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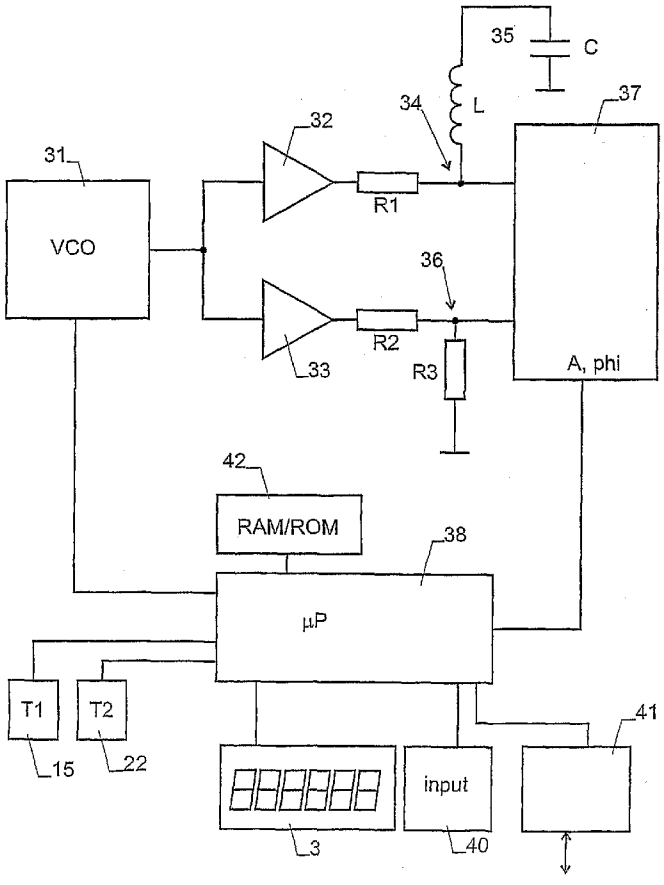
(54) Title: TECHNIQUES FOR DETERMINING GLUCOSE LEVELS



(57) Abstract: A device (100) for measuring the glucose level in a living body comprises an electrode arrangement (5, 6) to be applied to a surface of the body. The glucose level is derived from the response of the electrode arrangement (5, 6) to an electrical signal. Two temperature sensors (15, 22) are arranged at different positions within the device (100), the signals of which are used during calibration and measurements to improve the accuracy of the device. A further increase of accuracy is achieved by using an interpolation method during calibration. In addition, techniques for compensating shifts caused by a displacement of the device are applied. The device can also be used for a prediction of hyper- or hypoglycemia based on limits for the higher order derivatives of the glucose level.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Techniques for determining glucose levels

Technical Field

The invention relates devices for the determination of glucose, to methods for calibrating or operating such devices and to methods for measuring glucose.

Background Art

It has been known that the glucose of living tissue can be measured non-invasively by applying a sensor arrangement, in particular an electrode arrangement to the skin of a patient and measuring the response of the electrode arrangement to a suitable electric signal. Such a technique is described in WO 02/069791, the disclosure of which is enclosed herein in its entirety.

Even though this type of device is well able to monitor glucose, it needs careful calibration according to a well-defined protocol and must be operated under defined conditions in order to yield results of high accuracy.

One important purpose of these devices is to provide a prediction of the time when a patient's glucose level may exceed certain limits. In particular, an early prediction of a possible hypoglycemia or hyperglycemia is desirable such that a patient or accompanying person may take adequate steps to prevent such a state.

Disclosure of the Invention

Hence, in a first aspect, it is an object of the invention to provide a device and method of the type

mentioned above that allow a more accurate measurement of the glucose level in a living body.

This object is achieved by the device and method of claims 1 and 26.

According to this aspect of the invention, at least two temperatures are measured, wherein the first temperature depends in different manner on the skin temperature of the body and on the environmental temperature than the second temperature when the device is mounted on the body in its position of operation. This allows to compensate for the influence of both, the skin temperature and the environmental temperature, which has been found to be advantagous because, as discussed in the detailed description, both temperatures affect the signals measured with the sensor arrangement in different manners.

In a second aspect, the object of the first aspect is achieved by improving the calibration of the device. Two different calibration mechanisms are suggested, which can be used alternatively or in combination.

In both these mechanisms, the device is assumed to calculate, in normal operation, the glucose level from a function of the type $F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M)$, where F depends on input values $s_1 \ldots s_N$ and calibration parameters $a_0 \ldots a_M$.

In a calibration phase, series of reference values $g(t_i)$ are obtained at times t_i, e.g. using conventional glucose measurements. In the same phase, a series of raw input values $s_j(t'_i)$ are measured at times t'_i, which generally do not necessarily coincide with the times t_i. At least part of the parameters $a_0 \ldots a_M$ are then derived from these measurements by comparing the values obtained by function F against the reference values or against values derived from the reference values.

In most cases, the number of times the input values $s(t'_i)$ have been measured will be considerably

larger than the number of reference values $g(t_i)$. Hence, in the first mechanism, in order to fully exploit all data, a prediction (interpolation) of the glucose level g at the times t'_i is calculated from the reference values $g(t_i)$. Then the deviation of the values calculated by function F for the input values $s_j(t'_i)$ and the predicted glucose levels at times t'_j is minimized by varying the parameters $a_0 \ldots a_M$, thereby obtaining a set of calibrated parameters.

In the second mechanism, a "shift correction" is carried out during the calibration phase. For this purpose, the times τ_i are detected at which the device has shifted or moved in relation to the body during calibration. Such shifts generally cause the measured signals to change. When comparing the values obtained by function F against the reference values or against values derived from the reference values as mentioned above, at least one parameter a_0 is replaced by a sum

$$\sum_{i=0}^{P} a_{0i} \cdot b_i(t)$$

with $b_i(t)$ being 1 (or, equivalently, any other non-zero constant value) for $\tau_i < t < \tau_{i+1}$ and 0 otherwise. As explained in the detailed description, this allows to compensate for the effects of the shifts.

In any case it may be advantageous to carry out a recalibration step, e.g. each time after putting on the device. In this step, one of the parameters is recalibrated to find an optimum agreement between the glucose level calculated from the function F and a glucose level from a reference measurement. The reference measurement can e.g. be a conventional measurement, such as an invasive measurement. This allows to compensate for an offset caused by removing and remounting the device.

In another aspect, an object of the invention is to provide a device and method that are capable to provide early and reliable prediction of a possible hy-

per- or hypoglycemia. This object is achieved by the device and method of claims 16 and 37.

The various aspects and mechanisms can be used in combination or separately.

Brief Description of the Drawings

The invention will be better understood and objects other than those set forth above will become apparent when consideration is given to the following detailed description thereof. Such description makes reference to the annexed drawings, wherein:

Fig. 1 is a cross section of a device for measuring a glucose level,

Fig. 2 is a block circuit diagram of the device of Fig. 1,

Fig. 3 is an apparatus for calibrating the device,

Fig. 4 illustrates an advantageous aspect of the calibration method,

Fig. 5 shows a signal shift upon a displacement of the device, and

Fig. 6 illustrates a worst-case prediction of glucose levels with and without limits for the second order derivative.

Modes for Carrying Out the Invention

The device:

Fig. 1 shows a cross section of a device 100 for measuring a patient's glucose level. It comprises a housing 1 closed on one side by an electrode plate 2. A display 3 is arranged opposite electrode plate 2. Electronic circuitry is arranged between electrode plate 2 and display 3.

Electrode plate 2 comprises an electrically insulating substrate 4. A strip electrode 5 covered by an insulating layer 5a and a ring electrode 6 are arranged on an outer side 7 of insulating substrate 4. An inner side 8 of insulating substrate 4 is covered by a ground electrode 9. A plurality of though-contacts 10 connect ring electrode 6 to ground electrode 9. A further through-contact 11 connects one end of strip electrode 5 to a contact pad 12 arranged on inner side 8.

A first temperature sensor 15 is mounted to ground electrode 9 in direct thermal contact thereto. The large number of through-contacts 10 ensures that ground electrode 9 follows the temperature of ring electrode 6 and therefore the temperature of the specimen, the surface of which is indicated by a dotted line 16, closely.

Leads 18 are provided to connect ground electrode 9, contact pad 12 and first temperature sensor 15 to the electronic circuitry arranged on a printed circuit board 19 forming an assembly of electronic components. Printed circuit board 19 is advantageously arranged on a side of the device that is substantially opposite to the side of electrode plate 2. A battery 21 for powering the circuitry is arranged between printed circuit board 19 and electrode plate 2.

A second temperature sensor 22 is arranged on printed circuit board 19 and in direct thermal contact thereto.

