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(54) **Implantable biosensor with automatic calibration**

Implantierbarer Biosensor mit automatischer Kalibrierung

Biocapteur implantable avec étalonnage automatique

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Description

[0001] The need for biomedical sensors and in particular glucose sensors for preventing hypoglycemic and hyperglycemic events in diabetics and for closed-loop controlling the insulin infusion via a portable or implantable pump is well known.

[0002] There are currently commercially available needle-like continuous measurement sensors, such as the Guardian & CGMS system of Medtronic company and another of Dexcom, and prior art US 2008/161666 to Feldman, US 7,354,420 to Stell, US 7,136,689 to Shults, but with a large error margin and a need for frequent calibration, 3-4 times daily with strips using a drop of blood (such as One Touch Ultra of LifeScan Inc) by piercing of the finger.

[0003] Patents and patent applications such as Burton US 2003/0143746, Arvind US 2008/0234562, Korf U S, 601, 3029, Lu Wang US 2007/0163894, disclose methods of self calibration, which are excellent for a large supply of glucose such as intravenously, but unsuitable for accurate interstitial measurements, where their use could result in a deficiency of the measured glucose due to the small available amount and to the small but substantial microdilution via dialysis. Additionally, the microdilution measurements are delayed, and their accuracy depends on the accuracy of the flow rate of the circulating liquid and the stability of the temperature.

[0004] In the patent application «Nanostructured composite material and biosensor containing same» EP 2135843 (Chaniotakis), an enhanced form sensor which has a long life- span against in vivo erosion is presented, although it lacks self calibration, which is essential for the reliability of closed- loop injections- an autonomous robotic system.

[0005] The need for a fully implantable artificial pancreas with simultaneous glucose measurement and robotic insulin infusion is known, but the presently available technologies do not meet the need for a reliable, and longlasting accurate measurement.

[0006] In the continuous measurement with a needle-like sensor in the subcutaneous tissue, the measurement of glucose differs from that of blood with time-delay and a different standard. Algorithms that are known through the relevant literature have been developed using neural networks and other methods (Mougiakakou, A. Prountzou, D. Iliopoulou, et al. Nikita, A. Vazeou, C.S. Bartsocas, "Neural Network based Glucose - Insulin Metabolism Models for Children with Type 1 Diabetes," Engineering in Medicine and Biology Conference 2006 (EMBC '06), IEEE, New York City, USA. September 2006, & Mougiakakou, K. Prountzou, et al. Nikita, "A Real Time Simulation Model of Glucose-Insulin Metabolism for Type 1 Diabetes Patients,"Engineering in Medicine and Biology Conference 2005 (EMBC '05), IEEE, Shanghai, China, September 2005) with which we can predict the blood glucose at the instant of the subcutaneous measurement and 30 minutes later.

[0007] Yellambalase et al presented at the IMTC 2006 (Instrumentation and Measurement Technology Conference, Sorrento, Italy 24-27 April 2006) a needle-type biosensor system with fully automated operations, in which an oxidase-coupled amperometric sensor with an oxygen depleting/generating actuator is interfaced with an electrochemical instrument and a perfusion system.

[0008] Microfluidic capillary blood absorption lumens are known in the art, in strip type glucose sensors, see Cul US 2006/0175205, Karinka US 6,863,800, Say US 2008/167543.

[0009] It is also known that glucose penetrates microporous nanostructures, such as a nanofiber matrix with embedded glucose oxidase receptor (GOX) and an overcoat of a biomimetically-composed matrix film of silicon oxide, see the patent application EP 2135843 (Chaniotakis).

[0010] It is an intention of the present invention to provide a method for a reliable, accurate measurement of biomedical parameters with self-calibration and the prediction of blood

[0011] It is an intention of the present invention to provide a method for a reliable, accurate measurement of biomedical parameters with self-calibration and the prediction of blood glucose for the timely information of the user and the medical assessment and for the automatic closed-loop insulin infusion.

BRIEF DESCRIPTION OF THE INVENTION

[0012] The present invention is defined in the independent claim 1. Preferred embodiments are defined in the dependent claims. It refers to a hybrid implementation of a dialysis circuit arranged in the interior of a needle sensor, the dialysis circuit being used only for calibration, with sensor calibrating fluids (liquids and/or gases) circulating in a closed microfluidic circuit, and of two or three conducting regions in the exterior of the sensor, as is known for enzymatic sensors, in contact with the body, wherein the layers of the working electrode are in fluid communication with the interior microfluidic circuit through an opening, in a novel backward microdialysis device. The enzyme measures what there is in excess, if there is a posterior supply it measures the posterior concentration, if the posterior flow is stopped, it measures the anterior body concentration. The measurement, after the calibration procedure, may preferably be effected exactly as disclosed in the patent application EP 2135843 (Chaniotakis), as in a standard subcutaneously implantable sensor.

[0013] By means of the present invention, hyperglycemia and hypoglycemia are predictable, thus enabling the patient to have time to react before it is too late, since presently in some cases, the patient is conscious, but immobilized without being able to react.

[0014] The biosensor provides the technical and operational ability for complete implantation, solving the problem of the consumption of the enzyme, and with telemet-

ric transfer of data from and to the body. It also solves the problems of constructing an artificial pancreas, both at the level of closed-loop algorithms and at the level of securely transporting fluids from and to the body.

