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(54) **METHOD FOR DETERMINING GLUCOSE CONCENTRATION IN HUMAN BLOOD**

VERFAHREN ZUR BESTIMMUNG DER GLUCOSEKONZENTRATION IN MENSCHLICHEM BLUT

MÉTHODE PERMETTANT DE DÉTERMINER LA GLYCÉMIE D'UN INDIVIDU

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Description

FIELD OF THE INVENTION

[0001] The invention refers to non-surgical methods for medical examination of human health, namely, to methods for determining glucose concentration in human blood as a result of measuring the impedance of human body part.

BACKGROUND OF THE INVENTION

[0002] Non-invasive methods for determining glucose concentration in human blood based on measuring the electrical impedance of a human body part or impedance components are known.

[0003] For example, a method for the indication of sugar content in human blood is known [RU Pat. No. 2073242, G01N33/4, 1997], with which sugar content level is determined based on variation of dielectric permeability of a finger placed in the electrical field of transducer.

[0004] A method for monitoring the amount of sugar in human blood is also known [RU Pat. No. 2088927, G01N33/49, 1997], with which the measurement is taken by changing the reactance of oscillating circuits included in the secondary circuits of high-frequency generator via direct action of human upon oscillating circuits elements. With this method, the amount of sugar in blood is determined based on variation of current in the secondary circuits of high-frequency generator.

[0005] Another method is known [U.S. Pat. No. 5792668, G01N27/00, 1998], with which spectral analysis of high-frequency radiation reflected by human body or passing through the human body is conducted. The phase shift between direct and reflected (or transmitted) waves, which characterizes the reactive component of electrical impedance, represents a parameter to be measured by this method. The concentration of substances contained in the blood (in particular, glucose concentration) is determined based on measured parameters of phase spectrum.

[0006] Another method is known, which was embodied in a device described in the RU Pat. No. 9703U1, A61B5/00, 1999. Glucose concentration is determined by this device based on measurement of human body region impedance at two frequencies, determining capacitive component of impedance and converting the obtained value of capacitive component into glucose concentration in patient's blood.

[0007] A method for measuring glucose concentration in human blood non-invasively is known [U.S. Pat. No. 6517482, A61B5/00, 2003]. The method is based on measuring impedance between two electrodes at a number of frequencies and deriving the value of glucose concentration on the basis of measured values.

[0008] Another method for determining glucose concentration in blood non-invasively is known, which involves measuring electric transfer functions by means of two pairs of four-electrode sensors [RU Pat. No. 2342071, A61B5/053, 2008]. The concentration of glucose in blood is determined based mathematical model specified in advance.

[0009] Another method for determining glucose concentration in human blood is also known [U.S. Pat. No. 7050847, A61B5/00, 2006], with which impedance of a human body area is measured at different frequencies by means of sensors. Impedance value at high frequencies is related to fluid volume in body tissues, while impedance value at low frequencies - to volume of extracellular fluid. Parameters of biological fluids in the human body are determined based on the measured values, and then glucose concentration in human blood is derived from these parameters.

[0010] US 2011/0224521 discloses a method for estimating the variation of the glucose level in the blood of a person by a non-invasive conductometry measurement using electrodes placed in contact with the skin of the person overlying a portion of soft tissue including muscular fibers. To eliminate the adverse effect of the conductivity of the capillary vessels, the conductivity of the tissue is measured independently in two directions, namely parallel and transverse to the muscular fibers. Measurements are carried out at a low and at a high frequency. To obtain absolute glucose values from the variation, some calibration is required which may be achieved for example at the beginning of a measurement period by means of a standard invasive method.

[0011] However, the above-described methods are characterized by one common disadvantage - namely, the values of glucose concentration in human blood obtained through the use of these methods rank below the values obtained using direct invasive methods in terms of measurement accuracy. At the same time, invasive methods, which require taking samples of blood, rank below non-invasive ones in terms of convenience and safety.

[0012] An engineering problem to be solved by the present invention consists in working out a non-invasive method for continuous determination of glucose concentration in human blood that is characterized by higher accuracy as compared to currently known non-invasive methods.

SUMMARY OF THE INVENTION

[0013] A method of measuring of a concentration of blood glucose in a human, the method comprising:

using spaced apart electrodes attached to a region of a body of the human to successively measure values of high

frequency impedance and low frequency impedance of the region at predetermined time intervals;
using a measured value of the high frequency impedance to determine an estimate of a volume of fluid in tissue of the region between the electrodes;
using a measured value of the low frequency impedance to determine an estimate of a volume of an extracellular fluid in the tissue in the region between the electrodes;
determining an increment of a metabolic component of the volume of the extracellular fluid by:

determining an increment of the estimate of the volume of the fluid relative to a previously measured value of the volume of the fluid;
determining an increment of the estimate of the volume of the extracellular fluid relative to a previously measured value of the volume of the extracellular fluid;
determining a difference between the increment of the estimate of the volume of the fluid and the increment of the estimate of the volume of the extracellular fluid;

determining an increment of the concentration of the blood glucose by normalizing the increment of the metabolic component of the volume of the extracellular fluid; and
determining the concentration of the blood glucose by adding up the increment of the concentration of the blood glucose and a previously determined concentration of the blood;
wherein determining a concentration of the blood glucose at a first time interval comprises adding up an increment of the concentration at the first interval of time and an initial blood glucose concentration.

[0014] The principal physics of the method consists in measuring the volume of fluid in a human body region. The water in human body accounts for 70 % of body weight, and it is not present in the human body as a single space, but distributed among body tissues. Vascular walls and cell membranes (out of which consist all tissues of human body) serve as boundaries for fluids. It is generally accepted to distinguish three water spaces: intracellular fluid, intravascular fluid (blood plasma fluid) and intercellular fluid (fluid that fills the intercellular space).

[0015] The intracellular fluid or fluid contained within tissue cells and red blood cells accounts for approximately 30-40 % of human body weight.

[0016] Intravascular fluid and intercellular fluid form the space of extracellular fluid, which accounts for about 20 % of human body weight.

