration, for example by varying the skin temperature and measuring the associated change in the scattering coefficient.

The diffuse reflectance in the dermis as a function of water, blood, oxygen saturation, temperature, scattering coefficient change and the distance from the light source to the receivers, for each wavelength may be defined as:

$$R = \frac{a'}{4\cdot\pi}\cdot\left[\left(\frac{1}{\mu_t'}\right)\left(\mu_{eff}+\frac{1}{r_1}\right)\frac{e^{-\mu_{eff}r_1}}{r_1^2}+\left(\frac{1}{\mu_t'}+2\cdot z_b\right)\left(\mu_{eff}+\frac{1}{r_2}\right)\frac{e^{-\mu_{eff}r_2}}{r_2^2}\right] \quad \text{Equation 16}$$

where

$$a' = \frac{\mu_s'}{\mu_a+\mu_s'};$$

$$\mu_{eff} = \sqrt{3\cdot\mu_a\cdot(\mu_a+\mu_s')};$$

$$\mu_t' = \mu_a+\mu_s';$$

$$D = \frac{1}{3\cdot(\mu_a+\mu_s')};$$

$$A = 1;$$

$$z_b = 2\cdot A\cdot D;$$

$$z_0 = \frac{1}{\mu_t};$$

$$r_1 = \sqrt{z_0^2+\rho^2};$$

$$r_2 = \sqrt{(z_0+2\cdot z_b)^2+\rho^2}; \text{ and}$$

ρ is the distance from the light source to receiver.

The above implemented diffuse reflectance is modelized using a diffusion theory model of spatially resolved, steady-state diffuse reflectance such as disclosed in Farrell et al.; *A diffusion theory model of spatially resolves, steady-state diffuse reflectance for the non-invasive determination of tissue optical properties in vivo, Med. Phys.* 19 (4): 879-888 (July/August 1992).

Referring back to the algorithm of FIG. **7**, at block **210**, the constraints associated with each of the chromophores may be set as:

$$0.50<w<0.60; \quad \text{Equation 17}$$

$$0.1<b<0.3; \quad \text{Equation 18}$$

$$0.55<S<0.65; \quad \text{Equation 19}$$

$$-4\%<\delta\mu'_s<1\%. \quad \text{Equation 20}$$

Then, the initial values of block **212** may be set as:

w=0.55;

b=0.2;

S=0.65;

$\delta\mu'_s$=0%.

Thus, at block **214**, the algorithm computes the diffuse light reflectance for every wavelength λ and every receiver **114** using the model represented by Equation 5, varying the values of w, b, S and $\delta\mu'_s$ at block **218** so as to minimize the error between the measured data and the computed R for each distance ρ and wavelength λ at block **216**, simultaneously.

It should be noted that oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) chromophore concentration values may be used to detect an ischemic state. More specifically, normal oxygen saturation (S), i.e. the ratio of oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb), should be around 60%. An ischemic state may be detected when this ratio goes down to, for example, 40%.

Although the present invention has been described by way of particular embodiments and examples thereof, it should be noted that it will be apparent to persons skilled in the art that modifications may be applied to the above-described embodiments without departing from the scope of the present invention.

What is claimed is:

1. A method for detecting a clinical state in a subject, comprising:

acquiring a reference value of blood-glucose of the subject;

correlating one or more non-invasive physical measurements of the body of the subject with the reference value of blood-glucose of the subject;

measuring the one or more non-invasive physical measurements of the body of the subject;

computing an estimation parameter value representative of a variation in glucose value using the measured one or more non-invasive physical measurements and the correlation between the one or more non-invasive physical measurements of the body of the subject with the reference value of blood-glucose of the subject;

comparing the estimation parameter value with a critical parameter value, wherein the critical parameter value is indicative of a clinical state; and

indicating that a clinical state is detected if the estimation parameter value has reached the critical parameter value.

2. A method according to claim **1**, wherein if a clinical state is not detected, the method returns to measuring the one or more non-invasive physical measurements of the body of the subject.

3. A method according to claim **1**, wherein before returning to measuring the one or more non-invasive physical measurements of the body of the subject, the method verifies if a new reference value of blood-glucose of the subject is available, if so the method returns to acquiring a reference value of blood-glucose of the subject.