BRIEF REFERENCE TO THE DRAWINGS

[0015]

Fig. 1	shows a front view of the preferred embodiments A-D of the disposable (needle).
Fig. 2A-E	show a section of the sensor at the level of the working electrode, especially the junction of two (A) or three (B-C) films or tubes (D) for constructing two microfluidic lumens 8, 9 and (E) a section of a completed dual lumen tube.
Fig.3	shows the layers of the working electrode above the diffusion hole.
Fig. 4A and B	show the complete continuous measurement sensor, the extracorporeal part of the sensor and the electronic control in contact therewith, with the implanted needle folded 4A or extended 4B.
Fig. 5	shows a working electrode in a waterproof microbox with openable lid.

DETAILED DESCRIPTION OF THE INVENTION

[0016] A disposable needle-sensor (Fig. 1) is used which is implantable subcutaneously through its small width part, while the larger width part contains bags, a pump and electric contacts. The sensor in its disposable, needle-like part is of microscopic width and thickness, consisting of an external surface in contact with the body, and of descending and ascending lumens internally to the needle, forming a hydraulic microfluidic circuit, through which pass the fluids for calibrating the sensor. The microfluidic circuit transports fluid down to the level of the working electrode from the input lumen 8 and from there it short-circuits with the output lumen 9 and passes to the drain vessel 7, as is known for microdialysis devices.

[0017] The so-called microfluidic circuit, in a preferred embodiment (Fig. 2A), can consist of two insulating layers 26, 27, impermeable to liquids or gases, of a material such as a plastic sheet, which constitute, with the proper use such as by mechanical junction or laser bonding or with a third layer of material 28 (Fig. 2B) as in the above patents, a microfluidic circuit 8, 9.

[0018] In another embodiment (Fig. 2C), the microfluidic circuit can consist of three films 26, 27, 28 which, joined at the edges, create an anterior lumen 8 and a posterior lumen 9 between first-second and second-third film. The intermediate film is cut or pierced at the level of the working electrode for the necessary short-circuit between cathode and anode. The first film 26 comports externally the measuring electrodes 1, 2, 3.

[0019] In another embodiment (Fig. 2D), the microfluidic circuit can consist of two lumens 8, 9 inside of each other and joined externally along an edge, and the exterior can be closed at the distal end. Also, the exterior lumen comprises the measuring electrodes.

[0020] In another embodiment (Fig. 2E) the microfluidic circuit consists of a double-lumen plastic biocompatible needle of 0,33 mm in external diameter (an approximately 30G needle) such as those manufactured by Microspec 4 Corporation Petersborough, NH, USA, which is hydraulically and mechanically connected with an extracorporeal part manufactured by micromolding, which contains the pumping system, microfluidic lumens and the calibrating/draining fluid bags.

[0021] At the external surface of the sensor in the above preferred embodiments, there are conductive material lanes made using the thin film technology (Method of fabricating thin film sensors US 5, 391, 250), or thick film coating such as the "micropenning technology" of very small dimensions, of Micropen Technologies New York USA. The so- called lanes are: The surfaces of the three electrodes 1, 2, 3 on the measuring needle from precious metals or carbon and/or silver as detailed below, the signal transport conductors in the extracorporeal part up to the contacts 15, 16, 17 for the electronic part, and the pump valve contacts 18- 23 with the conductor lanes up to the valves 10- 14. The conductive coating is overcoated, wherever needed, with an insulating film. In particular, there are micro- surfaces on the exterior of the needle as above for the two or three measuring electrodes 1 (working electrode, carbon or platinum), 2 (counter electrode, gold), 3 (reference electrode, Ag/ AgCl) as is known from the conventional glucose oxidase measurement and the corresponding contacts 17, 15, 16 for the constant part containing the electronics. Alternatively a ferrocyanide/ carbon working electrode may be used, preferably in combination with a carbon counter electrode and a silver reference electrode. Alternatively other low curing temperature conductive electrodes can be used.

[0022] In particular (Fig. 3), in the microfluidic system the carbon or ferrocyanate/carbon or platinum 29 of the working electrode 1, but also the plastic wall 26, have a microsurface allowing for diffusion, which may comprise a central microhole 4. The central microhole 4 may be made by laser, microdrilling or another method, after the deposition of the metal electrodes but before the layering of the working electrode with the nanomaterials 30-32 for glucose measuring. Alternatively the microsurface allowing for diffusion may comprise a layer 26 which is eroded in the area behind the working electrode layers 29-32 in order to become porous, or a conventional microdialysis membrane is applied in the area of layer

26 behind the working electrode layers 29-32. A hole that pierces or extends through the layers 29-32 (although the extension of the hole 4 through the layers 29-32 is not depicted in figures 2 A-E and 3) and other diffusive topologies will be referred, for the purposes of the present invention, as a "hole".

[0023] The inventive operation of the above hole 4 is such that the calibration fluids circulating in the microfluidic circuit 8, 9 wet the rear side of the laminate nanomaterial (Fig. 3) made of nanofibers 30, nanofibers comprising immobilized Glucose oxidase (Gox) 31, biomimetiworking electrode 1 and covers the communication hole 4 which is in communication with the rear closed microfluidic circuit 8. Other simpler electrode chemistries may also be used to minimize costs. With the same ease that glucose in the interstitial space penetrates this layering from the anterior part and is measured by the two or three electrodes 1, 2, 3 using a potentiostat instrumentation as is known in the art, the calibration fluids penetrate inversely, from rear to front through said hole 4 by osmotic pressure proportionally to the concentration differential. The system is a hybrid of a backward microdialysis device in the interior side with replacement of the conventional diffusion membrane by the layering of nanomaterlals (Fig. 3) of the working electrode, and of a conventional needle-like sensor in the exterior side (Fig. 1). The technique is referred as backward microdialysis because diffusion proceeds to the exterior, where the measuring system is located, in contrast with the conventional microdialysis wherein biological fluids diffuse towards the circulating fluid and the measurement takes place inside the closed hydraulic circuit. The calibrating fluids may be one or more glucose concentrations (bag 6), preferably in injectable form since it is known that glucose is not stable with time, alternating with wash fluid (bag 5) without any glucose, preferably consisting of deionized water, buffer, surfactants, and preservatives. Those fluids are stored in micro-bags 5, 6 on the exterior extracorporeal part of the disposable enlarged section of the sensor. For the circulation of those fluids are preferably employed the noiseless, low cost and good linearity and low consumption electroactive polymers (EAP), such as in www.artificialmuscle.com, in three-finger configuration 10 or 11 fluid selecting valves working as input valves, a fluid transport finger 12, and an output valve 14 as a conventional peristaltic finger valve 3, wherein the optional finger 13 prevents the downflow of the fluid to the drain 7, alternatlvefy a piston pump may be used, with two passive or active valves by micromolding. Alternatively, piezoelectric pumping devices and valves may be employed, such as those of Bartels www.bartels-mikrotechnik.de, or electrostatic pumps such as MEMS chips.