[0017] Substances intended for sustaining the life of cells or products of their vital activity that are to be disposed of or reprocessed inside human body are present in each type of fluid. These substances move through cell membranes from one space to another in the process of vital activity of the human body. Osmotic pressure that depends upon difference in concentration (concentration gradient) of substances on different sides of the membrane represents one of the driving forces for this motion.

[0018] A dynamic equilibrium of metabolic processes is observed in the state of rest. The appearance of concentration gradient of osmotic pressure (e.g., together with glucose inflow from gastrointestinal tract after food intake) forces water to move though cell membrane in the direction of space characterized by higher concentration of solids dissolved in it. The volumes of water sectors are changed as a result of this process. But then regulatory mechanisms striving to restore the disturbed equilibrium of these spaces come into action. In other words, changes of water spaces volumes of human body have characteristic (cyclic) specific features. These specific features can be used as indicators of the character of metabolic processes in the human body, e.g. increase of glucose concentration in human blood after food intake.

[0019] The basis of the method consists in estimating an increase or decrease of glucose concentration in the blood based on changes of water spaces in the human body in time, which is determined in the course of periodic measurements of impedance of a human body region.

[0020] The following steps are performed in particular embodiments of the method.

[0021] Initial value of glucose concentration in human blood is determined in the beginning of measurements (using an alternative method - either invasive or non-invasive one). This absolute value is individual for every human being and it determines not only the nature of dynamics of glucose concentration changes, but also its absolute values during different periods of life activity of human being.

[0022] In particular, at least two electrodes installed at a certain distance from one another (preferably on peripheral body regions - e.g. a finger or an arm) can be used for measuring the impedance of a human body region.

[0023] Measurements of impedance of a human body region at high and low frequencies are taken with a predetermined time interval from 1 sec to 10 min. For the sake of convenience of hardware implementation of the method these time interval should be equal.

[0024] The moment of food intake is recorded during measurement taking, and this fact is used to adjust the indicators of dynamics of glucose supply into the human body.

[0025] Specifically, the following parameters are determined when implementing the method based on values of human

body region impedance measured at high and low frequencies at points in time t_k :

1) Volume of fluid contained in the tissues of the human body region between electrodes $W_{sum}(t_k)$ is calculated from the equation:

$$W_{sum}(t_k) = A \cdot L^2 / Z_{HF}(t_k),$$

where:

L - the distance between two electrodes;
$Z_{HF}(t_k)$ is the high frequency HF impedance measured at time t_k ;
A is a calibration factor determined as:

$$A = V_{sum} \cdot Z_{HF} / L^2 ,$$

where:

V_{sum} is a preliminary determined value of the volume of fluid in the tissue in the region between the electrodes;
Z_{HF} - preliminary determined high frequency HF impedance;

2) $W_{out}(t_k)$ is the volume of the extracellular fluid in the tissue of the region between the electrodes determined according to the following equation:

$$W_{out}(t_k) = B \cdot L^2 / Z_{LF}(t_k),$$

where:

$Z_{LF}(t_k)$ is the low frequency LF impedance measured at time t_k ;
B is a calibration factor, calculated as:

$$B = V_{out} \cdot Z_{LF} / L^2 ;$$

where:

V_{out} - preliminary determined volume of the extracellular fluid in region between the electrodes;
Z_{LF} - preliminary determined low-frequency LF impedance;

3) $\Delta W_{osm}(t_k)$ is the increment of the metabolic component determined as:

$$\Delta W_{osm}(t_k) = [W_{sum}(t_{k-1}) - W_{sum}(t_k)] - K_a [W_{out}(t_{k-1}) - W_{out}(t_k)],$$

where:

$W_{sum}(t_{k-1})$ - volume of fluid in the tissues of the human body region between the electrodes measured at time t_{k-1};
$W_{out}(t_{k-1})$ - volume of extracellular fluid in the tissues of the human body region between the electrodes measured at time t_{k-1} ;
K_a is a factor dependent on a human hematocrit volume selected from a range from 1.2 to 2.1;

4) $\Delta G(t_k)$ is the increment of the concentration of the blood glucose determined as:

$$\Delta G(t_k) = \Delta W_{osm}(t_k) \cdot K_E \cdot K_{PR} / K_g ,$$

where:

K_g is a normalizing factor ranging from 0.005 l^2millimole^{-1} to 0.006 l^2millimole^{-1};
K_E is a factor selected from a range of 0.23 to 0.4 before a meal intake, and selected from a range of 0.6 to 1.0 after the meal;
K_{PR} is a factor corresponding to measuring the concentration of the glucose in blood from 20 min to 45 min after the meal intake and wherein:

K_{PR} = 1, if $\Delta W_{osm}(t_k)$ is more than 0;
K_{PR} = -1, if $\Delta W_{osm}(t_k)$ is less than 0.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] The invention is illustrated with the following graphic drawings.

Fig. 1 shows the results of determining glucose concentration in the blood for the first volunteer.
Fig. 2 shows the results of determining glucose concentration in the blood for the second volunteer.
Fig. 3 shows the results of determining glucose concentration in the blood for the third volunteer.
Figs. 1a, 2a and 3a show the graphs of variation of glucose concentration determined through the use of different methods, including the method of the present invention, while Figs. 1b, 2b and 3b show graphs of measured values of impedance and temperature.

