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(54) **METHOD AND DEVICE FOR MEASURING GLUCOSE**

VERFAHREN UND VORRICHTUNG ZUR GLUKOSEMESSUNG

PROCEDE ET DISPOSITIF POUR MESURER LE TAUX DE GLUCOSE

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EP-A- 1 092 386 **WO-A-02/069791**

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Description

Technical Field

[0001] The invention relates to a method and a device for measuring glucose in a sample, in particular in a sample of living body tissue.

Background Art

[0002] Various non-invasive methods for measuring glucose in body tissue have been known. In particular, US 5 792 668 by Fuller et al. describes a device where a square wave signal or a plurality of sine waves with differing frequencies are fed to a first electrode applied to the tissue. A second electrode is used for measuring a signal transmitted through the tissue. The phase and/or amplitude of the transmitted signal are used for determining the glucose level.

[0003] EP 1092 386 A discloses a device for measuring a glucose level in a sample comprising:

- a probe having an end to be applied to the sample,
- a pulse generator for generating electric pulses in the probe,
- a measuring device for measuring pulses reflected from the end of the probe,
- an analyzer for determining at least one parameter of the reflected pulses measured by the measuring device and for determining the glucose level from said parameter.

[0004] WO 02/069791 discloses a device for measuring a glucose level in a sample comprising:

- a probe having an end comprising electrodes, wherein said end is to be applied to the sample in order to act as a fringing capacitor with field lines extending into the sample,
- a pulse generator for generating electric pulses in the probe,
- a measuring device for measuring pulses reflected from the end of the probe,
- an analyzer for determining at least one parameter of the reflected pulses measured by the measuring device and for determining the glucose level from said parameter.

Disclosure of the Invention

[0005] Hence, it is a general object of the invention to provide a method and a device for the non-invasive measurement of glucose.

[0006] This object is met by the independent claims. Accordingly, an end of a probe is applied to the sample. A pulse generator is used to generate single pulses to be fed into the probe. The pulses are reflected at the end of the probe, which acts as a fringing capacitor with field lines extending into the specimen, and the reflected pulses are measured by a reflection measuring device. An analyzer is used for determining at least one parameter of the reflected pulses and for determining the glucose level from this parameter or these parameters, e.g. by using calibration data stored in a memory.

[0007] In this context, the term "pulse" is understood to encompass not only isolated pulses having a rising and a trailing edge, but also pulses consisting of a rising or a trailing edge only, i.e. isolated transitions of the voltage level applied to the probe.

Brief Description of the Drawings

[0008] 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 block diagram of and embodiment of the invention,
Fig. 2 is a sectional view of a first embodiment of a probe,
Fig. 3 is a view of a second embodiment of a probe as seen from the electrode side,
Fig. 4 is a section along line IV-IV of Fig. 3,
Fig. 5 are sample traces of reflected pulses,
Fig. 6 are calculated charges for the traces of Fig. 5,
Fig. 7 are charges for two different glucose levels,
Fig. 8 are charges at 19 ns measured for a subject during an extended time period with an oral glucose intake at t = 26 min.

Modes for Carrying Out the Invention

[0009] The preferred embodiment of the present invention is based on Time Domain Spectroscopy, where a pulse if fed to a probe, and end of which is applied to a sample, and where the time resolved characteristics of the reflected pulse are analyzed. For an overview and description of the theory of this method, see:

- Y. D. Feldman et al., "Time domain dielectric spectroscopy. A new effective tool for physical chemistry investigation", Colloid & Polymer Science, vol. 270, pp. 768 - 780 (1992), in the following called Ref. 1, and
- Y. D. Feldman et al., "Time domain dielectric spectroscopy. An advanced measuring system", Rev. Sci. Instrum. Vol. 67 (9), pp. 3208 - 3216 (1996), in the following called Ref. 2.

[0010] An embodiment of a device for measuring the glucose concentration in a sample 1, in particular in the living human body, is shown in Fig. 1. It comprises a pulse generator 2 repetitively triggered by a clock 3 and generating pulses consisting of voltage transitions hav-

ing a rise or fall time of less than 1 ns. The pulses are fed to a node 4 and from there to a probe 5, and end 6 of which is applied to sample 1. In a preferred embodiment of the invention, end 6 of the sample is applied to the skin of a subject.