[0024] Alternatively for pumping may be used the pumping methods disclosed in US 6,013,029. The amounts needed are of the order of a few microliters and the whole system is particularly miniaturized.

[0025] The calibration procedure is similar to the prior art (Arvind US2008/0234562) sequence of three calibration fluids, with the exception constituting the inventive step that for the main glucose measurement, the calibration fluid is the last aqueous buffer that remains immobile during the intervals between calibrations.

[0026] During calibration, the glucose excess arrives rapidly from the rear and the measurement of the upper calibration point is fast, despite the low diffusion of glucose to the interstitial fluid. That is, due to the subsequent next calibration step depletion of intersticial fluid glucose backwards in the water of the microfluidic circuit, the body glucose penetrates the layers of the sensor to the rear, and the delay to deplete glucose in the interstitial fluid and to lower the concentration is small. The sensor "sees" this as an asymptotic curve tending to zero, and from the corresponding mathematical analysis calculates the theoretical zero. The glucose concentration of the patient is not affected by this calibration procedure because of two reasons. On one hand a very low amount is transported towards and from the body, this low amount being controlled by the size of the hole 4 and the density of the layers 29-32 of the sensor working electrode; and the increased level of glucose in the body due to the first glucose solution is cancelled by the subsequent lowering due to the second aqueous fluid. On the other hand the glucose concentration of the patient is not affected because the entire calibration procedure only lasts for a few seconds. The back fluid does not affect the main measurement, since it is situated behind the enzyme. The only negative effect achieved is that glucose continues to penetrate through the nanofibers to the back lumen until the concentrations are equilibrated, which is realized very rapidly, in one second, according to theory (diffusion time = x^2D wherein x = diffusion distance and D = diffusion constant 6,7X10-6 cm^2/sec for glucose in a low viscosity fluid such as water). Moreover, in most of the proposed embodiments of the invention, the plastic sheets or the elastic tubes are reconnected by the pressure of the body tissues, if there is no circulating fluid (pump stopped without circulation during the most part of the main measurement) and thus there is no back fluid during the main measurement or the concentration of the fluid is equilibrated.

[0027] In a preferred embodiment behind the hole 4 of the sensor wall 26 to the microfluidic channel 8, a miniature sub milllimeter valve is arranged capable of closing the hole 4 from inside the microfluidic channel. The valve remains closed during normal measurement and opens during calibration, to prevent circulation of body glucose backwards into the microfluidic channel. This type of angled valve is produced e.g. by company www.micromuscle.com.

[0028] The disposable part of the invention is similar to that of the Feldman patent application US 2008/01161666, but the extracorporeal part also contains the pumping systems 12, 14 with the valves 10, 11, the calibration fluid 5, 6 and drain 7 vessels, the ends of the input 8 and output 9 lumens, in the vessels 5 or 6 and 7 respectively, and the two or three contacts of the elec-

trodes 15, 16, 17, together with the contacts of the linear actuators EAP 18-23 (five digital inputs, equal to the fingers plus ground - GND).

[0029] Fig. 4 shows the extracorporeal part of the sensor, and electronic control in touch with it, and the implantable plastic needle 40. The needle 40 may be either angled (Fig. 4A) or straight (Fig. 4B), i.e. the needle can be straight within the embodiment as shown or bended - horizontal then angled. In Figures 4A and 4B, numeral 24 denotes the body under the skin, where the glucose concentration of the interstitial fluid is measured. Numeral 25 refers to the disposable sensor including electronics or plus electronics on top. Numeral 40 refers to the needle (as shown in the bottom of fig 1A/B) having microfluidic channel 8/9 in its interior (see sectional view of figs. 2A-E) and externally the electrodes (fig 2E or fig 1C/D).

[0030] The permanent, non-disposable electronic part of the sensor contains an analog or combined analog and digital potentiometer as is known, Wang US 2007/0163894, and the processing section, together with telemetry, according to patent US 7,161,484 to Tsoukalis, preferably Blue Tooth Low Energy (BLE) Continua protocol for an open system or Nordic Semiconductor ANT ultra low power embedded protocol for a closed system to others. The measurements are preferably collected in a mobile collecting and data broadcasting system with a permanent TCP/IP connection (through GPRS or WiFi or WiMax) such as the commercially available IP-Connect and server www.micrelcare.net of Micrel.

[0031] The system may be powered by a battery, rechargeable battery, rechargeable battery through magnetic waves (low frequency RF), or by pumping energy (energy harvesting) from the body glucose and other methods known in the art.