The design of the electrodes 5, 6, 9 of the present sensor can correspond to the one described in reference to Figs. 2 and 4 of WO 02/069791, which description is enclosed by reference herein.

Fig. 2 shows a block circuit diagram of the circuitry of device 100. It comprises a voltage controlled oscillator (VCO) 31 as a signal source for generating a sine wave signal or another periodic signal. This signal is fed to two amplifiers 32, 33. The output of first amplifier 32 is connected via a resistor R1 to a

first signal path 34. A resonant circuit 35 comprising an inductance L and a capacitor C in series is connected between first signal path 34 and ground. The output of second amplifier 33 is connected via a resistor R2 to a second signal path 36. Second signal path 36 can be substantially identical to first signal path 34 but comprises a resistor R3 as a reference load instead of resonant circuit 35.

Both signal paths 34, 36 are fed to a measuring circuit 37, which determines the relative amplitude A of both signals and/or their mutual phase shift phi. Relative amplitude A can e.g. be the amplitude of first signal path 34 in units of the amplitude of second signal path 36 (wherein the amplitudes are the peak values of the sine waves).

The output signal of measuring circuit 37 is fed to a microprocessor 38, which also controls the operation of VCO 31.

Microprocessor 38 further samples the first and second temperature signals T1, T2 from first and second temperature sensors 15, 22. It also controls display device 3, an input device 40 with user operable controls, and an interface 41 to an external computer. A memory 42 is provided for storing calibration parameters, measurement results, further data as well as firmware for microprocessor 38. At least part of memory 42 is non-volatile.

Inductance L of the device of Fig. 2 can be generated by a coil and/or by the leads and electrodes of capacitor C. Its value is generally known with reasonable accuracy.

Capacitor C of the device of Fig. 2 is formed between strip electrode 5 and ring electrode 6 and is used for probing the specimen. For this purpose, the electrodes are arranged on the skin 16 of the patient as shown in Fig. 1.

For a good and permanent contact with the patient's skin, the device is advantageously worn on an arm

or leg and provided with a suitable holder or wrist band 43.

The geometry of the electrodes is selected such that the electric field generated by them extends into the specimen and the body liquid to be measured. Advantageously, at least one of the electrodes of the capacitor is electrically insulated such that capacitor C is primarily a capacitive load, the capacitance and loss of which depend on the electrical properties (i.e. the response) of the specimen at the frequency of VCO 1.

In summary, the device shown in Figs. 1 and 2 comprises:

- an electrode arrangement or sensor arrangement comprising the electrodes 5 and 6 and
- processing circuitry including the elements 31 - 33, 37, 38 for measuring the response of the sensor arrangement or electrode arrangement to an electrical signal and deriving the glucose level therefrom.

In addition, it can comprise at least two temperature sensors 15, 22, the signals of which depend in different manner on the skin temperature of the body and on the environmental temperature. Both these temperatures can be taken into account when determining the glucose level.

Basic principle of operation:

The basic principle of operation of the device is described in WO 02/069791.

To measure the concentration of glucose in the body fluid of the patient, microprocessor 38 can e.g. initiate a measurement cycle consisting of a frequency sweep of VCO 1. The sweep should start at a frequency f_{max} above the expected resonance frequency f0 of the resonant circuit 5 and extend to a frequency f_{min} below resonance frequency f0 (or vice versa). Typical frequencies are given in WO 02/069791. During this sweep, the electrical properties of the two signal paths 34, 36 will

vary in different manner. The amplitude determined by measuring circuit A will fall to a minimum A0 at a characteristic frequency f0, as described in WO 02/069791. At the same time or close thereto, phase shift phi crosses zero.

Microprocessor 38 measures A0 and/or f0 as input values describing the physiological state of the patient's tissue. In addition to the input values of A0 and/or f0, microprocessor 38 measures the temperature values T1 and T2 as further input values. Using suitable calibration data, the glucose level can be derived from these input values.

Such calibration data can be determined in straightforward manner using methods known to the person skilled in the art. In the following, however, some advantageous techniques are presented for the determination of the glucose level with the type of device described here as well as for its calibration.

In general, microprocessor 38 will use a formula of the type

$$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M) \quad (1)$$

for determining the glucose level g (or a parameter indicative thereof) from N measured input values s_1, s_2, ... s_N ($N > 0$), where the function F has M+1 parameters a_0, a_1, ... a_M ($M \geq 0$), at least some of which have to be determined in suitable calibration experiments.

The measured input values s_i are e.g. values directly or indirectly derived from the amplitude A0, the corresponding frequency f0, and the temperatures T1, T2. The input values can e.g. be the most recent values measured or they can be a time average or a median over a given number of recent measurements.

In an advantageous embodiment, the values s_1 = A0, s_2 = f0, s_3 = T1 and s_4 = T2 are used.

The function F can be empirical or it can be based at least partially on a model describing the physical nature of the mechanisms involved.

Under the approximation that the relation between the glucose level g and the measured values s_i is linear, we have

$$g = a_0 + a_1 \cdot s_1 + a_2 \cdot s_2 + \ldots a_N \cdot s_N \qquad (2a)$$

with M = N.

Equation (2a) has the advantage of being linear in the input values s_i as well as the parameters a_j, which simplifies calibration as well as evaluation. More refined models can, however, be used as well.

Temperature compensation:

It is presently understood that electrical properties of the topmost skin layers and therefore of the signals A0 and f0 depend not only on the glucose level, but also on the temperature Ts of the skin and underlying tissue as well as on the temperature Te of the environment. This is at least in part due to the fact these properties depend on the amount of blood in the skin and underlying tissue, which in turn affects the temperature of the skin. Hence, it is advantageous to measure the skin temperature, a first approximation of which can be derived from the signal from temperature sensor T1.

However, the skin temperature is not only a function of the amount of blood in the skin and underlying tissue, but also of the environmental temperature Te. Hence, it is also advantageous to measure the environmental temperature, a first approximation of which can be derived from the signal from temperature sensor T2.

Hence, device 100 is advantageously equipped with at least two temperature sensors T1 and T2, the signals of which depend in different manner on the temperatures Ts and Te, such that a measurement of T1 and T2 is

indicative of both temperatures Ts and Te. Hence, at least one of the input values s_i should be derived from the signal of first temperature sensor 15 and at least another one of the input values s_i should be derived from the signals of second temperature sensor 22.

Advantageously, one of the temperature sensors is closer to the electrodes 5, 6 (and therefore to the body of the patient) than the other sensor. For example, the first temperature sensor 15 is arranged at the same side of housing 1 as the electrodes 5, 6 and the second temperature sensor 22 at the opposite side.

The measured values may also depend on the temperature of the electronic circuits because the properties of voltage sources, A/D-converters and other circuitry are generally temperature dependent. Hence, it may also be advantageous to measure a temperature that is indicative of the circuit temperature Tc. In the present embodiment, this is especially true for temperature T2, i.e. by using the signal from second temperature sensor 22, changes of the circuit temperature Tc can be accounted for. However, an additional third temperature sensor for specifically measuring circuit temperature Tc may be provided as well.

Calibration:

In the following, advantageous methods for calibrating the device are described.

a) Parameter Determination:

A basic calibration of the device is required for each new patient.

In a first step of the basic calibration, the patient undergoes a calibration phase in which the glucose level is measured repetitively by an alternative method of measurement, e.g. by a conventional invasive technique, in order to obtain a series of K reference values $g(t_1)$, $g(t_2)$, ... $g(t_K)$ at times t_1 through t_K. In

the same period, the input values s_i are measured repetitively at L times t'_1 through t'_L, wherein L can be much larger than K. All measured values $s_i(t'_j)$ (i = 1 ... N, j = 1 ... L) are stored, e.g. in memory 42 of the device.

In order to derive accurate and meaningful parameters over a wide range of measurement conditions, the blood glucose level g as well as the environment temperature Te is varied during the calibration phase. For example, the environment temperature is varied over at least 5 °C, preferably at least 10 °C, e.g. by carrying out indoors and outdoors measurements, and the glucose level is varied by at least 100 mg/dl, e.g. by the patient having a snack and by delaying and/or reducing insulin.

The calibration phase can e.g. extend over two days and include at least 10 reference values per day. Several reference values should be recorded in the periods during which the glucose level and/or temperature are varied as described above in order to obtain a full record of these events.

Alternatively to or in addition to an intensive calibration phase of two days, an extensive calibration can be carried out during a period of e.g. 15 days that allows the device to "adapt" to a given user. During this extensive calibration phase, reference measurements will again be carried out, e.g. invasively, even though at less frequent intervals.

The data recorded during the calibration phase can be used for finding appropriate values for at least part of the parameters a_i. For this purpose, the values obtained by function F according to equation (1) are compared against the reference values $g(t_i)$ or against values derived therefrom, and those parameters a_i are determined for which this comparison gives a closest match.