[0011] Pulses reflected from end 6 arrive back at node 4 and are fed to a measuring device 7. In the present embodiment, measuring device 7 records the reflected pulses in time resolved manner.

[0012] The data from measuring device 7 are digitized and fed to an analyzer 8, such as a computer system, where they are processed. Using calibration data stored in a calibration table 9, analyzer 8 converts the data to a glucose level, which is e.g. displayed on a display 10.

[0013] A first embodiment of a probe 5 of Chebishev-type symmetry as described in Ref. 2 is shown in Fig. 2. It comprises a coaxial transmission line 11 connected through a flaring section 12 to an annular electrode 13a and a circular central electrode 13b, wherein flaring section 12 provides impedance matching between transmission line 11 and electrodes 13a, 13b. Central electrode 13b may be covered by an anticorrosion coating 13c. A teflon layer 13d is arranged between the electrodes.

[0014] A second embodiment of a probe 5 is shown in Figs. 3 and 4. Here, the signal is fed through terminals 14a, 14b to a an annular electrode 15a and a central strip electrode 15b, wherein the latter or both may be covered by a dielectric coating 16 and are mounted on a dielectric substrate 17. Central strip electrode 15b is not exactly centered within annular electrode 15a but offset in a first direction. Annular electrode 15a is thicker at a side remote from central strip electrode 15b and partially covered by dielectric coating 16 at this side.

[0015] Fig. 5 shows typical signal traces of reflected pulses from the probe of Fig. 2 as a response to a pulse consisting of a single voltage transition of a rise time much smaller than 0.1 ns. The probe was applied to air or to three different subjects or it was short circuited at its electrode end.

[0016] As described in Ref. 1, an integration of the voltage traces of Fig. 5 allows to calculate a charge Q(t) accumulated on the capacitor formed by the electrodes. The corresponding curves for the three subjects of Fig. 5 are shown in Fig. 6.

[0017] Experiments show that the traces of Figs. 5 and 6 change when the glucose level in the tissues of the subjects vary. This is illustrated in Fig. 7 showing two charge traces measured with the probe of Figs. 3 and 4. A first trace (at 8 min) was recorded before an oral glucose intake and one afterwards (at 45 min). The curves show a clear difference at 10 ns and later. It has been found that the effect is pronounced at larger times, but 1 μS is considered to be an upper limit for measurements due to an increasingly strong influence from other relaxation processes.

[0018] Hence, in a preferred embodiment, measuring device 7 is designed for carrying out at least one, preferably more than one, measurement in the range of 10 to 1000 ns after the generation of the pulse.

[0019] The duration of a pulse is preferably at least 10 ns since the relevant polarization processes were found to set in at this time scale.

[0020] Fig. 8 shows the accumulated charge after 19 ns for a subject during a period of 100 min with oral glucose intake at t = 26 min.

[0021] When ignoring the measured point at t = 26 min (considered to be an outlier due to a sudden movement of the subject while drinking the glucose solution), the points show a clear increase of the charge after approximately 40 min when the glucose level in the subject's tissue starts to increase.

[0022] By running a calibration measurement where Q (t = 19 ns) as shown in Fig. 8 and a reference glucose concentration determined conventionally are measured, calibration data can be obtained that allows to determine the glucose level from the charge Q(t = 19 ns). This calibration data can be stored in calibration table 9 for being used to translate the measured charge to a glucose level.

[0023] For this purpose, the conventionally obtained glucose level c_{gl} and the charge Q measured in the calibration measurement can e.g. be fitted to a function f using one or more parameters p1, p2,..., i.e. c_{gl} = f(Q, p1, p2...). The parameters p1, p2... can be stored in calibration table 9, such that, during a later measurement, f(Q, p1, p2...) can be calculated for any value Q. The function f(Q) can e.g. be a straight line (i.e. f(Q, p1, p2) = p1 + Q-p2) or any other function that is found empirically or theoretically.