[0032] The processing section comprises neural networks capable of processing the glucose measurement in the subcutaneous tissue taking into account the insulin injection; and a prediction of blood glucose concentration is output, current and 30 minutes, for triggering alerts. The processing section preferably contains means capable of running the predictive algorithms of blood glucose according to the numerous above publications as known in the art, in such a way that we can use the current value in closed-loop injection algorithms, and the 30 minutes prediction for alerting the user of an imminent hyperglycemia or hypoglycemia and, through the long range system (GPRS) to notify the attending doctor and the ambulance. The glucose measurement, the insulin injection and the uptake or consumption through exercise of carbohydrates and lipids are employed for the prediction.

[0033] Preferably the processing section comprises means for current glucose prediction wherein those means allow for algebraic addition of the concentration prediction by means of the kinetics of meal digestion and of the prediction of the consumption kinetics during and after exercise, to obtain a global blood glucose concentration prediction for triggering alarms and calculating the closed-loop injection. Further preferably the processing section comprises means for feeding differences between the predicted blood glucose value and the desired glucose value to a PID (proportional/Integral/Differential) algorithm to obtain the corresponding insulin injection correction and the robotic (closed loop) insulin injection correction.

[0034] In case of closed-loop injection/measurement, the interconnection between sensor and pump may be effected by cable or the cable may be used in a bad interconnection alert. The closed-loop system, part of which is the sensor of the present invention, is composed of the present glucose sensor with means for the prediction of current blood glucose concentration, the insulin pump containing both means for closed-loop algorithms and conventional software as an alternate safety measure (plan B) in the event of an interconnection error, and a real time program through said local or long range telemetry system. The injection algorithm comprises:

data entry:

- previous value of insulin injection rate of the pump (output Rn-1),
- prediction of blood glucose of the sensor of the present invention,
  algorithmic prediction of additional glucose to the blood per minute (digestion and work metabolism kinetics) after informing the system of meals or exercise by means of the above hand-held mobile application system, that corrects the above prediction of the present sensor due to external parameters that cannot be correctly predicted exclusively by the rate of change of glucose,
- other known information about the patient from data bases deriving from the server through the internet,
- PID algorithm known in the art (US 7,354,420) for processing the above processed
  data and calculating corrections and

data output:

the current insulin injection rate of the system's pump Rn.

[0035] Preferably the biosensor comprises a mechanical introducer for the implantation. The sensor is implanted using an introducer similar to the prior art (Funderburk US2004/0133164), and the non-disposable part which has electric contacts with the mobile part, is fixed to the skin with self-adhesive, for this reason the whole non-disposable part is particularly miniaturized.

[0036] This biosensor of the present invention is appropriate for being used as an implantable sensor or in a combination of insulin pump- sensor (artificial pancreas) with the addition of removable lids 33 (Fig. 5) of elec-

troactive polymers (EAP), such as those in www.micromuscle.com to a plurality of sensors, wherein each sensor opens its lid for a measurement and closes it immediately after that for minimizing the enzyme erosion. Thus there is provided an implantable device comprising a plurality of biosensors comprising at least one biosensor of the type described above wherein each sensor comprises a lid, preferably of electroactive polymers. The lids are capable of exposing only the currently active sensor for a short interval, necessary for a measurement or a calibration and closing just after the measurement or calibration to protect the enzyme from erosion, while the others remaining hermetically closed and wherein said lids can have a protective filter to avoid the introduction of larger than desired particles or molecules. In this way the lifetime of the sensor increases from one month, as reported in the patent application EP 2135843 (Chaniotakis), to one year by being used only for a few minutes daily in total. This constitutes an inventive step compared to the patent applications of the Microchips company, Scott US 2009/030404, Santini US 2008/11536, where the exposure of the various sensors is effected by electroerosion and thus the sensor cannot be covered again for protection when exposed. In the device of the present invention, when a sensor shows a low sensitivity during the calibration, it is disconnected and replaced by another neighboring one which is closed up to that moment. Thus, a small number of sensors can maintain an active measurement for many years, which is essential for an implantable instrument.

[0037] In the implantable device the self-calibration is maintained. To achieve that, a transdermal needle is needed to fill the subcutaneously implanted artificial pancreas with holes at various heights, for the respective vessels disposed at different heights, filling with insulin, aqueous buffer, calibration and corrective injection glucose solution, and removing the drained fluid. The fluid transport is made by a special transport pump comprising position sensors in order to assess the correct position of the multiple fluid transport needle and to avoid a deleterious injection in the body. The transport of fluids is made automatically possible only after validating the correct position, and stops if a sensor signals a problem.

[0038] Preferably the implantable artificial pancreas comprises

- a sensor as described above
- means for closed-loop injection algorithms,
- vessels for insulin, aqueous buffer, calibration and corrective injection glucose solution, those vessels being arranged at different heights, the vessels being elastic or collapsible bags,
- insulin-injection dual pumps effecting the transport of insulin injection and calibration fluids and the drainage of calibration wastes.

[0039] In a preferred embodiment the implantable artificial pancreas comprises a filling pumping system comprising a multilumen catheter which has at its end a needle (more specifically, a multiple fluid transport needle) with position sensors for assessing the correct position of the needle, the multilumen having holes at various heights provided with valves allowing for communication with the vessels of the artificial pancreas and interruption of the fluid transport from and toward the artificial pancreas in the event of the identification of an error by said sensors.

[0040] The above-described filling pumping system can also be used for purposes independent of the implantable artificial pancreas of the present invention.