4. A method for detecting a clinical state in a subject, comprising:

acquiring a reference value of blood-glucose of the subject;

correlating the reflectance of light in the skin with the reference value of blood-glucose of the subject;

propagating at least one probing light beam into the skin of the subject from a propagation point;

measuring reflectance values of the at least one probing light beam from at least two distances from the propagation point;

computing an estimation parameter value representative of a variation in glucose value using the measured reflectance values and the correlation between the reflectance of light in the skin with the reference value of blood-glucose of the subject;

comparing the estimation parameter value with a critical parameter value, wherein the critical parameter value is indicative of a clinical state; and

indicating that a clinical state is detected if the estimation parameter value has reacted the critical parameter value.

5. A method according to claim **4**, wherein the blood-glucose value of the subject is acquired from a conventional blood-glucose monitor.

6. A method according to claim **4**, wherein the clinical state is one of a hypoglycemic state and hyperglycemic state.

7. A method according to claim **4**, wherein the at least one probing light beam has a wavelength between 500 nm and 1000 nm.

8. A method according to claim **4**, wherein the correlation between the reflectance of light in the skin of the subject with the reference value of blood-glucose of the subject includes a reflectance mathematical model.

9. A method according to claim **4**, wherein the correlation between the reflectance of light in the skin of the subject with the reference value of blood-glucose of the subject includes a chromophore concentration estimation mathematical model.

10. A method according to claim **4**, wherein the correlation between the reflectance of light in the skin of the subject with the reference value of blood-glucose of the subject includes a scattering coefficient estimation mathematical model.

11. A method according to claim **4**, further comprising measuring a temperature of the skin of the subject and wherein the correlation between the reflectance of light in the skin of the subject with the reference value of blood-glucose of the subject includes a skin temperature correction factor.

12. A method for detecting a clinical state in a subject, comprising:

acquiring a reference value of blood-glucose of the subject;

correlating at least two parameters of skin of the body of the subject with the reference value of blood-glucose of the subject;

propagating at least two probing light beams into the skin from at least one propagation point;

measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point;

estimating values representative of the at least two parameters of skin of the body of the subject using the measured reflectance values and a mathematical skin parameter estimation model;

computing an estimation parameter value representative of a variation in glucose value using the estimated values of the at least two parameters of skin of the body of the subject and the correlation between the at least two parameters of skin of the body of the subject with the reference value of blood-glucose of the subject;

comparing the estimation parameter value with a critical parameter value, wherein the critical parameter value is indicative of a clinical state; and

indicating that a clinical state is detected if the estimation parameter value has reached the critical parameter value.

13. A method according to claim **12**, wherein if a clinical state is not detected the method returns to measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point.

14. A method according to claim **12**, wherein before returning to measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point, the method verifies if a new reference value of blood-glucose of the subject is available, if so the method returns to acquiring a reference value of blood-glucose of the subject.

15. A method according to claim **12**, wherein the at least two parameters of skin of the body of the subject is selected from a group including chromophore concentrations, a scattering coefficient and the temperature of the skin.

16. A method according to claim **12**, wherein the blood-glucose value of the subject is obtained from a conventional blood-glucose monitor.

17. A method according to claim **12**, wherein the clinical state is one of a hypoglycemic state and a hyperglycemic state.

18. A method according to claim **12**, wherein the at least one probing light beam has a wavelength between 500 nm and 1000 nm.

19. A method according to claim **12**, further comprising measuring a temperature of the skin of the subject and wherein the mathematical skin parameter estimation model includes a skin temperature correction factor.

20. A method for computing an estimate of a value representative of at least one parameter of skin selected from a group including chromophore concentrations and a scattering coefficient, comprising:

propagating at least two probing light beams into the skin from at least one propagation point;

measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point;

computing estimates of the at least one parameter of skin of the body of the subject using a reflectance mathematical model; and

outputting the estimate of the value representative of the at least one selected parameters of skin.

21. A method according to claim **20**, wherein the at least one parameter of skin includes oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) chromophore concentrations and further comprising:

comparing the estimates of a ratio of oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) chromophore concentrations with a critical parameter value, wherein the critical parameter value is indicative of an ischemic state; and

indicating that a clinical state is detected if the estimation parameter value has reached the critical parameter value.

22. A method according to claim **21**, wherein if an ischemic state is not detected the method returns to propagating at least two probing light beams into the skin from at least one propagation point.

23. A method according to claim **20**, further comprising measuring a temperature of the skin of the subject and wherein the reflectance mathematical model includes a skin temperature correction factor.