DETAILED DESCRIPTION OF THE INVENTION

[0027] The method is implemented in the following way.
[0028] Two electrodes are secured on a human body region apart from one another - at distance *L*. It is preferable to secure electrodes on peripheral body regions - e.g. on an arm, specifically, on forearm or finger. The best result will be obtained in the case of using annular electrodes embracing forearm or a finger
[0029] Since the method according to the invention claimed herein is based on calculating the values of the increment of glucose concentration in human blood followed by summing up the calculated values, prior to taking measurements of impedance, blood glucose concentration should be measured (using any other method - invasive or non-invasive one), and the value of thus measured impedance is taken as the initial one.
[0030] Impedance of a human body region is measured between electrodes at two frequencies: high frequency *HF* and low frequency *LF*. High frequency *HF* is chosen from the range from 200 kHz to 2 MHz; low frequency *LF* is chosen from the range from 20 kHz to 80 kHz. Electrical impedance of components of electrical impedance of body region tissues can be measured using one of the known methods, - specifically, by radiating high-frequency oscillations and subsequent measuring the impedance by means of capacitive sensors. Impedance of a human body region is measured at time intervals chosen from the range from 1 sec to 10 min.
[0031] A moment of food intake (characterizing glucose supply into the human body from the outside) is recorded in the course of measurements. This is done to derive the increment of metabolic component of the volume of extracellular fluid related to glucose, taking into account the time that have elapsed since the recorded moment of food intake beginning.
[0032] Based on the initial glucose concentration volume in human blood, current successive measurements of impedance of a human body region at high and low frequencies, and taking into account the time moment of food intake, glucose concentration in human blood is derived as follows.

1. The volume of fluid contained in a human body region between the electrodes $W_{sum}(t_k)$ *is* derived based on impedance value for human body region measured at high frequency *HF* at point in time t_k - $Z_{HF}(t_k)$, taking into account distance *L* between the electrodes, as follows:

$$W_{sum}(t_k) = A \cdot L^2 / Z_{HF}(t_k),$$

where: *A* - calibration factor, calculated from the formula:

$$A = V_{sum} \cdot Z_{HF} / L^2 .$$

Here, V_{sum} - value (obtained in advance) of the volume of fluid contained in the tissues of human body region between the electrodes. This value can be, for instance, calculated using anatomical relationships of the human body region chosen for impedance measuring. Also, the value of impedance of a human body region measured at high frequency Z_{HF} (and obtained in advance prior to the beginning of measurements intended for determining glucose concentration in human blood according to the invention claimed herein) is used for deriving calibration factor *A*.

2. The volume of extracellular fluid contained in the tissues of a human body region between the electrodes $W_{out}(t_k)$ is derived based on impedance value for human body region measured at low frequency *LF* at point in time t_k - $Z_{LF}(t_k)$, taking into account distance *L* between the electrodes, as follows:

$$W_{out}(t_k) = B \cdot L^2 / Z_{LF}(t_k),$$

where:

B - calibration factor, calculated from the formula:
$B = V_{out} \cdot Z_{LF} / L^2$.

Here, V_{out} - value (obtained in advance) of the volume of extracellular fluid contained in the human body region between the electrodes. This value can be, for instance, calculated using anatomical relationships of the human body region chosen for impedance measuring. Also, the value of impedance of a human body region measured at low frequency Z_{LF} is used for determining the calibration factor *B.* This impedance value is determined in advance prior to measurements of glucose concentration in human blood according to the present invention.

3. Then obtained value of volume of fluid contained in the tissues of the human body region between electrodes, and volume of extracellular fluid contained in the tissues of the human body region between electrodes, are used for calculating the increment of metabolic component of the extracellular fluid volume $\Delta W_{osm}(t_k)$. The values of fluid volumes obtained for measurements of impedance at point in time t_k and for the previous measurement at point in time t_{k-1} are used for this calculation. The increment of metabolic component of extracellular fluid volume is calculated from the formula:

$$\Delta W_{osm}(t_k) = [W_{sum}(t_{k-1}) - W_{sum}(t_k)] - K_a [W_{out}(t_{k-1}) - W_{out}(t_k)],$$

where:

$W_{sum}(t_k)$ - volume of fluid contained in the tissues of the human body region between the electrodes, for the current measurement taken at point in time t_k ;
$W_{sum}(t_{k-1})$ - volume of fluid contained in the tissues of the human body region between the electrodes, for the previous measurement taken at point in time t_{k-1};
$W_{out}(t_k)$ - volume of extracellular fluid contained in the tissues of the human body region between the electrodes, for the current measurement taken at point in time t_k ;
$W_{out}(t_{k-1})$ - volume of extracellular fluid contained in the tissues of the human body region between the electrodes, for the previous measurement taken at point in time t_{k-1};
K_a - factor dependent on the value of human hematocrit (this factor is chosen from the range from 1.2 to 2.1).

4. The value of the increment of glucose concentration in human blood is determined based on the obtained value of $\Delta W_{osm}(t_k)$ taking into account the moment of food intake:

$$\Delta G(t_k) = \Delta W_{osm}(t_k) \cdot K_E \cdot K_{PR} / K_g ,$$

where:

K_g - the normalizing factor chosen from the range from 0.005 $l^2 millimole^{-1}$ to 0.006 $l^2 millimole^{-1}$.
K_E - factor dependent on food intake; when determining glucose concentration in human blood prior to food intake, K_E value is chosen from the range from 0.23 to 0.4, and when determining glucose concentration in

human blood after food intake, K_E value is chosen from the range from 0.6 to 1.0;
K_{PR} - factor used for determining glucose concentration in human blood in the time period from 20 to 45 minutes after food intake, with this factor taking the value either 1 or -1 depending on the sign of the said increment of metabolic component of the extracellular fluid volume according to the following rule:

K_{PR} = 1, if the said increment of metabolic component of the extracellular fluid volume $\Delta W_{osm}(t_k)$ is greater than 0,
K_{PR} =-1, if the said increment of metabolic component of the extracellular fluid volume $\Delta W_{osm}(t_k)$ is less than 0.

5. The final value of glucose concentration in human blood by point in time t_k is derived as follows:

$$G(t_k) = G_0 + \sum_{i=1}^{k} \Delta G(t_i),$$

where:

G_0 - initial value of glucose concentration in human blood;
$\Delta G(t_i)$ - values of all increments of glucose concentration in human blood obtained from the beginning of measurements till point in time t_k, where $i = \{1,k\}$.