Claims

1. Self-calibrating disposable biosensor comprising an electronic part and an electrochemical part **characterized in that** the electrochemical part comprises

   - a needle having in its interior a microfluidic circuit (8, 9) for the circulation of at least one calibration fluid,
   - two or three electrodes (1,2,3) arranged on the on the external surface of the needle which is in contact with the body, one of the electrodes being a working electrode (1) comprising porous bio-chemical sensing materials (30-32), configured to be in contact with living tissues after the implantation,
   and
   - means (4) for fluid communication of the microfluidic circuit (8,9) with the layers of the working electrode.

2. Biosensor as in claim 1, wherein in the disposable nonimplantable extracorporeal part comprises bags (5,6) with or without a protective metal cover, the bags containing calibration and draining fluids, a drain vessel (7) and pumps and flow control valves and contacts with the permanent electronic part both for the measurement and for the control of the calibration microflow, or alternatively the whole circuit of bag pumping and measuring electronics consists of an electromechanical MEMS circuit and/or of an electromechanical autonomous circuit.

3. Biosensor as in any preceding claim for measuring glucose, wherein the working electrode (1) comprises a conductive base made preferably of carbon or ferrocyanide/carbon or platinum or gold (29), nanofibers (30) with embedded immobilized glucose oxidase (31) and a coating of biomimetically synthesized silicon dioxide matrix (32)

4. Biosensor as in any preceding claim wherein In the interior microfluidic circuit (8, 9) intermittently one or

more glucose solutions and fluids without glucose can be circulated for the self-calibration with a curve of two or more points of the sensor.

5. Biosensor as in any preceding claim, wherein the pumping of the microflow and the selection of the circulating fluid is effected through pumping fingers and valves (10-14) of electroactive polymers.

6. Biosensor as in any preceding claim, wherein the electronic part comprises a processing section comprising neural networks capable of processing the glucose measurement in the subcutaneous tissue taking into account the insulin injection and of putting out a prediction of venal blood glucose concentration, current and 30 minutes, for triggering alerts.

7. Biosensor as in claim 6, wherein the processing section comprises means for current glucose prediction, those means are configured to allow for algebraic addition of the concentration prediction by means of the kinetics of meal digestion and of the prediction of the consumption kinetics during and after exercise, to obtain a global blood glucose concentration prediction for triggering alarms and to calculate the closed-loop injection.

8. Biosensor as in claim 7, wherein the processing section comprises means for feeding differences between the predicted blood glucose value and the desired glucose value preferably to a PID (proportional/Integral/Differential) algorithm to obtain the corresponding insulin injection correction and the robotic (closed loop) insulin injection correction.

9. Biosensor as in any preceding claim further comprising a mechanical introducer for the implantation.

10. Implantable device comprising a plurality of biosensors comprising at least one biosensor according to any of claims 1-9, wherein each sensor comprises a lid, preferably of electroactive polymers, the lids being capable of exposing only the currently active sensor for a short interval, necessary for a measurement or a calibration and remaining closed for most of the day, while the others remaining hermetically closed till replacing the active one and wherein said lids can have a protective filter to avoid the introduction of larger than desired particles or molecules.

11. Implantable artificial pancreas comprising

- a sensor according to any of claims 1-9,
- means for closed-loop injection algorithms,
- vessels for insulin, aqueous buffer, calibration and corrective injection glucose solution, those vessels being arranged at different heights, the vessels being elastic or collapsible bags.
- insulin-injection dual pumps effecting the transport of insulin injection and calibration fluids and the drainage of calibration wastes.

12. Implantable artificial pancreas according to claim 11, comprising a filling pumping system comprising a multilumen catheter which has at its end a needle with position sensors for assessing the correct position of the needle, the multilumen having holes at various heights provided with valves configured to allow for communication with the vessels of the artificial pancreas and interruption of the fluid transport from and toward the artificial pancreas in the event of the identification of an error by said sensors.

Patentansprüche

1. Selbstkalibrierender Einweg-Biosensorumfassend einen elektronischen Teil und einen elektrochemischen Teil,
dadurch gekennzeichnet, dass der elektrochemische Teil umfasst:

- eine Nadel, die in ihrem Inneren einen Mikrofluidkreislauf (8, 9) zur Zirkulation mindestens einer Kalibrierflüssigkeit aufweist,
- zwei oder drei Elektroden (1, 2, 3) angeordnet auf der äußeren Oberfläche der Nadel, die mit dem Körper in Kontakt steht, wobei eine der Elektroden eine Arbeitselektrode (1) ist umfassend poröse biochemische Erfassungsmaterialien (30 - 32), die dazu konfiguriert sind, nach der Implantation mit lebenden Geweben in Kontakt zu stehen, und
- Mittel (4) zur Flüssigkeitskommunikation des Mikrofluidkreislaufs (8, 9) mit den Schichten der Arbeitselektrode.

2. Biosensor nach Anspruch 1, wobei der nicht implantierbare extrakorporale Einwegteil Beutel (5, 8) mit oder ohne eine Metallschutzabdeckung, wobei die Beutel Kalibrier- und Entleerungsflüssigkeiten enthalten, einen Entleerungsbehälter (7) und Pumpen und Strömungssteuerungsventile und Kontakte mit dem permanenten elektronischen Teil sowohl zur Messung als auch zur Steuerung der Kalibriermikroströmung umfasst oder alternativ dazu der gesamte Kreislauf der Beutelpump- und Messelektronik aus einer elektromechanischen MEMS-Schaltung und/oder einer elektromechanischen autarken Schaltung besteht.

3. Biosensor nach einem vorhergehenden Anspruch zum Messen von Glukose, wobei die Arbeitselektrode (1) eine leitfähige Basis, die vorzugsweise aus Kohlenstoff oder Ferrocyanid/Kohlenstoff oder Platin oder Gold hergestellt ist (29), Nanofasern (30) mit

eingebetteter immobilisierter Glucoseoxidase (31) und eine Beschichtung aus einer biomimetisch synthetisierten Siliciumdioxidmatrix (32) umfasst.