In a most simple approach, the parameters a_i can be obtained from a conventional least-squares fitting

algorithm. Suitable algorithms are known to a person skilled in the art and are e.g. described by Press, Teukolsky, Vetterling and Flannery in "Numerical Recipes in C", Cambridge University Press, 2nd edition, 1992, Chapter 15. For evaluating the function F at the times t_1 through t_k, only the input values s_i at the times closest to t_1 through t_k are required.

This simple approach, however, will only exploit part of the available information. In particular, it ignores the information obtained by the measurements of the input values $s_i(t'_j)$ at times t'_j other than the times t_1 through t_k.

In an advanced approach, the reference values $g(t_i)$ are used to calculate a prediction (interpolation) of the actual glucose levels at times between the measurement times t_1, ... t_k, in particular at all times t'_1 ... t'_L. Then, the deviation of this prediction from the value of function F for the corresponding input values s_i is calculated and the total deviation is minimized by varying the parameters a_i.

An empirical, semi-empirical or theoretical model of the variation of the glucose level in a body can be used for calculating the prediction (interpolation).

An advantageous model is based on the understanding that the rate of change of the glucose level is limited. For human beings, a typical maximum rate of increase is $\dot{g}_{incr} = 3.5\ mg \cdot dl^{-1} \cdot min^{-1}$ and a typical maximum rate of decrease is $\dot{g}_{decr} = 4\ mg \cdot dl^{-1} \cdot min^{-1}$ as well. This allows to predict a set S of possible glucose values for any time t between the times t_1 through t_K as depicted in Fig. 4. S is the set of values delimited by lines of slope $\dot{g}_{incr}$ and $\dot{g}_{decr}$ extending from the measured points $g(t_i)$.

Taking this model into account, a possible calibration procedure is based on the following steps:

- Step 1: The patient undergoes the calibration phase as mentioned above in which the K reference values

$g(t_i)$ and the LxN input values $s_j(t'_i)$ are measured and recorded.

- Step 2: Equation (1) is fitted to the measured reference values $g(t_1)$ ... $g(t_K)$ by evaluating

$$f_i = F(s_1(t_i) \ldots s_N(t_i), a_0 \ldots a_M) \qquad (3)$$

at each time t_i and comparing f_i to $g(t_i)$. If the input values $s_j(t_i)$ at time t_i are not known (because none of the t'_k matches t_i exactly, an estimate of the values $s_j(t_i)$ from measured input values $s_j(t'_k)$ for at least one t'_k close to t_i can be used. Then the parameters a_1 ... a_M are varied to find a set of parameters where the total deviation between the values f_i and $g(t_i)$ is at a minimum, e.g. by minimizing the sum of the squares of all f_i. This basic fitting process provides a set of starting values for the parameters a_i in the following step 3.

- Step 3: The deviation of

$$F(t'_i) = F(s_1(t'_i) \ldots s_N(t'_i), a_0 \ldots a_M) \qquad (4)$$

for all times t'_i from the prediction S at the corresponding times t'_i is minimized by varying the parameters a_i. This can e.g. be achieved by defining, for each time t'_i, a predicted distribution $S(t'_i)$ of the glucose value and by calculating a deviation d_i by comparing the predicted distribution $S(t'_i)$ with the value $F(t'_i)$. In the model of Fig. 4, a suitable deviation d_i can e.g. be defined as

$$d_i = \begin{cases} F(t'_i) - S_{max}(t'_i) \text{ if } F(t'_i) > S_{max}(t'_i) \\ S_{max}(t'_i) - F(t'_i) \text{ if } F(t'_i) < S_{min}(t'_i) \\ 0 \text{ otherwise} \end{cases} \qquad (5)$$

with $S_{min}(t'_i)$ and $S_{max}(t'_i)$ being the range of the set S of Fig. 4 at time t'_i, i.e.

$$S_{max}(t'_i) = \min(g(t_j) + \dot{g}_{incr} \cdot (t'_i - t_j), \; g(t_{j+1}) + \dot{g}_{decr} \cdot (t_{j+1} - t'_i)) \quad (6a)$$

and

$$S_{min}(t'_i) = \max(g(t_j) - \dot{g}_{decr} \cdot (t'_i - t_j), \; g(t_{j+1}) - \dot{g}_{incr} \cdot (t_{j+1} - t'_i)) \quad (6b)$$

where t_j is the closest of the times $t_1 \ldots t_K$ prior to t'_i.

The parameters $a_1 \ldots a_M$ can then e.g. be found by minimizing the value

$$D = \sum d_i \quad (7)$$

numerically. Corresponding techniques are known to the person skilled in the art and e.g. described in Chapter 10 of the book "Numerical Recipes in C" cited above.

It must be noted that step 2 is optional if the starting values of step 3 are obtained by some different method, e.g. from typical values, or if step 3 uses an algorithm that does not require starting values for the parameters. Alternatively, step 3 can be omitted if the results from step 2 are to be used directly.

It must further be noted that equations (5) through (7) are advantageous examples but can be replaced by other suited definitions.

For example, instead of using a prediction S that gives a simple range, a prediction providing a probability density $S(g, t'_i)$ can be used, indicating the probability to observe a given glucose value g at time t'_i. Such a probability can e.g. be derived from an empirical or semi-empirical model that predicts how prob-

able a given value of the glucose level is at time t'_i, given the reference values $g(t_j)$. Apart from the reference values, a suitable model can e.g. take the physiological parameters of the patient (e.g. body weight) as well as events during the calibration phase (e.g. food intake, insulin administration etc.) into account for improving the accuracy of the prediction.

Equation (7) can also be replaced by any other suitable measure for the deviation of the function F from the prediction S. In particular if the probability of a certain deviation d_i is known, the formula for D should be defined in such a manner that its minimum coincides with the set of parameters having the highest statistical probability. For details, we refer to the book "Numerical Recipes in C" cited above.

Calibration is preferably carried out with a system as shown in Fig. 3, where an external computer 102 can be connected to the device 100 through interface 41. Computer 102 can instruct device 100 to start a calibration process, whereupon device 100 can be disconnected from the computer and be applied to the patient for carrying out above step 1. Then the reference values $g(t_i)$ are entered into computer 102, and the measured input values $s_j(t'_i)$ are transferred to computer 102 via interface 41. Above steps 2 and 3 are carried out in computer 102 and the resulting parameters a_i are transferred back to device 100, which, after a final test of the performance of the calculated parameters a_i, is then ready for regular operation.

Even though the capabilities of computer 102 may be integrated directly into device 100, it is generally advantageous to use a separate computer system for the convenience of its use and its computational power.

b) Shift correction during calibration:

During the above basic calibration, movements of the patient or other events may cause device 100 to

change its position in respect to the patient's body. Displacements of this type will usually lead to a change in signal that should be accounted for.

For taking such shifts into account, it is advantageous to introduce additional auxiliary parameters a_{00}, a_{01},... a_{0P} during the above calibration steps. Assuming that a_0 is a purely additive parameter in function F (such as in the example of equation (2)), equations (3) and (4) above are replaced by

$$f_i = F(s_1(t_i) \ldots s_N(t_i), 0, a_1 \ldots a_M) + a_{00} \cdot b_0(t_i) + \ldots + a_{0P} \cdot b_P(t_i) \qquad (3')$$

and

$$F(t'_i) = F(s_1(t'_i) \ldots s_N(t'_i), 0, a_1 \ldots a_M) + a_{00} \cdot b_0(t'_i) + \ldots + a_{0P} \cdot b_P(t'_i), \qquad (4')$$

where the functions $b_i(t)$ are 0 unless the time t is in the range $\tau_i \ldots \tau_{i+1}$, where they are 1.

In other words, the additive parameter a_0 of function F is set to 0 (or, equivalently, another fixed value), and it is replaced by parameter a_{00} in time interval $\tau_0 \ldots \tau_1$, by parameter a_{01} in time interval $\tau_1 \ldots \tau_2$, etc.

The times τ_0 and τ_P are the start and end times of the calibration phase and the other times τ_i are the times when a "shift" of device 100 is detected during the calibration phase. Such a shift can e.g. be detected because at least one of the input values s_i (such as the amplitude A_0 or frequency f_0) changes by more than a given threshold value Δs_i during two consecutive measurements. Details on how to detect such "shifts" are discussed in the section "shift correction during measurements" below.

By using equations (3') and (4') instead of (3) and (4), the parameters $a_{00} \ldots a_{0P}$ and $a_1 \ldots a_M$ can

be determined using steps 2 and 3 described in the previous section. The parameters a_1 ... a_M can then be used during normal operation of the device.