[0024] In the examples shown so far, measuring device 7 carries out a time resolved measurement of the reflected pulses. This data is digitized and integrated in analyzer 8 as described in Ref. 2 for calculating the charge Q(t) at t = 19 ns. In another embodiment, the integration could also be carried out by analog circuitry before converting the charge Q(t = 19 ns) to a digital value.

[0025] Also, the integration could be started at a time later than t = 0 because the period up to t = 1 ns shows only a very weak dependence on the glucose level (see Fig. 7). For a strong signal, the integration should, however, start not later than 1 ns after the start of the pulse.

[0026] The parameter measured by measuring device 7 is the voltage V(t) applied to probe 5, which includes a contribution of the reflected pulse. It is the sum of the input voltage V0(t) and the reflected voltage R(t). Instead of integrating the voltage V(t) as shown in Ref. 2, it is also possible to use V(t = 19 ns) directly or to use another characteristic value derived from V(t), for example:

- The current IQ through probe 5 can be calculated as shown in Ref. 2 and its value after e.g. 19 ns can be used.
- The dielectric property $\varepsilon^*(\omega)$ calculated from Eqn. (14) - (17) of Ref. 2 at a frequency ω of approximately 50 MHz can be used.
- The difference of two voltages V(t) at different pre-

defined times t1 and t2 or a slope of the voltage V(t) at a given time can be used.

[0027] 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 sample comprising
a probe (5) having an end (6) to be applied to the sample in order to act as a fringing capacitor with field lines extending into the sample,
a pulse generator (2) for generating electric pulses in the probe (5),
a reflection measuring device (7) for measuring pulses reflected from the end of the probe (5), and
an analyzer (8) for determining at least one parameter (Q, V, I_Q, ε^*) of the reflected pulses measured by the measuring device (7) and for determining the glucose level from said parameter, wherein

    a) the reflection measuring device (7) is designed for carrying out at least one measurement in a period of 10 to 1000 ns after generation of a pulse in the pulse generator, or
    b) the pulses generated by the pulse generator (2) have rise and/or fall times of less than 1 ns and a duration of at least 10 ns.

2. The device of claim 1 having a memory (9) for storing calibration data for transforming the at least one parameter to the glucose level.

3. The device of any of the preceding claims wherein the reflection measuring device (7) is designed for carrying out a time resolved measurement of the reflected pulses.

4. The device of any of the preceding claims wherein the reflection measuring device (7) is designed for carrying out at least one measurement in a period of 10 to 1000 ns after generation of a pulse in the pulse generator.

5. The device of any of the preceding claims wherein the pulses generated by the pulse generator (2) have rise and/or fall times of less than 1 ns, and a duration of at least 10 ns.

6. The device of any of the preceding claims wherein the parameter is an integral over a period of time of a voltage (V) including the reflected pulse, and in particular wherein the period of time ends less than 100 ns after generating the corresponding pulse in the pulse generator.

7. The device of claim 6 wherein the integral starts less than 1 ns after generating the corresponding pulse in the pulse generator, and in particular wherein the integral starts when generating the corresponding pulse in the pulse generator.

8. The device of any of the preceding claims wherein the parameter is a value of a voltage (V) including the reflected pulse measured at a given time after generating the corresponding pulse in the pulse generator.

9. The device of any of the preceding claims wherein the parameter is a difference of two voltages including the reflected pulse measured at different times (t1, t2) after generating the corresponding pulse in the pulse generator.

10. The device of any of the preceding claims wherein the parameter is a slope of a voltage (V) including the reflected pulse measured at a given time after generating the corresponding pulse in the pulse generator.

11. A method for measuring a glucose level in a sample comprising
applying an end (6) of a probe (5) to the sample, wherein said probe acts as a fringing capacitor with field lines extending into the sample,
feeding electric pulses to the probe (5),
measuring a voltage (V) depending on pulses reflected from the end of the probe (5), and
determining at least one parameter (Q, V, I_Q, ε^*) of the voltage and determining the glucose level from said parameter, wherein

    a) at least one measurement in a period of 10 to 1000 ns after a pulse is carried out, or
    b) the pulses have rise and/or fall times of less than 1 ns and a duration of at least 10 ns.