[0033] Thus, knowing the initial value of glucose concentration in human blood G_0 and periodically taking measurements of impedance of the human body region at high and low frequencies - $Z_{HF}(t_k)$ and $Z_{LF}(t_k)$, one can derive the current value of glucose concentration in human blood. The present invention can be embodied as quite simple measuring device capable of calculating of the above-indicated parameters characterizing changes in volumes of water spaces in human tissues, and finally, the current value of glucose concentration in human blood, including the option of taking into account the individual physiological features of human being and moments of food intake.

EXAMPLES

Example 1. Processing of measurement data for healthy Volunteer #1.

[0034] A 38-year-old healthy male, took a meal (food load) of 300 g of sweet beverage (Pepsi Cola). Fig. 1b shows the graphs of impedance value variation Z_{HF} and Z_{LF} and temperature $T°C$ recorded by the sensor located on the forearm, while Fig. 1a shows the graph of variation of glucose concentration in the blood of Volunteer #1. Dots indicate values of blood sample taken during the measurements (Roche Accu-Chek Active glucometer was used). The mean error for the measurement interval of 150 minutes was equal to 6.8 %.

Example 2. Processing of measurement data for healthy Volunteer #2.

[0035] A 45-year-old healthy male, took a meal (food load) of two 200 g glasses of sweet beverage (Pepsi Cola). Fig. 2b shows the graphs of impedance value variation Z_{HF} and Z_{LF} and temperature $T°C$ recorded by the sensor located on the forearm, while Fig. 2a shows the graph of variation of glucose concentration in the blood of Volunteer #2. Dots indicate values of blood sample taken during the measurements (Roche Accu-Chek Active glucometer was used). The mean error for the measurement interval of 140 minutes was equal to 7.2 %.

Example 3. Processing of measurement data for healthy Volunteer #3.

[0036] A 42-year-old healthy male, took a combined meal (food load) of 200 g of sweet beverage (Pepsi Cola) and banana. Fig. 3b shows the graphs of impedance value variation Z_{HF} and Z_{LF} and temperature $T°C$ recorded by the sensor located on the forearm, while Fig. 3a shows the graph of variation of glucose concentration in the blood of Volunteer #3. Dots indicate values of blood sample taken during the measurements (Roche Accu-Chek Active glucometer was used). The mean error for the measurement interval of 150 minutes was equal to 9.5 %.

[0037] The conducted tests showed that the method claimed herein is characterized by lesser error when determining the value of glucose concentration in human blood as compared to the known non-invasive methods.

Claims

1. Method of measuring of a concentration of blood glucose in a human, the method comprising:

using spaced apart electrodes attached to a region of a body of the human to successively measure values of high frequency impedance and low frequency impedance of the region at predetermined time intervals;
using a measured value of the high frequency impedance to determine an estimate of a volume of fluid in tissue of the region between the electrodes;
using a measured value of the low frequency impedance to determine an estimate of a volume of an extracellular fluid in the tissue in the region between the electrodes;
determining an increment of a metabolic component of the volume of the extracellular fluid by:

determining an increment of the estimate of the volume of the fluid relative to a previously measured value of the volume of the fluid;
determining an increment of the estimate of the volume of the extracellular fluid relative to a previously measured value of the volume of the extracellular fluid;
determining a difference between the increment of the estimate of the volume of the fluid and the increment of the estimate of the volume of the extracellular fluid;

determining an increment of the concentration of the blood glucose by normalizing the increment of the metabolic component of the volume of the extracellular fluid; and
determining the concentration of the blood glucose by adding up the increment of the concentration of the blood glucose and a previously determined concentration of the blood;
wherein determining a concentration of the blood glucose at a first time interval comprises adding up an increment of the concentration at the first interval of time and an initial blood glucose concentration.

2. Method according to Claim 1, wherein the initial blood glucose concentration is determined invasively.

3. Method according to Claim 1, wherein at least two spaced apart electrodes attached to the region of the body of the human are used.

4. Method according to Claim 3, wherein the at least two spaced apart electrodes are attached to the peripheral body regions as an arm or a finger.

5. Method according to Claim 1, wherein the predetermined time intervals range from 1 s to 10 min.

6. Method according to Claim 1, wherein:

$W_{sum}(t_k)$ is the volume of fluid in tissue of the region between the electrodes, determined according to the following equation:

$$W_{sum}(t_k) = A \cdot L^2 / Z_{HF}(t_k),$$

wherein:

L - is a distance between the two electrodes;
$Z_{HF}(t_k)$ - is the high frequency HF impedance measured at time t_k ;
A is a calibration factor determined as $A = V_{sum} \cdot Z_{HF}/L^2$;
wherein V_{sum} - is a preliminary determined value of the volume of fluid in the tissue in the region between the electrodes;
Z_{HF} - preliminary determined high frequency HF impedance;

$W_{out}(t_k)$ is the volume of the extracellular fluid in the tissue of the region between the electrodes determined according to the following equation:

$$W_{out}(t_k) = B \cdot L^2 / Z_{LF}(t_k),$$

wherein

$Z_{LF}(t_k)$ - is the low frequency *LF* impedance measured at time t_k ;
B is a calibration factor, calculated *as* $B = V_{out} \cdot Z_{LF}/L^2$;
wherein V_{out} - preliminary determined volume of the extracellular fluid in region;
Z_{LF} - preliminary determined low-frequency *LF* impedance;

$\Delta W_{osm}(t_k)$ is the increment of the metabolic component determined as:

$$\Delta W_{osm}(t_k) = [W_{sum}(t_{k-1}) - W_{sum}(t_k)] - K_a[W_{out}(t_{k-1}) - W_{out}(t_k)],$$

wherein

$W_{sum}(t_{k-1})$ is the volume of the fluid in the tissue measured at time t_{k-1};
$W_{out}(t_{k-1})$ is the volume of the extracellular fluid measured at time t_{k-1};
K_a is a factor dependent on a human hematocrit volume selected from a range from 1.2 to 2.1;

$\Delta G(t_k)$ is the increment of the concentration of the blood glucose determined as:

$$\Delta G(t_k) = \Delta W_{osm}(t_k) \cdot K_E \cdot K_{PR} / K_g ,$$

wherein

K_g is a normalizing factor ranging from 0.005 l^2 millimole^{-1} to 0.006 l^2millimole^{-1};
K_E is a factor selected from a range of 0.23 to 0.4 before a meal intake, and selected from a range of 0.6 to 1.0 after the meal;
K_{PR} is a factor corresponding to measuring the concentration of the glucose in blood from 20 min to 45 min after the meal intake and wherein:

K_{PR} = 1 if $\Delta W_{osm}(t_k)$ is more than 0; and
K_{PR} = -1 if $\Delta W_{osm}(t_k)$ is less than 0.