As to additive parameter a_0, that parameter can be roughly approximated to be the median or average of parameters a_{00} ... a_{0P}, but it is preferably determined from later recalibration measurements as described in section "Recalibration" below.

Instead of using additive parameters a_{00} ... a_{0P}, multiplicative parameters might be used for this kind of correction as well. In that case, equations (3') and (4') should be changed accordingly.

In more general terms, a compensation of "shifts" or displacements of device 100 during calibration can be achieved by replacing at least one of the parameters, e.g. a_0, in equations (3) and (4) by

$$\sum_{i=0}^{P} a_{0i} \cdot b_i(t), \qquad (8)$$

with $b_i(t)$ being 1 for $\tau_i < t < \tau_{i+1}$ and 0 otherwise. The parameters to be replaced in this way are those parameters that are most sensitive to shifts of the device.

In most cases, it will be sufficient to apply this technique to the one additive or one multiplicative parameter in F. (Definition: A parameter *a* is additive if function f(*a*, ...) can be re-written as *a* + f'(...) with f' being independent of *a*; a parameter *a* is multiplicative if function f(*a*, ...) can be re-written as *a*·f"(...) with f" being independent of *a*).

Normal operation:

After calibration of the device, all or at least most of the parameters a_0 ... a_M are known. In a very simple device, such as described in WO 02/069791, all parameters can be determined completely during calibration and then equation (1) can be used for determining the glucose level from the measured input values $s_i(t)$ in regular operation.

In the following, however, some additional steps are described that allow to improve the accuracy of the device.

a) Recalibration

After the calibration steps described above, all parameters a_i are known if it is assumed that no shift correction is necessary, i.e. if it is assumed that the device is being held at a fixed position on the patient's body.

If a shift of the device against the body is to be compensated for, at least one parameter, such as the additive or multiplicative parameter a_0, can only be determined inaccurately during calibration because the device may have been displaced during calibration or between calibration and regular measurement. In that case it is advantageous to carry out recalibration measurements during regular operation, e.g. once a day after affixing the device to the body.

A recalibration measurement consists, in a simple embodiment, of a single measurement of the glucose level $g(t_0)$ by conventional means. This glucose level is then entered into device 100 with a command to carry out recalibration.

When ordered to carry out a recalibration, microprocessor 38 finds the solution or optimum agreement of

$$g(t_0) = F(s_1(t_0) \ldots s_N(t_0), a_0, a_1, \ldots a_M) \quad (9)$$

by varying one of the parameters, usually the additive or multiplicative parameter a_0. The parameter found in this way is then used for following measurements.

For solving equation (9), the input values $s_1(t_0) \ldots s_N(t_0)$ may be derived from a single measurement at time t_0 or from an average, median or interpolation value of several measurements around time t_0. Assum-

ing that parameters a_1 to a_M are known, parameter a_0 can then be calculated e.g. numerically by a root finding algorithm as known to the person skilled in the art.

A corresponding recalibration means can e.g. be implemented as a firmware program for microprocessor 38.

b) Shift correction during normal operation

As mentioned in the section "shift correction during calibration" above, a movement or "shift" of the device 100 in respect to the body may cause a change in measured signals. Even if all parameters are known from calibration or recalibration measurements as described above, such a shift may invalidate subsequent measurements.

To avoid this, microprocessor 38 of device 100 is advantageously programmed to detect such a shift. For this purpose, at least one signal value v(t) can be monitored, wherein the signal value v(t) is any value that is derived directly or indirectly from at least one of the input values $s_i(t)$ and that shows a characteristic shift when device 100 is moved in respect to the patient's body.

In particular, the signal value v(t) can be one of the following:

- One of the input values $s_i(t)$; for example, frequency f_0 or amplitude A_0 can be used since both these values show a change when device 100 is moved.
- The glucose value g derived from function F in equation (1). This value also shows a change when the device is moved.
- Any intermediate result generated during the evaluation of function F that shows a easily detected change when device 100 is moved.

Fig. 5 shows a typical shift of signal value v(t) when device 100 is displaced along the patient's

body at a time ts. As can be seen, prior and after the event, the signal value is fairly continuous (e.g. linear) while there is a sudden change between the measurements before and after time ts.

To detect a shift of this type, the following three steps are carried out at a given time t:

- Step 0: Calculate an extrapolated signal value $v_{ext}(t)$ as an extrapolation from a number of previous signal values v. Advantageously, $v_{ext}(t)$ is calculated only from signal values v older than t - Δt. Δt is a window length, which can e.g. be 5 minutes if one measurement is carried out each minute.
- Step 1: Determine an actual signal value $v_{act}(t)$ from one or more current signal values v. Advantageously, $v_{act}(t)$ is calculated from a median or average of the signal values within the time window t - Δt and t.
- Step 2: Compare the actual signal value $v_{act}(t)$ to the extrapolated signal value $v_{ext}(t)$ and assume that a "shift" has occurred if the values differ by a given threshold amount. This threshold should be larger than a typical noise-induced variation between consecutive signals and is e.g. in the order of 5% of a typical value of v(t) if $v(t) = f_0(t)$ is used. If the change exceeds the threshold amount, a shift correction procedure is started.

The shift correction procedure includes the following steps:

- Step 3: Define the exact time t_s of the shift. This can e.g. be done by iterating over a given number of recent signal values v(t), e.g. the values in the above time window t - Δt and t, and looking for the largest change of consecutive values $v(t_i)$ and $v(t_{i-1})$.

- Step 4: Derive a shift correction Δv from an extrapolation of older values (e.g. the extrapolation $v_{ext}(t)$ mentioned above) and from values measured after the time t_s of the shift. For example, the difference or ratio between
  - the median or average of the signal values in interval t_s ... t and
  - the extrapolation $v_{ext}(t)$

  can be calculated and be used as shift correction Δv. If the difference is used, the shift correction will be an additive correction to be added to v, otherwise it will be multiplicative correction to be multiplied to value v.
- Step 5: Use the shift correction for correcting subsequently measured glucose values. The specific implementation of this step depends on the definition of the signal value v(t). Examples:
  - If signal value v(t) is equal to an input value $s_i(t)$, such as $f_0(t)$ or $A_0(t)$, subsequently measured input values should be corrected by $s_i(t) + \Delta v$ (additive correction) or by $s_i(t) \cdot \Delta v$ (multiplicative correction) before inserting them into function F for evaluation.
  - If signal value v(t) is equal to the glucose value g(t) evaluated from function F, Δv can be added to or multiplied with the returned function value. Alternatively, if F has an additive or multiplicative parameter a_0, that parameter can be corrected by addition of or multiplication with Δv.

  Corrections for other types of signal values v(t) can also be implemented by correcting the input values, parameters, intermediate results or return value of function F in order to make sure that function F returns the same results before and after time t_s.

Above steps 0 to 5 can be implemented in a shift correction by suitable firmware in microprocessor 38 of device 100. In general, the shift correction should be able to

- detect a displacement of device 100 along the body of the patient, e.g. based on steps 0 to 2 above or any other method that is able to determine a sudden shift in a signal value,
- determine an effect of the shift on the measured glucose level, e.g. based on step 4 above, and
- correct the measured glucose levels after the shift to compensate for the determined effect.

It must be noted that the signal value used in steps 0 to 3 does not need to be the same as the one used in steps 4 and 5. It may be advantageous to use a raw input signal, such as f_0 and A_0 for sensitively detecting a displacement of the device in steps 0 to 3, while it may be easier to carry out the correction on the function's F return value or an additive or multiplicative parameter a_0 in steps 4 and 5.

Range monitoring:

As mentioned above, an important purpose of device 100 is to provide a prediction of the time when a patient's glucose level may cross given safety limits.

For this purpose, microprocessor 38 comprises a software-implemented predictor that tries to predict when, at an earliest time, the glucose level g is likely to fall below a lower limit g_{min} and/or to rise above an upper limit or g_{max}. Typical values for g_{min} are in the order of 50 to 80 mg/dl, e.g. 70 mg/dl, and for g_{max} they are above 160 mg/dl, e.g. 250 mg/dl.

Such predictors have been known to rely on the maximum rate of decrease is $\dot{g}_{decr}$ mentioned above, assuming that the first derivative $\dot{g}$ of the glucose level will never fall below the maximum rate of decrease,

i.e. $\dot{g} \geq -\dot{g}_{decr}$ (if $\dot{g}_{decr}$ is defined to be a positive value).

It has been found, however, that this type of prediction can be improved. It has been found that not only the first derivative $\dot{g}$ of the glucose level is limited, but also the second derivative $\ddot{g}$. Typical lower and upper limits $\ddot{g}^-$ and $\ddot{g}^+$ were found to be both at 0.1 $mg \cdot dl^{-1} \cdot min^{-2}$.