Patentansprüche

1. Vorrichtung zur Messung eines Glukosespiegels in einer Probe umfassend
eine Sonde (5) mit einem Ende (6) für den Einsatz an der Probe, um wie eine Fringing-Kapazität (fringing capacitor) mit sich in die Probe erstreckende Feldlinien zu wirken,
einen Impulsgenerator (2) zur Generierung elektrischer Impulse in der Sonde (5),
ein Reflektionsmessgerät (7) zur Messung von Impulsen, welche vom Ende der Sonde (5) reflektiert werden, und

einen Analysator (8) zur Ermittlung mindestens eines Parameters (Q, V, I_Q, ε^*) des reflektierten, vom Reflektionsmessgerät (7) gemessenen Impulses und zur Bestimmung des Glukosespiegels aus dem Parameter, wobei

a) das Reflektionsmessgerät (7) zur Ausführung mindestens einer Messung in einer Zeitspanne von 10 bis 1000 ns nach der Generierung eines Impulses in dem Impulsgenerator ausgestaltet ist, oder
b) die vom Impulsgenerator (2) generierten Impulse haben Anstiegs- und/oder Abfallzeiten von weniger als 1 ns und eine Dauer von mindestens 10 ns.

2. Vorrichtung nach Anspruch 1, umfassend einen Speicher (9) zur Speicherung von Kalibrationsdaten für die Umwandlung des mindestens einen Parameters in den Glukosespiegel.

3. Vorrichtung nach einem der vorangehenden Ansprüche, wobei das Reflektionsmessgerät (7) zur Ausführung einer zeitaufgelösten Messung des reflektierten Impulses ausgestaltet ist.

4. Vorrichtung nach einem der vorangehenden Ansprüche, wobei das Reflektionsmessgerät (7) zur Ausführung mindestens einer Messung in einer Zeitspanne von 10 bis 1000 ns nach der Generierung eines Impulses in dem Impulsgenerator ausgestaltet ist.

5. Vorrichtung nach einem der vorangehenden Ansprüche, wobei die von dem Impulsgenerator (2) generierten Impulse Anstiegs- und Abfallzeiten von weniger als 1 ns und eine Dauer von mindestens 10 ns haben.

6. Vorrichtung nach einem der vorangehenden Ansprüche, wobei der Parameter ein Integral über eine Zeitspanne einer Spannung (V) ist, einschliesslich des reflektierten Impulses, und insbesondere wobei die Zeitspanne nach weniger als 100 ns nach der Generierung des zugehörigen Impulses in dem Impulsgenerator endet.

7. Vorrichtung nach Anspruch 6, wobei die Integrierung nach weniger als 1 ns nach der Generierung des zugehörigen Impulses in dem Impulsgenerator beginnt, und insbesondere wobei die Integrierung bei der Generierung des zugehörigen Impulses in dem Impulsgenerator beginnt.

8. Vorrichtung nach einem der vorangehenden Ansprüche, wobei der Parameter ein Spannungswert (V) ist, einschliesslich des reflektierten Impulses, welcher zu einer gegebenen Zeit nach der Generierung des zugehörigen Impulses in dem Impulsgenerator, gemessenen wird.

9. Vorrichtung nach einem der vorangehenden Ansprüche, wobei der Parameter eine Differenz zweier Spannungen ist, einschliesslich des reflektierten Impulses, welcher zu verschiedenen Zeitpunkten (t1, t2) nach der Generierung des zugehörigen Impulses in dem Impulsgenerator gemessenen wird.

10. Vorrichtung nach einem der vorangehenden Ansprüche, wobei der Parameter eine Steigung einer Spannung (V) ist, einschliesslich des reflektierten Impulses, welcher zu einer gegebenen Zeit nach der Generierung des zugehörigen Impulses in dem Impulsgenerator, gemessenen wird.