4. Biosensor nach einem vorhergehenden Anspruch, wobei im inneren Mikrofluidkreislauf (8, 9) intermittierend eine oder mehrere Glukoselösungen und Flüssigkeiten ohne Glukose zur Selbstkalibrierung mit einer Kurve von zwei oder mehr Punkten des Sensors zirkuliert werden können.

5. Biosensor nach einem vorhergehenden Anspruch, wobei das Pumpen der Mikroströmung und die Auswahl der zirkulierenden Flüssigkeit durch Pumpfinger und -ventile (10-14) aus elektroaktiven Polymeren bewirkt wird.

6. Biosensor nach einem vorhergehenden Anspruch, wobei der elektronische Teil einen Verarbeitungsabschnitt umfassend neuronale Netze umfasst, die in der Lage sind, die Glukosemessung im subkutanen Gewebe unter Berücksichtigung der Insulininjektion zu verarbeiten und eine gegenwärtige und 30-Minuten-Vorhersage der Venenblutglukosekonzentration auszugeben zum Auslösen von Warnungen.

7. Biosensor nach Anspruch 6, wobei der Verarbeitungsabschnitt Mittel zur gegenwärtigen Glukosevorhersage umfasst, wobei diese Mittel dazu konfiguriert sind, eine algebraische Addition der Konzentrationsvorhersage mittels der Kinetik der Essensverdauung und der Vorhersage der Verbrauchskinetik während und nach Leibesübungen zu ermöglichen, um eine globale Blutglukosekonzentrationsvorhersage zum Auslösen von Warnmeldungen zu erhalten und die Regelkreis-Injektion zu berechnen.

8. Biosensor nach Anspruch 7, wobei der Verarbeitungsabschnitt Mittel zum Einspeisen von Differenzen zwischen dem vorhergesagten Blutglukosewert und dem gewünschten Glukasewert vorzugsweise in einen PID (Proportional/ Integral/ Differential-)-Algorithmus umfasst, um die entsprechende Insulininjektionskorrektur und die robotische (Regelkreis) Insulininjektionskorrektur zu erhalten.

9. Biosensor nach einem vorhergehenden Anspruch, der weiterhin eine mechanische Einführhilfe zur Implantation umfasst.

10. Implantierbare Vorrichtungumfassend mehrere Biosensoren umfassend mindestens einen Biosensor nach einem der Ansprüche 1 - 9, wobei jeder Sensor einen Deckel vorzugsweise aus elektroaktiven Polymeren umfasst, wobei die Deckel in der Lage sind, nur den gegenwärtig aktiven Sensor für ein kurzes für eine Messung oder eine Kalibrierung erforderliches Zeitintervall freizulegen , und für den Großteil des Tages geschlossen zu bleiben, während die anderen hermetisch verschlossen bleiben, bis der aktive gewechselt wird, und wobei die Deckel einen Schutzfilter aufweisen können, um das Einbringen von größeren als den gewünschten Teilchen oder Molekülen zu vermeiden.

11. Implantierbare künstliche Bauchspeicheldrüse, die Folgendes umfasst:

- einen Sensor nach einem der Ansprüche 1 - 9,
- Mittel für Regelkreis-Injektionsalgorithmen,
- Behälter für Insulin, wässrigen Puffer, Glukoselösung zur Kalibrierung und Korrekturinjektion, wobei diese Behälter in unterschiedlichen Höhen angeordnet sind, wobei die Behälter elastische oder zusammenlegbare Beutel sind,
- Insulininjektionsdualpumpen, die den Transport von Insulininjektions- und Kalibrierflüssigkeiten und den Abfluss von Kalibrierreststoffen bewirken.

12. Implantierbare künstliche Bauchspeicheldrüse nach Anspruch 11 umfassend ein Füllpumpensystem umfassend einen Multilumen-Katheter, der an seinem Ende eine Nadel mit Positionssensoren zum Beurteilen der korrekten Position der Nadel aufweist, wobei das Multilumen Löcher in verschiedenen Höhen aufweist, die mit Ventilen versehen sind, die dazu konfiguriert sind, eine Kommunikation mit den Behältern der künstlichen Bauchspeicheldrüse und ein Unterbrechen des Flüssigkeitstransports von und zu der künstlichen Bauchspeicheldrüse im Fall der Feststellung eines Fehlers durch besagte Sensoren zu ermöglichen.

Revendications

1. Biocapteur jetable auto-étalonneur comprenant une partie électronique et une partie électrochimique, **caractérisé en ce que** la partie électrochimique comprend

- une aiguille comportant à l'intérieur un circuit microfluidique (8, 9) pour la circulation d'au moins un fluide d'étalonnage,
- deux ou trois électrodes (1, 2, 3) agencées sur la surface externe de l'aiguille qui est en contact avec le corps, une des électrodes étant une électrode de travail (1) comprenant des matériaux de détection biochimiques poreux (30-32) configurés pour être en contact avec des tissus vivants après l'implantation, et
- des moyens (4) pour la communication fluidique du circuit microfluidique (8, 9) avec les couches de l'électrode de travail.

2. Biocapteur selon la revendication 1, dans lequel la partie extracorporelle non implantable jetable comprend des sacs (5, 6) avec ou sans couverture métallique de protection, les sacs contenant des fluides d'étalonnage et de drainage, un récipient de drainage (7) et des pompes et des valves de régulation de débit et des contacts avec la partie électronique permanente à la fois pour la mesure et pour la commande du microflux d'étalonnage, ou en variante le circuit entier d'éléments électroniques de pompage et de mesure de sac est constitué d'un circuit MEMS électromécanique et/ou d'un circuit autonome électromécanique.