24. An apparatus for detecting a clinical state in a subject, comprising:

an input for acquiring a reference value of blood-glucose of the subject;

a measurement mechanism for measuring one or more non-invasive physical measurements of the body of the subject;

a display;

a microcontroller in operatively connected to the input, the measurement mechanism and the display, wherein the microcontroller comprises an algorithm for:

computing an estimation parameter value representative of a variation in glucose value using the mea-

sured one or more non-invasive physical measurements and a correlation between the one or more non-invasive physical measurements of the body of the subject with the reference value of blood-glucose of the subject;

comparing the estimation parameter value with a critical parameter value, wherein the critical parameter value is indicative of a clinical state; and

indicating on the display that a clinical state has been detected if the estimation parameter value has reached the critical parameter value.

25. An apparatus according to claim **24**, wherein the one or more non-invasive physical measurements of the body of the subject is the reflectance of light in the skin of the subject and wherein the measurement mechanism includes:

an emitter for propagating at least one probing light beam into the skin of the subject from a propagation point; and

a receiver for measuring reflectance values of the at least one probing light beam from at least two distances from the propagation point.

26. An apparatus according to claim **25**, wherein the at least one probing light beam has a wavelength between 500 nm and 1000 nm.

27. An apparatus according to claim **25**, further comprising a temperature sensor for measuring the temperature of the skin of the subject and wherein the computing of the estimation parameter value representative of a variation in glucose value includes a skin temperature correction factor.

28. An apparatus for computing an estimate of a value representative of at least one parameter of skin selected from a group including chromophore concentrations and a scattering coefficient, comprising:

emitter for propagating at least two probing light beams into the skin from at least one propagation point;

at least two receivers for measuring reflectance values of the at least two probing light beams from at least two distances from the at least one propagation point;

a display;

a microcontroller in operatively connected to the receivers and the display, wherein the microcontroller comprises an algorithm for:

computing estimates of the at least one parameter of skin of the body of the subject using a reflectance mathematical model; and

outputting to the display the estimate of the value representative of the at least one selected parameters of skin.

29. An apparatus according to claim **28**, further comprising a temperature sensor for measuring the temperature of the skin of the subject and wherein the reflectance mathematical model includes a skin temperature correction factor.

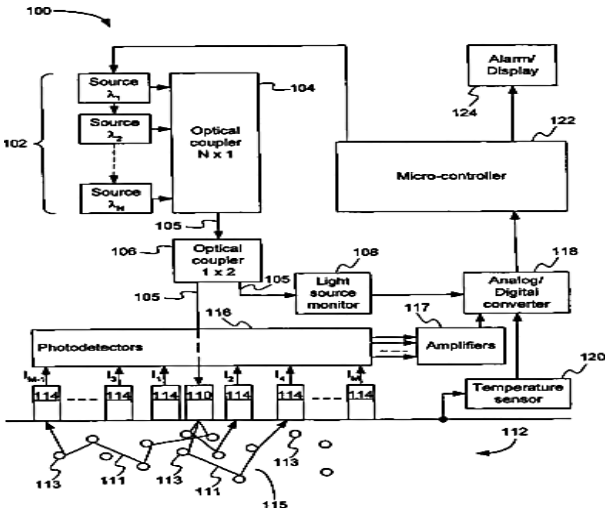
30. An apparatus according to claim **28**, wherein the at least one parameter of skin includes oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) chromophore concentrations and wherein the algorithm further comprises:

comparing the estimates of a ratio of oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) chromophore concentrations with a critical parameter value, wherein the critical parameter value is indicative of an ischemic state; and

indicating on the display that a clinical state has been detected if the estimation parameter value has reached the critical parameter value.

* * * * *

专利名称(译)	用于监测临床状态的方法和设备		
公开(公告)号	US7623988	公开(公告)日	2009-11-24
申请号	US11/165003	申请日	2005-06-23
[标]申请(专利权)人(译)	贝达德MICHEL 诺莱特丹妮		
申请(专利权)人(译)	贝达德MICHEL 诺莱特丹妮		
[标]发明人	BEDARD MICHEL NOLET DANY		
发明人	BEDARD, MICHEL NOLET, DANY		
IPC分类号	G06F15/00 A61B5/00		
CPC分类号	A61B5/1455 A61B5/14532 A61B5/01		
优先权	60/581727 2004-06-23 US		
其他公开文献	US20060004270A1		
外部链接	Espacenet USPTO		

摘要(译)

一种监测临床状态（例如低血糖，高血糖或缺血状态）并检测用户是否受这种状态影响的方法和装置。在一个实施例中，该方法和装置使用受试者身体的一个或多个非侵入性物理测量值与受试者的血糖参考值之间的相关性来计算估计参数值，并比较该估计参数值。具有指示临床状态存在的临界参数值，例如低血糖，高血糖症。在另一个实施方案中，该算法估计发色团浓度和散射系数，以便计算氧饱和度水平并检测缺血状态的存在。