11. Verfahren zur Messung eines Glukosespiegels in einer Probe umfassend
einen Einsatz eines Endes (6) einer Sonde (5) an der Probe, wobei die Sonde als Fringing-Kapazität (fringing capacitor) mit sich in die Probe erstreckende Feldlinien wirkt,
eine Einspeisung von elektrischen Impulsen in die Sonde (5),
eine Messung einer Spannung (V) abhängig von Impulsen, welche vom Ende der Sonde (5) reflektiert werden,
eine Bestimmung mindestens eines Parameters (Q, V, I_Q, ε^*) der Spannung und eine Bestimmung des Glukosespiegels aus dem Parameter, wobei

a) mindestens eine Messung in einer Zeitspanne von 10 bis 1000 ns nach der Generierung eines Impulses ausgeführt wird, oder
b) die Impulse haben Anstiegs- und/oder Abfallzeiten von weniger als 1 ns und eine Dauer von mindestens 10 ns.

Revendications

1. Dispositif de mesure d'un taux de glucose d'un échantillon comprenant
une sonde (5) ayant une extrémité (6) à appliquer à l'échantillon afin de servir condensateur à effet de bord ayant des lignes de champ s'étendant dans l'échantillon,
un générateur (2) d'impulsions pour engendrer des impulsions électriques dans la sonde (5),
un dispositif (7) de mesure d'une réflexion pour mesurer des impulsions réfléchies par l'extrémité de la sonde (5), et
un analyseur (8) pour déterminer au moins un paramètre (Q, V, I_Q, ε^*) des impulsions réfléchies mesurées par le dispositif (7) de mesure et pour déterminer le taux de glucose à partir dudit paramètre, dans lequel

a) le dispositif (7) de mesure d'une réflexion est conçue pour effectuer au moins une mesure dans une durée de 10 à 1000 ns après production d'une impulsion dans le générateur d'impulsions, ou
b) les impulsions engendrées par le générateur (2) d'impulsions ont des temps de montée et/ou de descente de moins de 1 ns et une durée d'au moins 10 ns.

2. Dispositif suivant la revendication 1, ayant une mémoire (9) pour mémoriser des données d'étalonnage pour transformer le au moins un paramètre en le taux de glucose.

3. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel le dispositif (7) de mesure d'une réflexion est conçu pour effectuer une mesure résolue dans le temps des impulsions réfléchies.

4. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel le dispositif (7) de mesure d'une réflexion est conçu pour effectuer au moins une mesure dans une durée de 10 à 1000 ns après production des impulsions dans le générateur d'impulsions.

5. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel les impulsions produites par le générateur (2) d'impulsions ont des durées de montée et/ou de descente de moins de 1 ns et une durée d'au moins 10 ns.

6. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel le paramètre est une intégrale sur un laps de temps d'une tension (V) comprenant l'impulsion réfléchie et, en particulier, dans lequel le laps de temps se termine moins de 100 ns après production de l'impulsion correspondante dans le générateur d'impulsions.

7. Dispositif suivant la revendication 6, dans lequel l'intégrale débute moins de 1 ns après production de l'impulsion correspondante dans le générateur d'impulsions et, en particulier, dans lequel l'intégral débute lors de la production de l'impulsion correspondante dans le générateur d'impulsions.

8. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel le paramètre est une valeur d'un tension (V) comprenant l'impulsion réfléchie mesurée à un instant donné après production de l'impulsion correspondante dans le générateur d'impulsions.

9. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel le paramètre est une différence de deux tensions comprenant l'impulsion réfléchie mesurée à des instants (t1, t2) différents après production de l'impulsion correspondante dans le générateur d'impulsions.

10. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel le paramètre est une pente d'une tension (V) comprenant l'impulsion réfléchie mesurée à un instant donné après production de l'impulsion correspondante dans le générateur d'impulsions.

11. Procédé de mesure d'un taux de glucose dans un échantillon, dans lequel
on applique une extrémité (6) d'une sonde à l'échantillon, la sonde servant de condensateur à effet de bord ayant des lignes de champ s'étendant dans l'échantillon,
on envoie des impulsions électriques à la sonde (5),
on mesure une tension (V) en fonction d'une impulsion réfléchie par l'extrémité de la sonde (5), et
on détermine au moins un paramètre (Q, V, I_Q, ε^*) de la tension et on détermine le taux de glucose à partir dudit paramètre, dans lequel

a) on effectue au moins une mesure dans une durée de 10 à 1000 ns après une impulsion, ou
b) des impulsions ont des temps de montée et/ou de descente de moins de 1 ns et une durée d'au moins 10 ns.