3. Biocapteur selon une quelconque revendication précédente pour mesurer du glucose, dans lequel l'électrode de travail (1) comprend une base conductrice faite de préférence de carbone ou de ferrocyanure/carbone ou de platine ou d'or (29), des nanofibres (30) avec une oxydase de glucose immobilisée incorporée (31) et un revêtement de matrice de dioxyde de silicium synthétisé de façon biomimétique (32).

4. Biocapteur selon une quelconque revendication précédente, dans lequel, dans le circuit microfluidique intérieur (8, 9), de façon intermittente, une ou plusieurs solutions de glucose et un ou plusieurs fluides sans glucose peuvent circuler pour l'auto-étalonnage du capteur avec une courbe de deux, ou plusieurs points.

5. Biocapteur selon une quelconque revendication précédente, dans lequel le pompage du microflux et la sélection du fluide de circulation sont effectués par l'intermédiaire de doigts de pompage et de valves (10- 14) en polymères électroactifs.

6. Biocapteur selon une quelconque revendication précédente, dans lequel la partie électronique comprend une section de traitement comprenant des réseaux neuronaux capables de traiter la mesure de glucose dans le tissu sous-cutané en prenant en compte l'injection d'insuline et de produire une prédiction de glycémie veineuse, actuelle et à 30 minutes, pour déclencher des alertes.

7. Biocapteur selon la revendication 6, dans lequel la section de traitement comprend des moyens pour la prédiction de glucose actuelle, ces moyens sont configurés pour permettre l'addition algébrique de la prédiction de concentration au moyen de la cinétique de digestion de repas et de la prédiction de la cinétique de consommation durant et après l'exercice, pour obtenir une prédiction de concentration de glycémie globale pour déclencher des alarmes et pour calculer l'injection à boucle fermée.

8. Biocapteur selon la revendication 7, dans lequel la section de traitement comprend des moyens pour fournir des différences entre la valeur de glycémie prédite et la valeur de glucose souhaitée, de préférence à un algorithme PID (proportionnel/intégral/différentiel), pour obtenir la correction correspondante d'injection d'insuline et la correction d'injection d'insuline robotique (boucle fermée) .

9. Biocapteur selon une quelconque revendication précédente, comprenant en outre un introducteur mécanique pour l'implantation.

10. Dispositif implantable comprenant une pluralité de biocapteurs comprenant au moins un biocapteur selon une quelconque des revendications 1 à 9, dans lequel chaque capteur comprend un couvercle, de préférence en polymères électroactifs, les couvercles étant capables d'exposer seulement le capteur actuellement actif pendant un court intervalle nécessaire pour une mesure ou un étalonnage et restant fermés pendant la plupart de la journée, alors que les autres restent fermés hermétiquement jusqu'au remplacement de celui actif et dans lequel lesdits couvercles peuvent posséder un filtre de protection pour éviter l'introduction de particules ou de molécules plus grosses que ce qui est souhaité.

11. Pancréas artificiel implantable comprenant

- un capteur selon une quelconque des revendications 1 à 9,
- des moyens pour des algorithmes d'injection à boucle fermée,
- des récipients pour insuline, tampon aqueux, étalonnage et solution d'injection de glucose corrective, ces récipients étant agencés à des hauteurs différentes, les récipients étant des sacs élastiques ou aplatissables,
- des pompes doubles d'injection d'insuline effectuant le transport de fluides d'injection d'insuline et d'étalonnage et le drainage de déchets d'étalonnage.

12. Pancréas artificiel implantable selon la revendication 11, comprenant un système de pompage de remplissage comprenant un cathéter multilumière qui comporte, à son extrémité, une aiguille avec des capteurs de position pour détecter la position correcte de l'aiguille, la multilumière comportant des trous à diverses hauteurs pourvus de valves configurées pour permettre la communication avec les récipients du pancréas artificiel et l'interruption du transport de fluide à partir du, et vers le, pancréas artificiel dans le cas de l'identification d'une erreur par lesdits capteurs.