This is illustrated in Fig. 6 showing a series of glucose level measurements g(t) indicated by dots. The lines p1 and p2 represent worst-case decay predictions starting from time t0. p1 is calculated on the mere assumption that $\dot{g} \geq -\dot{g}_{decr}$, while p2 is calculated from the refined assumption that $\dot{g} \geq -\dot{g}_{decr}$ and $\ddot{g} \geq -\ddot{g}^-$. As can be seen, the time t1 where prediction p1 reaches g_{min} is smaller than the time t2 where prediction p1 reaches g_{min}. Hence, using prediction p2 allows to avoid unnecessary alerts and allows a more precise prediction.

To make a prediction of type p2, it is necessary to use not only the actual values g(t0) of the glucose, but also a first derivative $\dot{g}(t0)$ thereof. In the example of Fig. 6, time t2 - t0 can e.g. be calculated from g(t0), $\dot{g}(t0)$, $\ddot{g}^-$ and $\dot{g}_{decr}$ using simple analysis.

Instead of calculating a time t2 where a worst-case prediction g(t) is expected to reach g_{min}, it is also possible to make a worst-case prediction at a time $t + \Delta t$, where Δt is a fixed "safety margin" of e.g. 20 minutes, and to compare this worst-case prediction $g(t + \Delta t)$ e.g. to the lower threshold value g_{min}. If the worst-case prediction is below the threshold value, an alert is issued.

In general, range monitoring will therefore advantageously calculate a prediction of the glucose level from an estimate of the current value of the glucose level g(t0) as well as its derivative $\dot{g}(t0)$, taking into account that the prediction must fulfil the conditions $\dot{g} \geq -\dot{g}_{decr}$ and $\ddot{g} \geq -\ddot{g}^-$ and/or $\dot{g} \leq \dot{g}_{incr}$ and $\ddot{g} \leq \ddot{g}^+$

This type of monitoring can be used in the device 100 but also in any other type of device that has a detector for repetitively measuring the glucose level of a living body. The prediction can, in particular, be used to provide an alert if the worst-case time until a hypoglycemia ($g(t) < g_{min}$) or hyperglycemia ($g(t) > g_{max}$) is below a given threshold time.

Remarks:

As it will be clear to the person skilled in the art, the methods described above can also be carried out with devices different from the one of Figs. 1 and 2, such as any of the devices shown in WO 02/069791 (taking into account that the temperature compensation described above will require the addition of a second temperature sensor).

Most aspects of the present invention, such as a temperature compensation, shift correction and various calibration methods, also work with devices using other types of sensors, such as optical sensors or inductive sensors.

While there are shown and described presently preferred embodiments of the invention, it is to be distinctly understood that the invention is not limited thereto but may be otherwise variously embodied and practiced within the scope of the following claims.

Claims

1. A device for measuring a glucose level in a living body, said device comprising

a sensor arrangement (5, 6) to be applied to a surface of the body,

processing circuitry (31 - 33, 37, 38) for measuring a response of the sensor arrangement and deriving the glucose level therefrom, and

at least a first and a second temperature sensor (15, 22) wherein a signal of the first temperature sensor depends in different manner on a skin temperature of the body and on an environmental temperature than a signal of the second sensor.

2. The device of claim 1 wherein the first temperature sensor (15) is closer to said sensor arrangement (5, 6) than the second temperature sensor (22).

3. The device of any of the preceding claims further comprising a housing (1) having a first side and a second side, wherein said sensor arrangement (5, 6) is arranged on said first side and wherein said first temperature sensor (15) is arranged at said first side and said second temperature sensor (22) at said second side.

4. The device of any of the preceding claims wherein said first temperature sensor (15) is in thermal contact with said sensor arrangement.

5. The device of any of the preceding claims further comprising an assembly (19) of electronic circuits wherein said second temperature sensor (22) is in thermal contact with said assembly (19).

6. A device (100, 102), in particular of any of the preceding claims, for measuring a glucose level in a living body, said device comprising

a sensor arrangement (5, 6) to be applied to a surface of the body,

processing circuitry (31 - 33, 37, 38) for measuring a response of the sensor arrangement and deriv-

ing the glucose level therefrom, wherein said processing circuitry (31 - 33, 37, 38) is adapted for calculating the glucose level g from

$$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M),$$

where F is a function depending on $N \geq 1$ measured input values $s_1 \ldots s_N$, wherein the function F has M+1 calibration parameters $a_0 \ldots a_M$ with $M \geq 0$, and

calibration means (38, 102) for storing a series of input values $s_j(t'_i)$ recorded at times t'_i in a given calibration phase and a series of reference values $g(t_i)$ measured at times t_i in the calibration phase and deriving at least part of the parameters a_i therefrom by comparing values obtained from the input values by function F against the reference values or against values derived from the reference values.

7. The device of claim 6 wherein said calibration means (102) is adapted for calculating at least part of said parameters a_i by minimizing a deviation of the values

$$F(t'_i) = F(s_1(t'_i) \ldots s_N(t'_i), a_0 \ldots a_M)$$

from a prediction S of the glucose level at the times t'_i, wherein said prediction is derived from the reference values $g(t_i)$.

8. The device of claim 7 wherein said calibration means (102) is adapted to minimize the deviations

$$d_i = \begin{cases} F(t'_i) - S_{max}(t'_i) \text{ if } F(t'_i) > S_{max}(t'_i) \\ S_{max}(t'_i) - F(t'_i) \text{ if } F(t'_i) < S_{min}(t'_i) \\ 0 \text{ otherwise} \end{cases}$$

wherein $S_{min}(t'_i)$ and $S_{max}(t'_i)$ are minimum and maximum values of the glucose level at time t'_i.

9. The device of claim 8 wherein said calibration means (102) are adapted to minimize a sum of absolute values of the values d_i.

10. The device of any of the claims 6 to 9, wherein said calibration means (102) is adapted for

detecting the times τ_1 ... τ_P when a shift of said device in respect to said body occurs during said calibration phase, and,

for comparing values obtained by function F against the reference values $g(t_i)$ or against values derived from the reference values $g(t_i)$, replacing at least parameter a_0 of said parameters by

$$\sum_{i=0}^{P} a_{0i} \cdot b_i(t)$$

with $b_i(t)$ being 1 for $\tau_i < t < \tau_{i+1}$ and 0 otherwise, wherein τ_0 and τ_{P+1} are the start and end times of the calibration phase.

11. The device of any of the claims 6 to 10 further comprising a recalibration means (38) for carrying out a recalibration step during which one of said parameters is varied to find an optimum agreement between the glucose level calculated from the function F and a glucose level from a reference measurement.

12. A device (100, 102), in particular of any of the preceding claims, for measuring a glucose level in a living body, said device comprising

a sensor arrangement (5, 6) to be applied to a surface of the body,

processing circuitry (31 - 33, 37, 38) for measuring a response of the sensor arrangement and deriving the glucose level therefrom, wherein said processing circuitry (31 - 33, 37, 38) is adapted for calculating the glucose level from

$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M)$,

where g is the glucose level and F is a function depending on $N \geq 1$ measured input values s_1 ... s_N, wherein the function F has M+1 calibration parameters a_0 ... a_M with $M \geq 0$, and

a shift correction (38) adapted for detecting a displacement of said device in respect to said body,

determining an effect of the shift on the measured glucose level and correcting the measured glucose level after the shift to compensate for the determined effect.

13. The device of claim 12 wherein said shift correction (38) is adapted for detecting the displacement by monitoring for a shift in a signal value v derived from at least one of the input values s_i.

14. The device of any of the claims 12 or 13 wherein said shift correction (38) is adapted to determine the effect of the shift on the measured glucose level by comparing an extrapolation ($v_{ext}(t)$) of signal values measured prior to the displacement with at least one signal value measured after the displacement.

15. The device of claim 14 wherein said shift correction (38) is adapted to determine the effect of the shift on the measured glucose level by calculating a difference between or a ratio of the extrapolation ($v_{ext}(t)$) and at the least one signal value measured after the displacement.

16. A device, in particular of any of the preceding claims, for measuring a glucose level in a living body, comprising

a detector comprising processing circuitry (31 - 33, 37, 38) for measuring the glucose level g(t) repetitively,

a predictor for predicting a glucose level, wherein said predictor is designed for calculating a prediction of the glucose level from an estimate of the current value of the glucose level g(t) as well as its derivative $\dot{g}(t)$, taking into account that the prediction must fulfil the conditions

$\dot{g} \geq -\dot{g}_{decr}$ and $\ddot{g} \geq -\ddot{g}^{-}$ and/or

$\dot{g} \leq \dot{g}_{incr}$ and $\ddot{g} \leq \ddot{g}^{+}$

17. The device of claim 16 wherein said predictor is designed for calculating a worst-case time until the glucose level reaches a lower or upper limit and

to issue an alert if the worst-case time is less than a given threshold time.