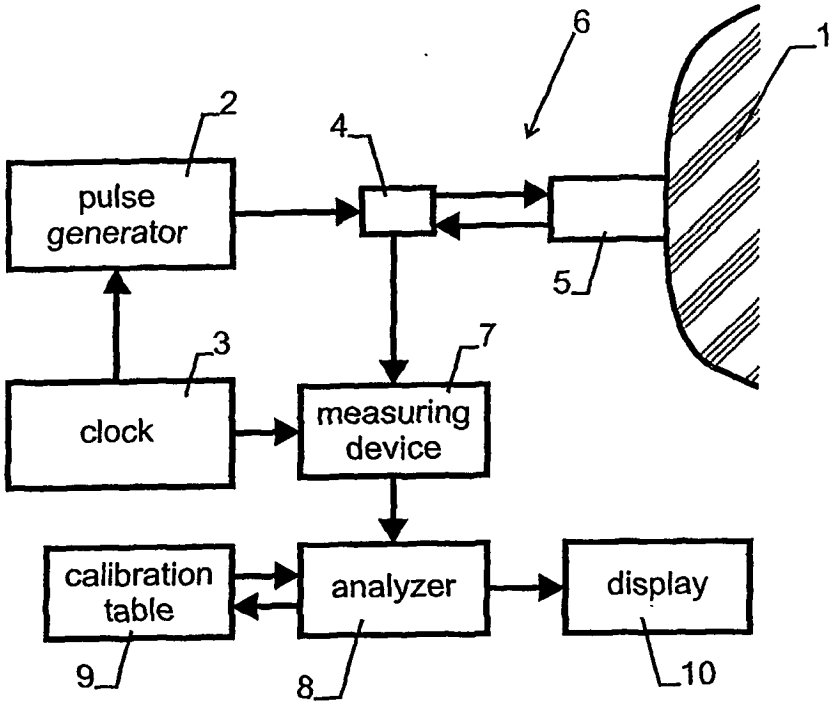
6
1
2
4
pulse generator
5
3
7
clock
measuring device
calibration table
analyzer
display
9
8
10