Patentansprüche

1. Verfahren zum Messen der Blutzuckerkonzentration in einem Menschen, wobei das Verfahren Folgendes umfasst:

Verwenden von voneinander beabstandeten Elektroden, die an einem Bereich eines Körpers des Menschen befestigt werden, um in vorbestimmten Zeitintervallen nacheinander Werte der Hochfrequenzimpedanz und der Niederfrequenzimpedanz des Bereichs zu messen;
Verwenden eines gemessenen Werts der Hochfrequenzimpedanz, um einen Schätzwert eines Fluidvolumens im Gewebe des Bereichs zwischen den Elektroden zu bestimmen;
Verwenden eines gemessenen Werts der Niederfrequenzimpedanz, um einen Schätzwert eines Volumens eines extrazellulären Fluids im Gewebe im Bereich zwischen den Elektroden zu bestimmen;
Bestimmen einer Zunahme einer metabolischen Komponente des Volumens des extrazellulären Fluids durch:

Bestimmen einer Zunahme des Schätzwerts des Volumens des Fluids relativ zu einem vorher gemessenen Wert des Volumens des Fluids;
Bestimmen einer Zunahme des Schätzwerts des Volumens des extrazellulären Fluids relativ zu einem vorher gemessenen Wert des Volumens des extrazellulären Fluids;
Bestimmen einer Differenz zwischen der Zunahme des Schätzwerts des Volumens des Fluids und der Zunahme des Schätzwerts des Volumens des extrazellulären Fluids;

Bestimmen einer Zunahme der Blutzuckerkonzentration durch Normalisieren der Zunahme der metabolischen Komponente des Volumens des extrazellulären Fluids; und
Bestimmen der Blutzuckerkonzentration durch Addieren der Zunahme der Blutzuckerkonzentration und einer vorher bestimmten Blutkonzentration;
wobei das Bestimmen einer Blutzuckerkonzentration nach einem ersten Zeitintervall das Addieren einer Zunahme der Konzentration beim ersten Zeitintervall und einer anfänglichen Blutzuckerkonzentration umfasst.

2. Verfahren nach Anspruch 1, wobei die anfängliche Blutzuckerkonzentration invasiv bestimmt wird.

3. Verfahren nach Anspruch 1, wobei wenigstens zwei voneinander beabstandete Elektroden, die an dem Bereich des Körpers des Menschen befestigt sind, verwendet werden.

4. Verfahren nach Anspruch 3, wobei die wenigstens zwei voneinander beabstandeten Elektroden an peripheren Körperbereichen wie einem Arm oder einem Finger befestigt werden.

5. Verfahren nach Anspruch 1, wobei die vorbestimmten Zeitintervalle von 1 s bis 10 min betragen.

6. Verfahren nach Anspruch 1, wobei:

$W_{sum}(t_k)$ das Fluidvolumen im Gewebe des Bereichs zwischen den Elektroden ist, das gemäß der folgenden Gleichung bestimmt wird:

$$W_{sum}(t_k) = A \cdot L^2 / Z_{HF}(t_k),$$

wobei: L ein Abstand zwischen den zwei Elektroden ist;
$Z_{HF}(t_k)$ die zum Zeitpunkt t_k gemessene Hochfrequenz-*HF*-Impedanz ist;
A ein Kalibrationsfaktor ist, der als $A = V_{sum} \cdot Z_{HF} / L^2$ bestimmt wird;
wobei V_{sum} ein vorab bestimmter Wert des Fluidvolumens im Gewebe im Bereich zwischen den Elektroden ist;
Z_{HF} die vorab bestimmte Hochfrequenz-*HF*-Impedanz ist;
$W_{out}(t_k)$ das Volumen des extrazellulären Fluids im Gewebe des Bereichs zwischen den Elektroden ist, das gemäß der folgenden Gleichung bestimmt wird:

$$W_{out}(t_k) = B \cdot L^2 / Z_{LF}(t_k),$$

wobei

$Z_{LF}(t_k)$ die zum Zeitpunkt t_k gemessene Niederfrequenz-*NF*-Impedanz ist;
B ein Kalibrationsfaktor ist, der als $B = V_{out} \cdot Z_{LF} / L^2$ gemessen wird;
wobei V_{out} das vorab bestimmte Volumen des extrazellulären Fluids in dem Bereich ist;
Z_{LF} die vorab bestimmte Niederfrequenz-*NF*-Impedanz ist;
$\Delta W_{osm}(t_k)$ die Zunahme der metabolischen Komponente ist, die wie folgt bestimmt wird:

$$\Delta W_{osm}(t_k) = [W_{sum}(t_{k-1}) - W_{sum}(t_k)] - K_a[W_{out}(t_{k-1}) - W_{out}(t_k)],$$

wobei

$W_{sum}(t_{k-1})$ das zum Zeitpunkt t_{k-1} gemessene Volumen des Fluids im Gewebe ist;
$W_{out}(t_{k-1})$ das zum Zeitpunkt t_{k-1} gemessene Volumen des extrazellulären Fluids ist;
K_a ein von einem menschlichen Hämatokritvolumen abhängiger Faktor ist, der aus einem Bereich von 1,2 bis 2,1 ausgewählt wird;
$\Delta G(t_k)$ die Zunahme der Blutzuckerkonzentration ist, die wie folgt bestimmt wird:

$$\Delta G(t_k) = \Delta W_{osm}(t_k) \cdot K_E \cdot K_{PR} / K_g,$$

wobei

K_g ein Normalisierungsfaktor ist, der von 0,005 l^2Millimol^{-1} bis 0,006 l^2Millimol^{-1} reicht;
K_E ein Faktor ist, der vor der Einnahme einer Mahlzeit aus einem Bereich von 0,23 bis 0,4 ausgewählt wird und nach der Mahlzeit aus einem Bereich von 0,6 bis 1,0 ausgewählt wird;
K_{PR} ein Faktor ist, welcher der Messung der Blutzuckerkonzentration 20 min bis 45 min nach der Einnahme der Mahlzeit entspricht und wobei:

K_{PR} = 1, falls $\Delta W_{osm}(t_k)$ mehr als 0 ist; und
K_{PR} = -1, falls $\Delta W_{osm}(t_k)$ weniger als 0 ist.