18. The device of any of the preceding claims wherein said processing circuitry (31 - 33, 37, 38) is adapted for calculating the glucose level g from

$$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M),$$

where g is the glucose level and F is a function depending on $N \geq 1$ measured input values $s_1, s_2, \ldots s_N$, wherein the function F has M+1 calibration parameters $a_0, a_1, \ldots a_M$ with $M \geq 0$.

19. The device of claim 18 wherein parameter a_0 is an additive or multiplicative parameter in function F.

20. The device of any of the claims 18 or 19 wherein said processing circuitry (31 - 33, 37, 38) is adapted for calculating the glucose level g from $g = a_0 + a_1 \cdot s_1 + a_2 \cdot s_2 + \ldots a_N \cdot s_N$.

21. The device of any of the claims 18 to 19 wherein at least one of said measured input values is indicative of a response of the sensor arrangement (5, 6).

22. The device of any of the claims 18 to 21 further comprising

a signal source (31) for applying a frequency sweep to a signal path (34), wherein said sensor arrangement (5, 6) is connected to said signal path, and

a detector (37) for determining a characteristic frequency (f0) and/or amplitude (A0) at which a signal in said signal path (34) becomes minimum and/or a phase shift in said signal path goes through zero,

wherein said measured input values $s_1, s_2, \ldots s_N$ comprise a value indicative of said characteristic frequency (f0) and/or amplitude (A0).

23. The device of any of the claims 18 to 22 further comprising at least a first and a second temperature sensor (15, 22) wherein a signal of the first temperature sensor (15) depends in different manner on a skin temperature (Ts) of the body and on an environmental

temperature (Te) than a signal of the second sensor (22), wherein said measured input values s_1, s_2, ... s_N comprise signals (T1, T2) from said first and said second temperature sensors.

24. The device of any of the preceding claims comprising a holder (52) for affixing it to the body.

25. The device of any of the preceding claims wherein said sensor arrangement (5, 6) comprises an electrode arrangement with at least one electrode (5, 6), in particular at least two electrodes, and said processing circuitry comprises at least one signal source (31) for applying a signal to said electrode arrangement and a signal detector (37) for detecting a response from said electrode arrangement to said signal.

26. A method for measuring a glucose level in a living body comprising the steps of

applying a sensor arrangement (5, 6) to a surface of the body,

measuring a response of the sensor arrangement and deriving at least one first value (A0, f0) therefrom,

measuring at least a second and a third value (T1, T2) with a first and a second temperature sensor (15, 22), wherein the second value (T1) depends in different manner on a skin temperature of the body and on an environmental temperature than the third value (T2),

calculating from said first, second and third values (A0, f0; T1; T2) said glucose level using calibration parameters (a_0 ... a_M).

27. A method for operating a device for measuring a glucose level in a living body, said device comprising a sensor arrangement (5, 6) to be applied to a surface of the body, and processing circuitry (31 - 33, 37, 38) for measuring a response of the sensor arrangement and deriving the glucose level therefrom, wherein said processing circuitry (31 - 33, 37, 38) is adapted for calculating the glucose level g from

$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M)$,

where F is a function depending on $N \geq 1$ measured input values $s_1 \ldots s_N$, wherein the function F has M+1 calibration parameters $a_1, \ldots a_M$ with $M \geq 0$, wherein said method comprises the steps of:

detecting a displacement of the device in respect to the body,

determine an effect of the shift on the measured glucose level, and

correcting the measured glucose levels after the shift to compensate for the determined effect.

28. The method of claim 27 wherein the displacement is detected by monitoring for a shift in a signal value (v) derived from at least one of the input values s_i.

29. The method of any of the claims 27 or 28, wherein the effect of the shift on the measured glucose level is determined by comparing an extrapolation ($v_{ext}(t)$) of signal values (v(t)) measured prior to the displacement with at least one signal value (v(t)) measured after the displacement.

30. The method of claim 29, wherein the effect of the shift on the measured glucose level is determined by calculating a difference between or a ratio of the extrapolation ($v_{ext}(t)$) and the at least one signal value measured after the displacement.

31. A method for calibrating a device for measuring a glucose level in a living body, said device comprising a sensor arrangement (5, 6) to be applied to a surface of the body and processing circuitry (31 - 33, 37, 38) for measuring a response of the sensor arrangement and deriving the glucose level therefrom, wherein said processing circuitry (31 - 33, 37, 38) is adapted for calculating the glucose level g from

$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M)$,

where F is a function depending on $N \geq 1$ measured input values $s_1 \ldots s_N$, wherein the function F has M+1 calibration parameters $a_1, \ldots a_M$ with $M \geq 0$, and

said method comprising the step deriving at least part of said parameters a_i from a series of input values $s_j(t'_i)$ recorded at times t'_i in a given calibration phase and a series of reference values $g(t_i)$ measured at times t_i in the calibration phase by comparing values obtained by function F against the reference values or against values derived from the reference values.

32. The method of claim 31 wherein at least part of said parameters a_i is calculated by minimizing a deviation of the values

$$F(t'_i) = F(s_1(t'_i) \ldots s_N(t'_i), a_0 \ldots a_M)$$

from a prediction S at the times t'_i, wherein said prediction is derived from the reference values $g(t_i)$.

33. The method of any of the claims 31 or 32 comprising the steps of

detecting the times $\tau_1 \ldots \tau_P$ when a shift of said device in respect to said body occurs during said calibration phase, and,

for comparing values obtained by function F against the reference values $g(t_i)$ or against values derived from the reference values $g(t_i)$, replacing at least one parameter a_0 by

$$\sum_{i=0}^{P} a_{0i} \cdot b_i(t),$$

with $b_i(t)$ being 1 for $\tau_i < t < \tau_{i+1}$, wherein τ_0 and τ_{P+1} are the start and end times of the calibration phase.

34. The method of any of the claims 31 to 33 wherein, during said calibration phase, an environment temperature is varied by at least 5 °C, in particular by at least 10 °C, and wherein at least one, in particular two, of said input values is/are an input temperature (T1, T2) the value of which depends on the environment temperature, and in particular wherein two input tempera-

tures T1 and T2 are measured, wherein the temperature T1 depends in different manner on a skin temperature of the body and on an environmental temperature than the temperature T2.

35. The method of any of the claims 31 to 34 wherein, during said calibration phase, the glucose level is varied by at least 100 mg/dl.

36. The method of any of the claims 31 to 35 further comprising a recalibration step during which one of said parameters is varied to find an optimum agreement between the glucose level calculated from the function F and a glucose level from a reference measurement.

37. A method for predicting the glucose level in a living body comprising the steps of

measuring the glucose level g(t) repetitively,

predicting a future glucose level from an estimate of the current value of the glucose level g(t) as well as its derivative $\dot{g}(t)$, taking into account that the prediction must fulfil the conditions

$\dot{g} \geq -\dot{g}_{decr}$ and $\ddot{g} \geq -\ddot{g}^{-}$ and/or

$\dot{g} \leq \dot{g}_{incr}$ and $\ddot{g} \leq \ddot{g}^{+}$.

38. The method of any of the claims 26 to 37 wherein said glucose level g is determined by

$g = F(s_1, s_2, \ldots s_N, a_0, a_1, \ldots a_M)$,

where F is a function depending on $N \geq 1$ measured input values $s_1, s_2, \ldots s_N$, wherein the function F has M+1 calibration parameters $a_0, a_1, \ldots a_M$.

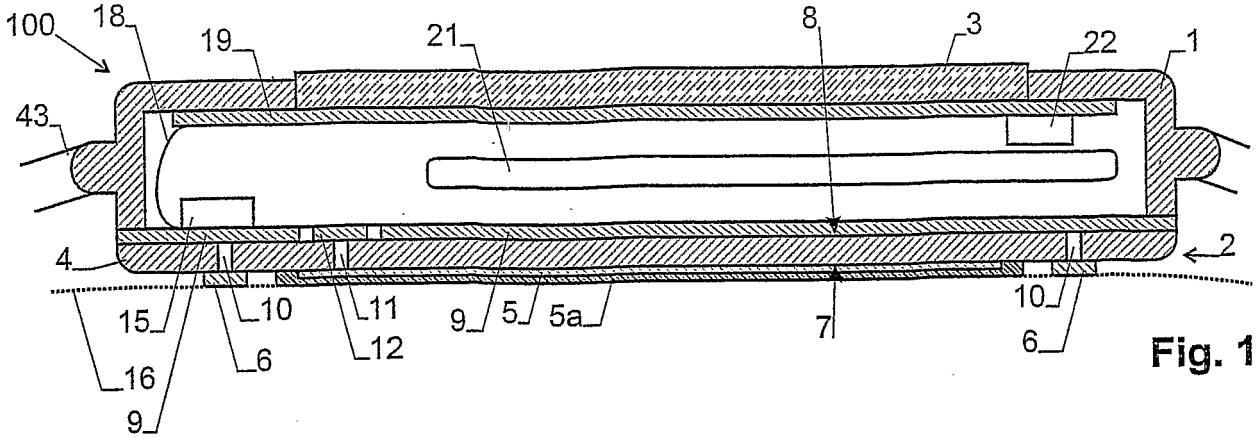
39. The method of claim 38 wherein parameter a_0 is an additive of multiplicative parameter in function F.