Fig. 1

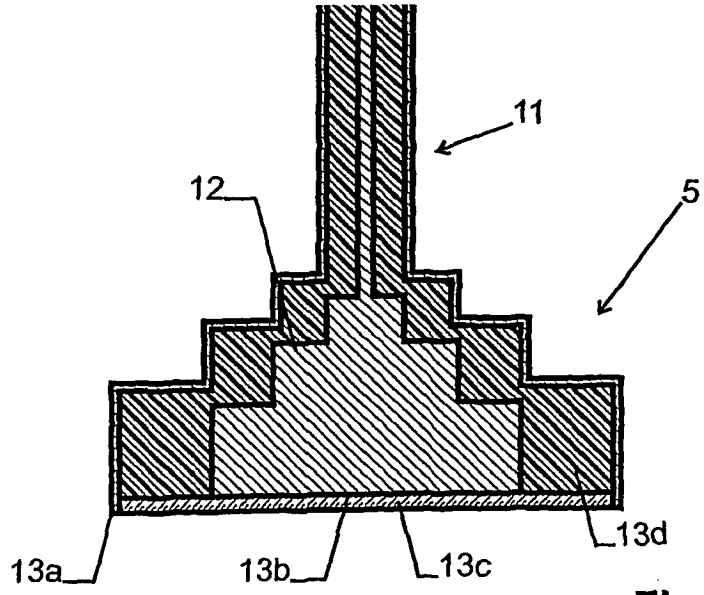
11
12
5
13a
13b
13c
13d

Fig. 2

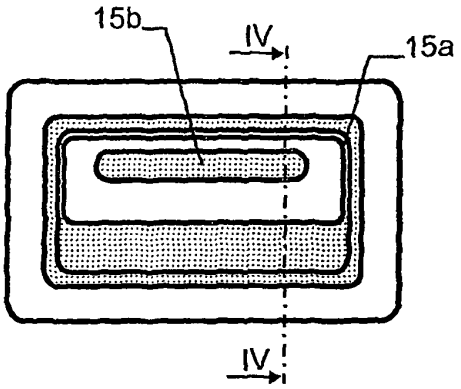

Fig. 3

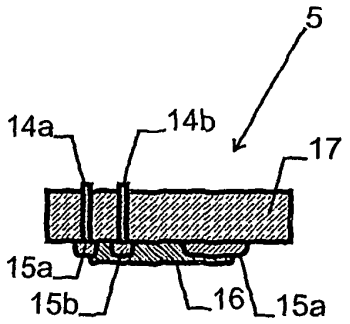

Fig. 4

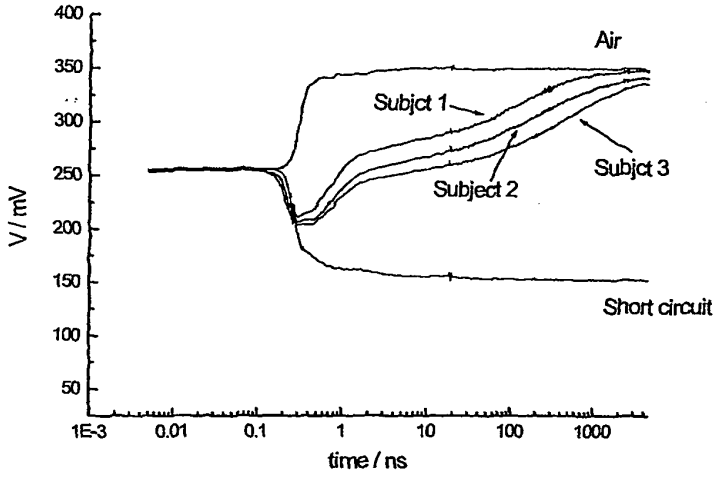

Fig. 5

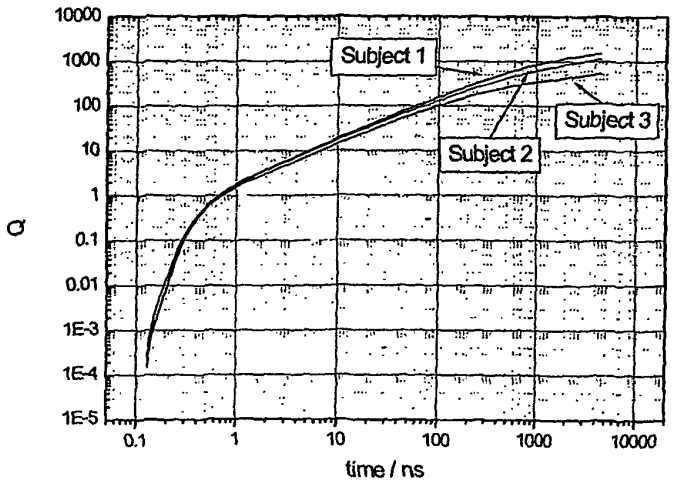

Fig. 6

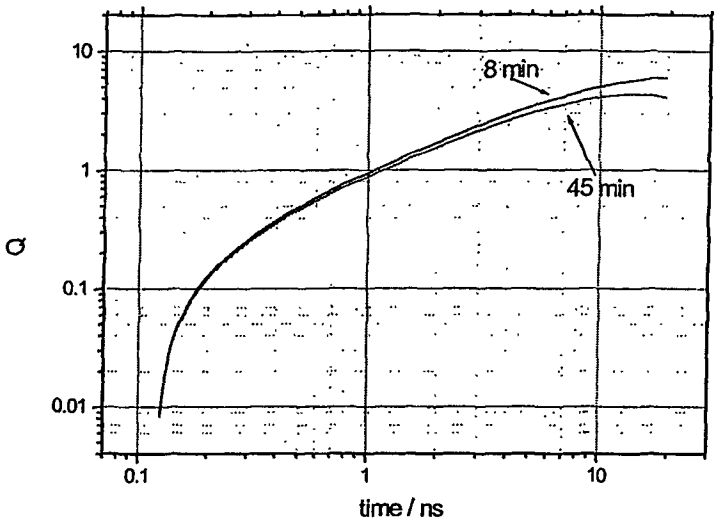
10
1
0.1
0.01
Q
0.1
1
10
time / ns
8 min
45 min