Revendications

1. Procédé pour mesurer une concentration de glucose sanguin chez un sujet humain, lequel procédé comprend :

   l'utilisation d'électrodes espacées fixées à une région du corps du sujet humain pour mesurer successivement des valeurs d'impédance à haute fréquence et d'impédance à basse fréquence de la région à des intervalles de temps prédéterminés ;
   l'utilisation d'une valeur mesurée de l'impédance à haute fréquence pour déterminer une estimation d'un volume de fluide dans le tissu de la région située entre les électrodes ;
   l'utilisation d'une valeur mesurée de l'impédance à basse fréquence pour déterminer une estimation d'un volume de fluide extracellulaire dans le tissu de la région située entre les électrodes ;
   la détermination d'un incrément d'une composante métabolique du volume de fluide extracellulaire par :

      la détermination d'un incrément de l'estimation du volume du fluide par rapport à une valeur du volume du fluide mesurée précédemment ;
      la détermination d'un incrément de l'estimation du volume du fluide extracellulaire par rapport à une valeur du volume du fluide extracellulaire mesurée précédemment ;
      la détermination d'une différence entre l'incrément de l'estimation du volume du fluide et l'incrément de l'estimation du volume du fluide extracellulaire ;
      la détermination d'un incrément de la concentration du glucose sanguin par la normalisation de l'incrément de la composante métabolique du volume du fluide extracellulaire ; et

   la détermination de la concentration du glucose sanguin par l'addition de l'incrément de la concentration du glucose sanguin et d'une concentration du sang déterminée précédemment ;
   la détermination d'une concentration du glucose sanguin à un premier intervalle de temps comprenant l'addition d'un incrément de la concentration au premier intervalle de temps et d'une concentration initiale du glucose sanguin.

2. Procédé selon la revendication 1, dans lequel la concentration initiale du glucose sanguin est déterminée de façon invasive.

3. Procédé selon la revendication 1, dans lequel au moins deux électrodes espacées, fixées à la région du corps du sujet humain, sont utilisées.

4. Procédé selon la revendication 3, dans lequel les au moins deux électrodes espacées sont attachées à des parties périphériques du corps telles qu'un bras ou un doigt.

5. Procédé selon la revendication 1, dans lequel les intervalles de temps prédéterminés vont de 1 s à 10 min.

6. Procédé selon la revendication 1, dans lequel :

   $W_{somme}(t_k)$ est le volume de fluide dans le tissu de la région située entre les électrodes, déterminé par l'équation

suivante :

$$W_{somme}(t_k) = A \times L^2/Z_{HF}(t_k)$$

où

L est une distance entre les deux électrodes ;
$Z_{HF}(t_k)$ est l'impédance à haute fréquence *HF* mesurée au temps t_k;
A est un facteur d'étalonnage déterminé par $A = V_{somme} \times Z_{HF}/L^2$,

où V_{somme} est une valeur du volume de fluide dans le tissu de la région située entre les électrodes déterminée au préalable ;
Z_{HF} est l'impédance à haute fréquence *HF* déterminée au préalable ;

$W_{ext}(t_k)$ est le volume de fluide extracellulaire dans le tissu de la région située entre les électrodes, déterminé par l'équation suivante :

$$W_{ext}(t_k) = A \times L^2/Z_{BF}(t_k),$$

où

$Z_{BF}(t_k)$ est l'impédance à basse fréquence *BF* mesurée au temps t_k;
B est un facteur d'étalonnage calculé par $B = V_{ext} \times Z_{BF}/L^2$,

où V_{ext} est une valeur du volume de fluide extracellulaire dans la région déterminée au préalable ;
Z_{BF} est l'impédance à basse fréquence *BF* déterminée au préalable ;

$\Delta W_{osm}(t_k)$ est l'incrément de la composante métabolique, déterminé par :

$$\Delta W_{osm}(t_k) = [W_{somme}(t_{k-1}) - W_{somme}(t_k)] - K_a[W_{ext}(t_{k-1}) - W_{ext}(t_k)],$$

où

$W_{somme}(t_{k-1})$ est le volume de fluide dans le tissu mesuré au temps t_{k-1} ;
$W_{ext}(t_{k-1})$ est le volume de fluide extracellulaire mesuré au temps t_{k-1} ;
K_a est un facteur dépendant du volume d'hématocrite humain et choisi dans une plage allant de 1,2 à 2,1 ;

$\Delta G(t_k)$ est l'incrément de la concentration du glucose sanguin, déterminé par :

$$\Delta G(t_k) = \Delta W_{osm}(t_k) \times K_E \times K_{PR}/K_g, \text{ où}$$

où

K_g est un facteur de normalisation qui va de 0,005 l^2 millimole^{-1} à 0,006 l^2 millimole^{-1} ;
K_E est un facteur choisi dans une plage de 0,23 à 0,4 avant la prise d'un repas, et choisi dans une plage de 0,6 à 1,0 après le repas ;
K_{PR} est un facteur correspondant à la mesure de la concentration du glucose dans le sang entre 20 minutes et 45 minutes après la prise du repas, où :

$K_{PR} = 1$ si $\Delta W_{osm}(t_k)$ est supérieur à 0 et
$K_{PR} = -1$ si $\Delta W_{osm}(t_k)$ est inférieur à 0.