40. The method of claim 39 wherein the glucose level g is calculated from $g = a_0 + a_1 \cdot s_1 + a_2 \cdot s_2 + \ldots a_N \cdot s_N$.

41. The method of any of the claims 27 to 40 wherein said sensor arrangement (5, 6) comprises an electrode arrangement with at least one electrode (5, 6), in

particular at least two electrodes, wherein a signal is applied to said electrode arrangement and a response from said electrode arrangement to said signal is measured.

5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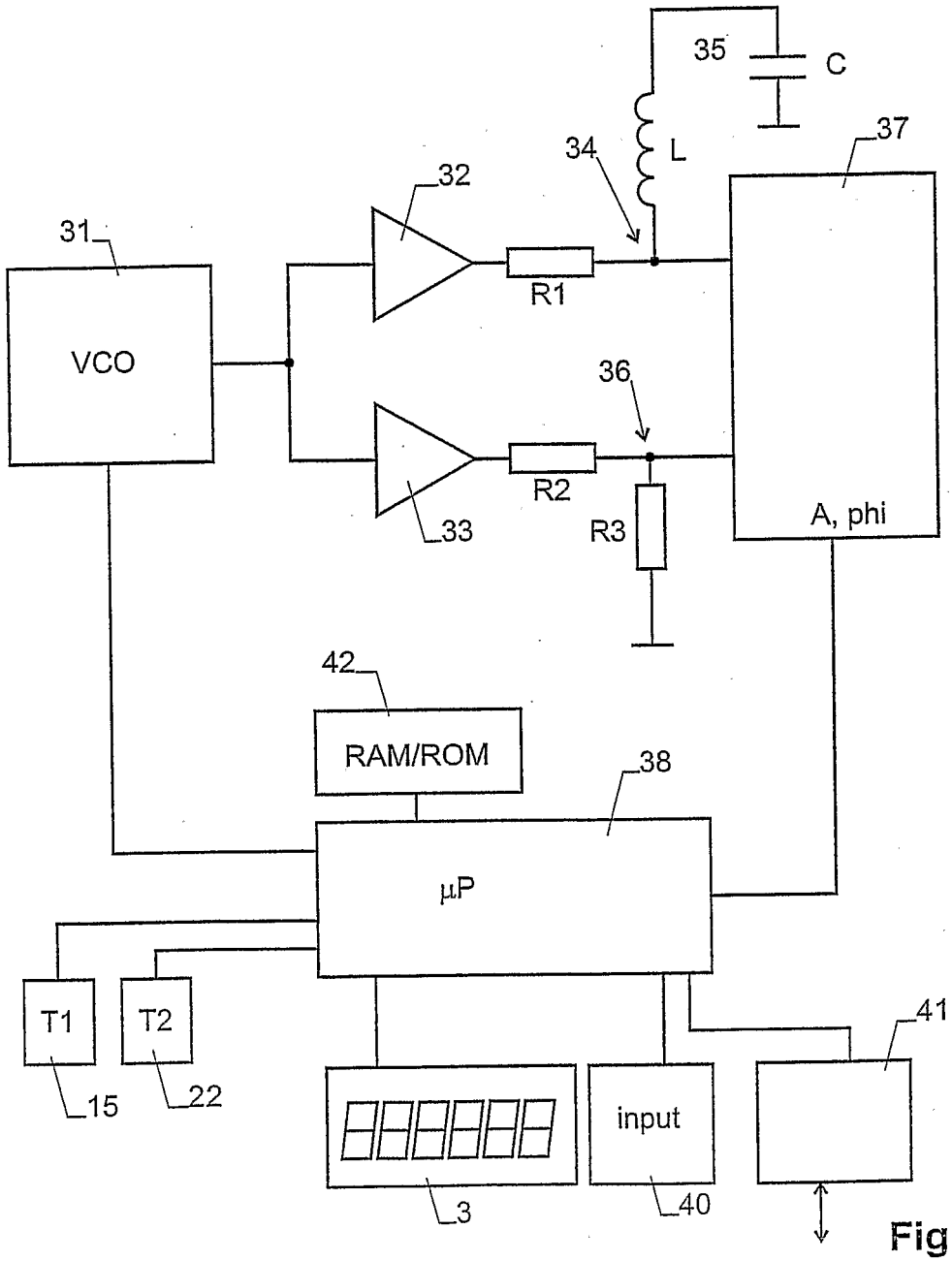
6
12

Fig. 1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C
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R2
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T2
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input
3
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Fig. 2

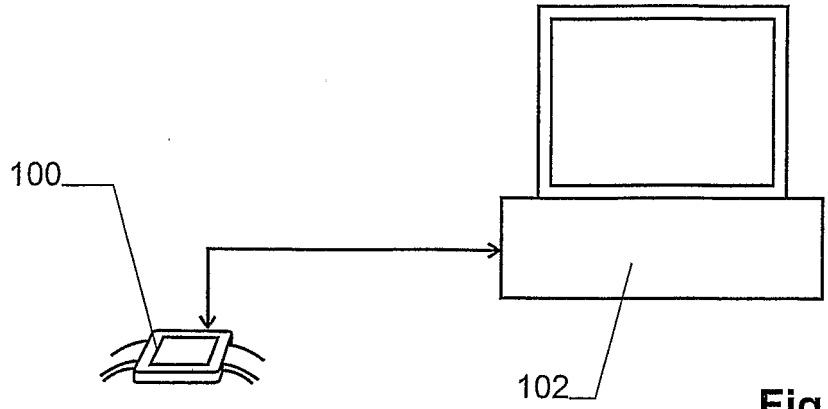
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Fig. 3

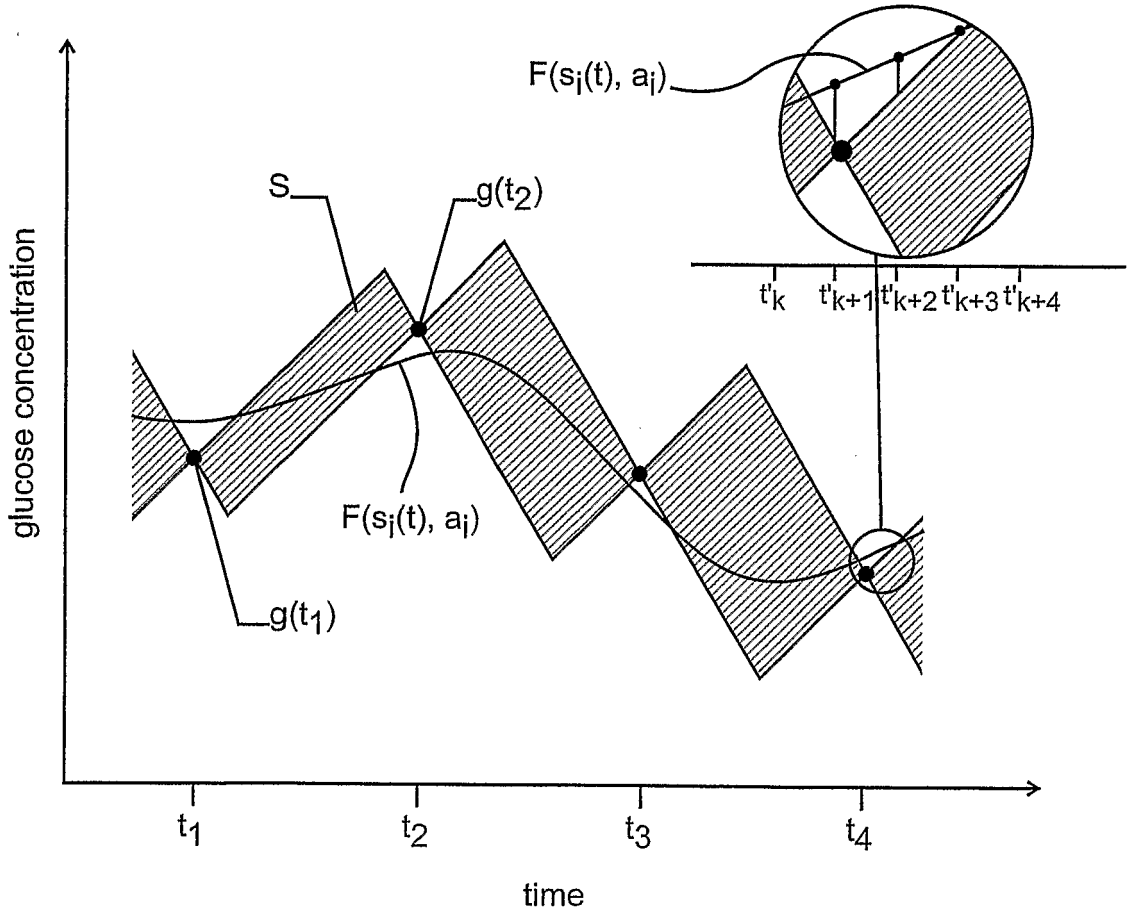
glucose concentration
time
S
g(t2)
g(t1)
F(si(t), ai)
F(si(t), ai)
t1
t2
t3
t4
t'k
t'k+1
t'k+2
t'k+3
t'k+4