Fig. 7

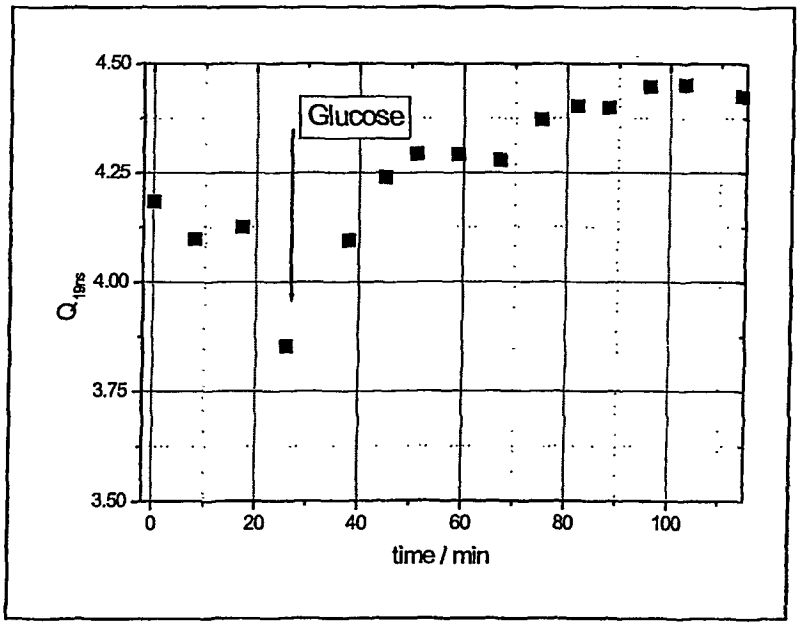
4.50
4.25
4.00
3.75
3.50
Q_{19ns}
0
20
40
60
80
100
time / min
Glucose

Fig. 8

REFERENCES CITED IN THE DESCRIPTION

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- EP 1092386 A **[0003]**
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- **Y. D. Feldman et al.** Time domain dielectric spectroscopy. An advanced measuring system. *Rev. Sci. Instrum.,* 1996, vol. 67 (9), 3208-3216 **[0009]**

专利名称(译)	测量葡萄糖的方法和装置		
公开(公告)号	EP1691671B1	公开(公告)日	2009-10-21
申请号	EP2002760503	申请日	2002-09-04
申请(专利权)人(译)	SOLIANIS HOLDING AG		
当前申请(专利权)人(译)	SOLIANIS HOLDING AG		
[标]发明人	CADUFF ANDREAS FELDMAN YURI		
发明人	CADUFF, ANDREAS FELDMAN, YURI		
IPC分类号	A61B5/00 A61B5/05		
CPC分类号	A61B5/05 A61B5/14532		
其他公开文献	EP1691671A1		
外部链接	Espacenet		

摘要(译)

为了测量受试者（1）的身体组织中的葡萄糖水平，将探针（5）施用于受试者的皮肤。来自脉冲发生器（2）的电脉冲被馈送到探头并部分地反射回测量装置（7），在那里进行时间分辨测量。使用来自校准表（9）的数据将从测量电压的积分获得的电荷转换为葡萄糖水平。该方法允许非侵入地监测葡萄糖。

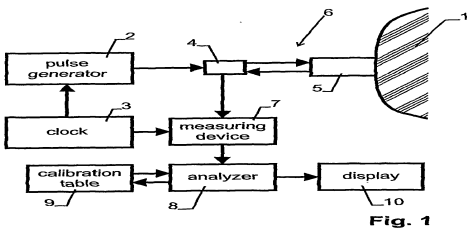

Fig. 1

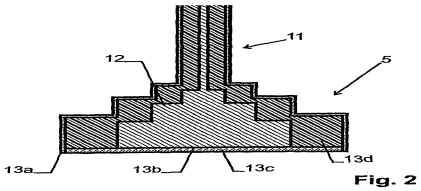

Fig. 2