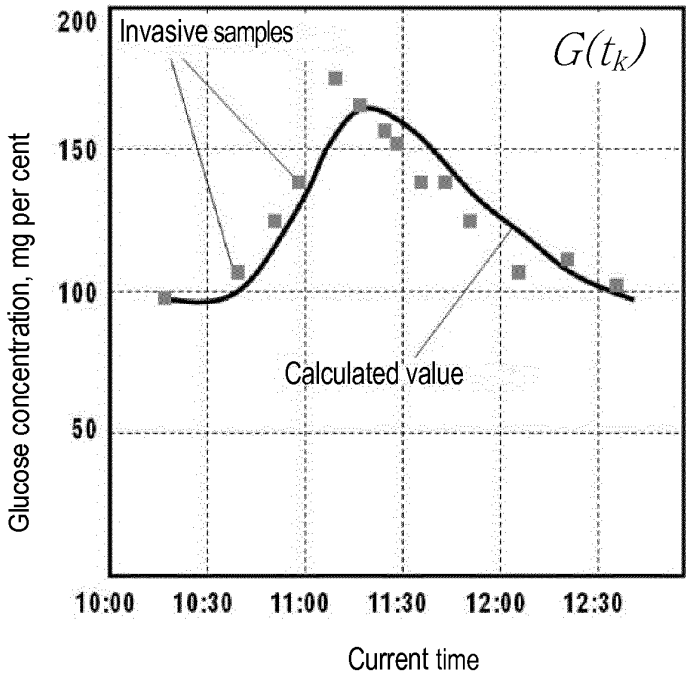
Invasive samples
$G(t_k)$
Calculated value
Glucose concentration, mg per cent
200
150
100
50
10:00
10:30
11:00
11:30
12:00
12:30
Current time

Fig. 1A

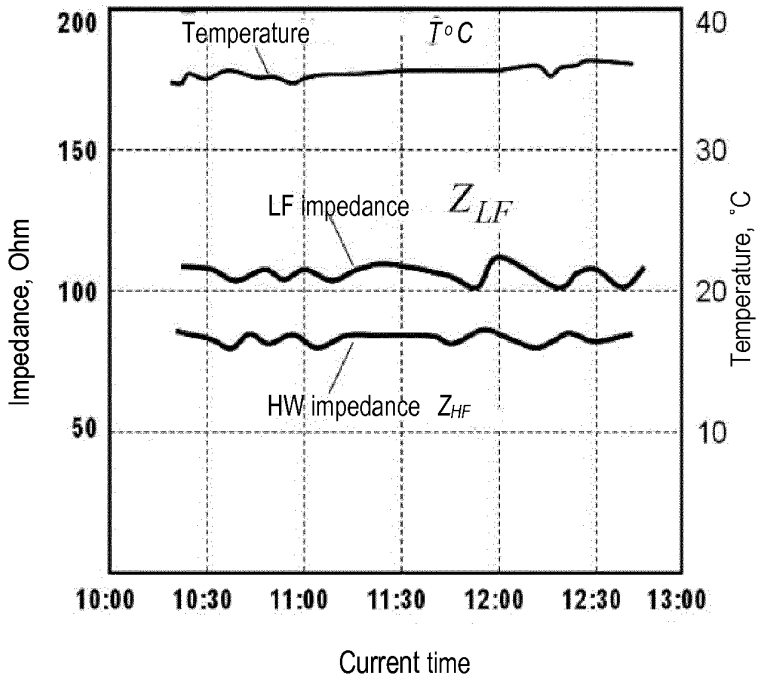
Temperature
$\bar{T}^{o}C$
LF impedance
Z_{LF}
HW impedance Z_{HF}
Impedance, Ohm
Temperature, °C
200
150
100
50
40
30
20
10
10:00
10:30
11:00
11:30
12:00
12:30
13:00
Current time

Fig. 1B

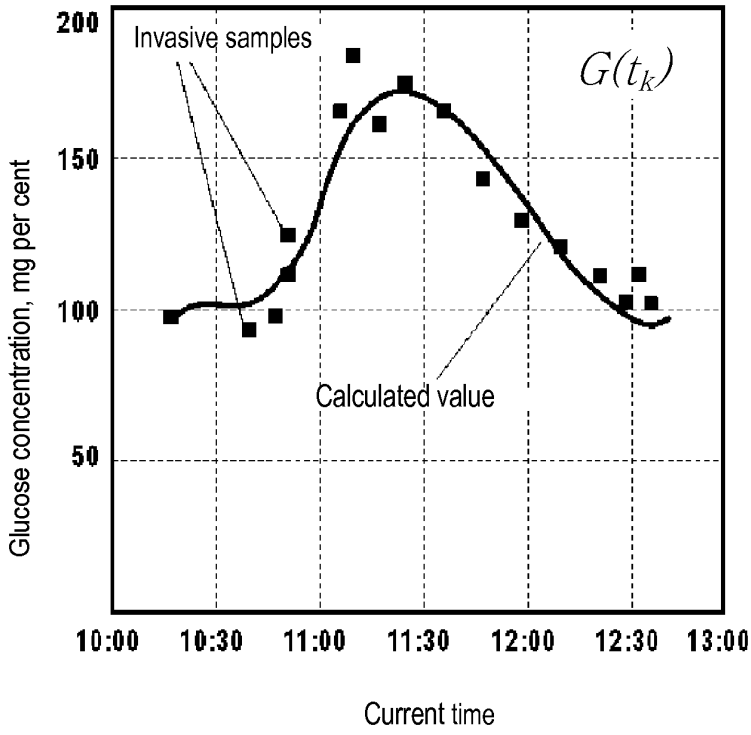
200
150
100
50
Invasive samples
$G(t_k)$
Calculated value
Glucose concentration, mg per cent
10:00
10:30
11:00
11:30
12:00
12:30
13:00
Current time