Fig. 4

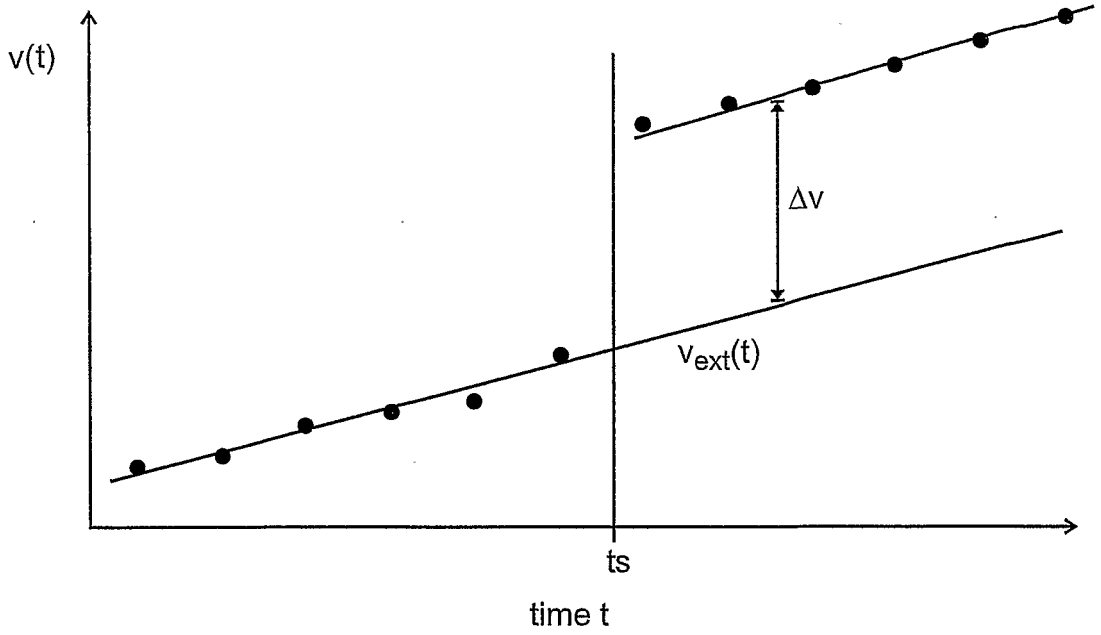

Fig. 5

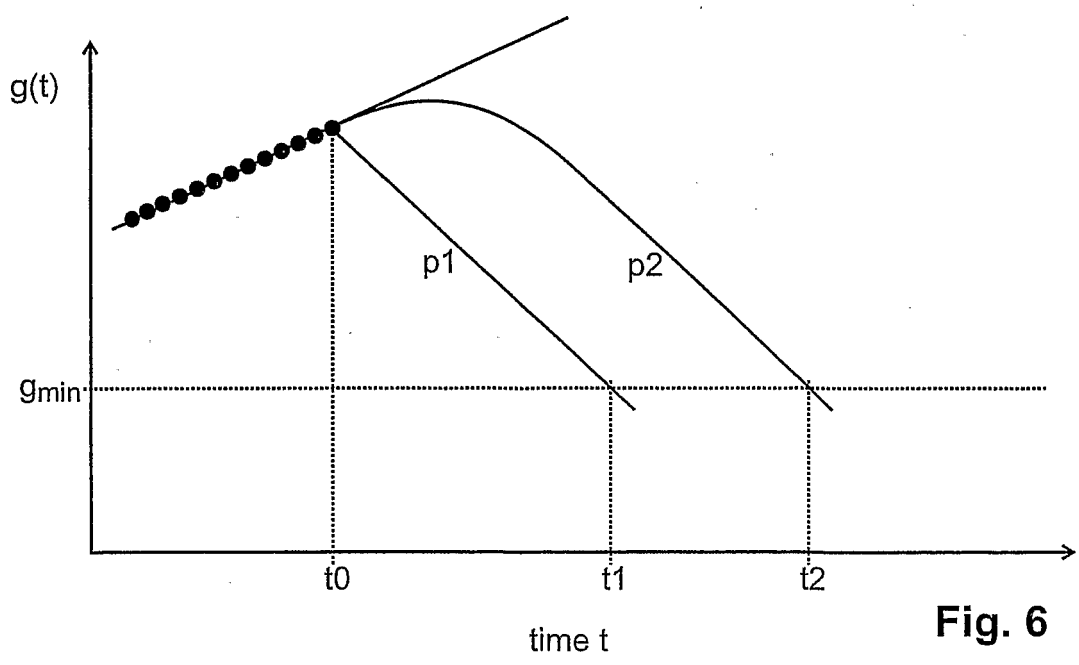

Fig. 6

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/IB 03/05704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 077 476 A (ROSENTHAL ROBERT D) 31 December 1991 (1991-12-31) column 3, line 51 -column 6, line 40	1-3,6, 18-21, 23,26, 38-40
Y	column 8, line 29 - line 46	11-13, 16,17, 27,28,37
A	claims 1,16-23	7-9

Y	US 6 309 884 B1 (BARKER TODD Q ET AL) 30 October 2001 (2001-10-30) column 2, line 16 - line 30 column 3, line 20 -column 8, line 62	11-13, 27,28
A	claims 1,9,15,16	1,10,14, 15,29,30

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2004	30/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Beck, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/106709 A1 (TIERNEY MICHAEL J ET AL) 8 August 2002 (2002-08-08) paragraph '0095! paragraph '0120! - paragraph '0133! ---	16,17,37
Y	WO 02 069791 A (PENDRAGON MEDICAL LTD ;CADUFF ANDREAS (CH); HIRT ETIENNE (CH); SCH) 12 September 2002 (2002-09-12) cited in the application the whole document ---	1-6, 18-26, 38-41
Y	US 5 050 612 A (MATSUMURA KENNETH N) 24 September 1991 (1991-09-24) column 5, line 51 -column 7, line 26 ---	1-6, 18-26, 38-41
A	US 2003/153821 A1 (TIERNEY MICHAEL J ET AL) 14 August 2003 (2003-08-14) paragraph '0165! - paragraph '0200! -----	6,11,19, 20,39,40

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/IB 03/05704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 31-36
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery (reference values are measured by invasive technique - see description p.10, l.32-37)

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir onal Application No
PCT/IB 03/05704

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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专利名称(译)	确定葡萄糖水平的技术		
公开(公告)号	EP1694196A1	公开(公告)日	2006-08-30
申请号	EP2003775695	申请日	2003-11-27
申请(专利权)人(译)	SOLIANIS HOLDING AG		
当前申请(专利权)人(译)	BIOVOTION AG		
[标]发明人	CADUFF ANDREAS DEWARRAT RODOLPHE		
发明人	CADUFF, ANDREAS DEWARRAT, RODOLPHE		
IPC分类号	A61B5/00 A61B5/05		
CPC分类号	A61B5/01 A61B5/05 A61B5/14532 A61B5/1477 A61B5/7207 A61B5/7239		
其他公开文献	EP1694196B1		
外部链接	Espacenet		

摘要(译)

用于测量活体中葡萄糖水平的装置（100）包括待施加到身体表面的电极装置（5,6）。葡萄糖水平源自电极布置（5,6）对电信号的响应。两个温度传感器（15,22）布置在装置（100）内的不同位置，其信号在校准和测量期间使用以提高装置的精度。通过在校准期间使用插值方法来实现精度的进一步提高。另外，应用了用于补偿由设备的位移引起的偏移的技术。该装置还可以用于基于葡萄糖水平的高阶导数的限制来预测高血糖症或低血糖症。