Fig. 2A

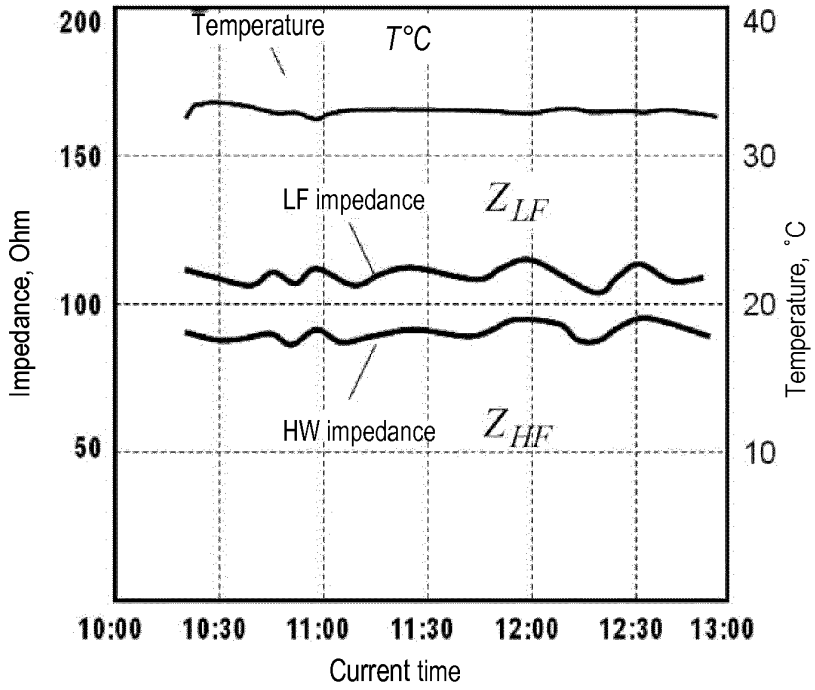
200
150
100
50
Temperature
$T°C$
LF impedance
Z_{LF}
HW impedance
Z_{HF}
Impedance, Ohm
40
30
20
10
Temperature, °C
10:00
10:30
11:00
11:30
12:00
12:30
13:00
Current time

Fig. 2B

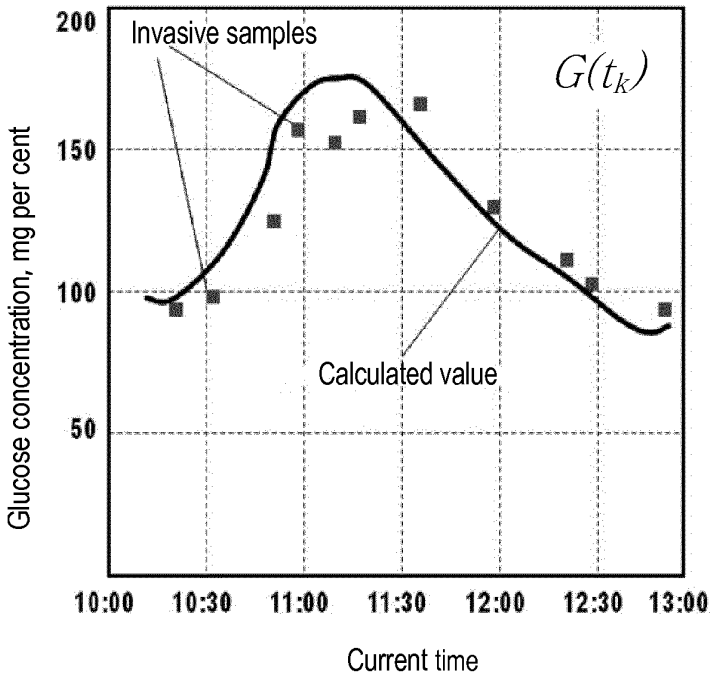
200
150
100
50
Invasive samples
$G(t_k)$
Calculated value
Glucose concentration, mg per cent
10:00
10:30
11:00
11:30
12:00
12:30
13:00
Current time

Fig. 3A

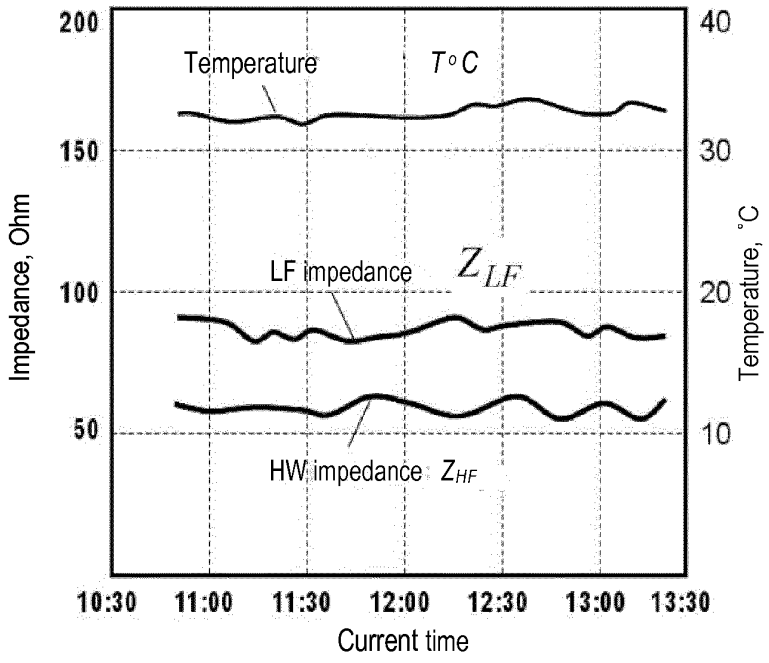
200
150
100
50
40
30
20
10
Temperature
T°C
LF impedance
Z_{LF}
HW impedance Z_{HF}
Impedance, Ohm
Temperature, °C
10:30
11:00
11:30
12:00
12:30
13:00
13:30
Current time

Fig. 3B

REFERENCES CITED IN THE DESCRIPTION

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