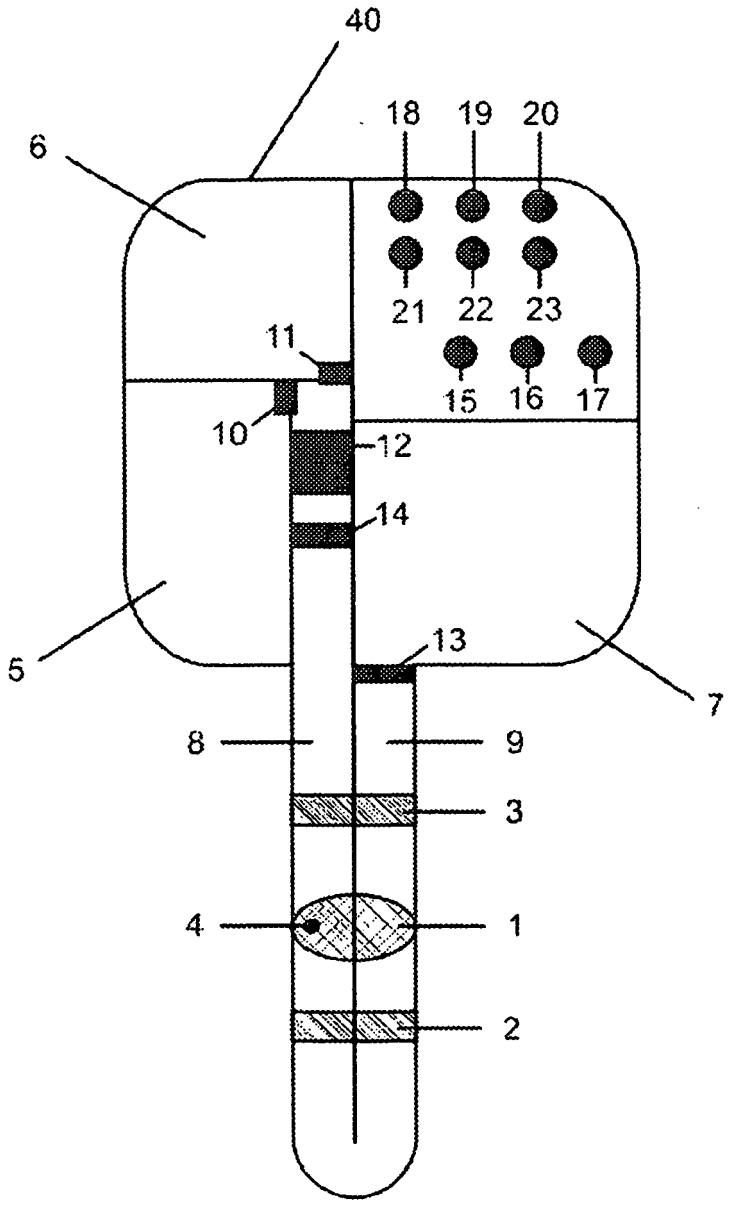

Fig. 1a/b

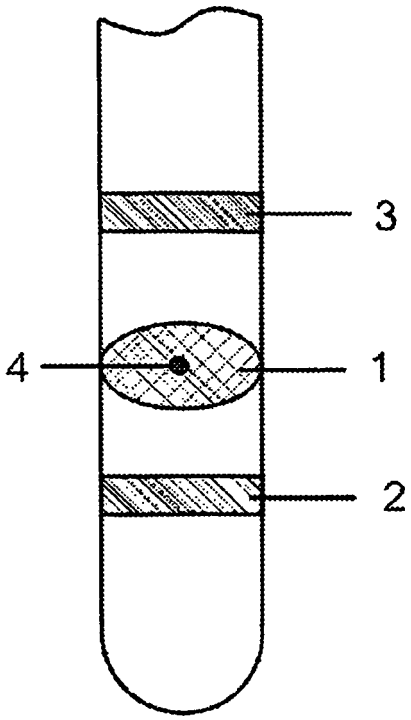

Fig. 1c/d

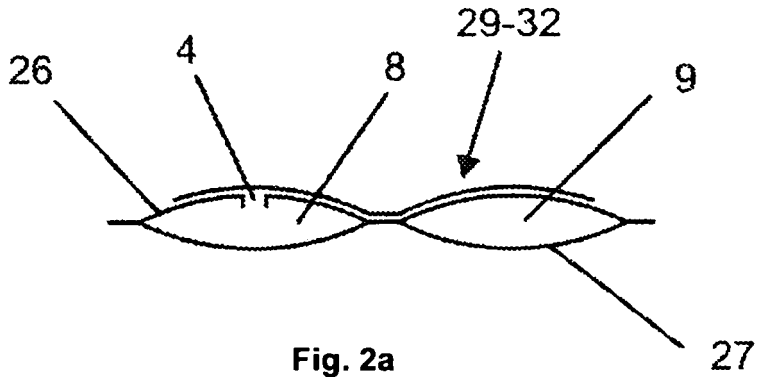

Fig. 2a

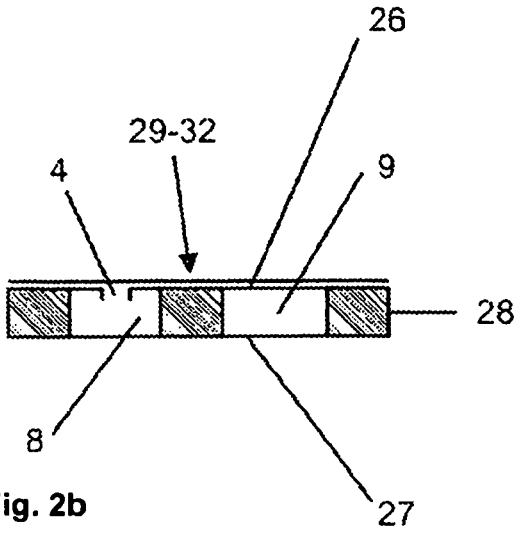

Fig. 2b

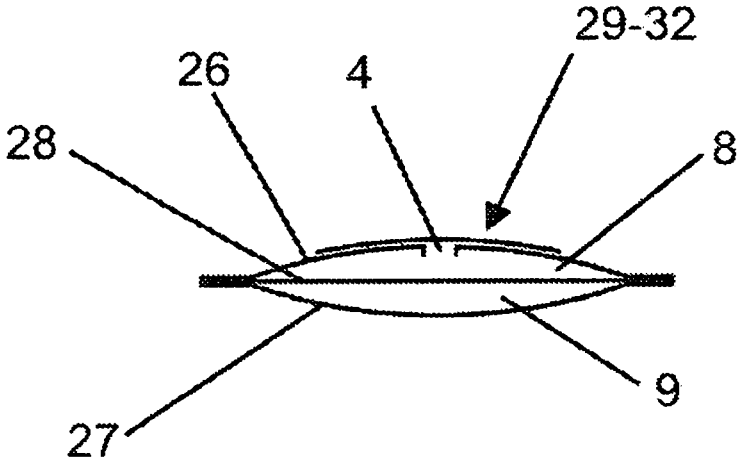

Fig. 2c

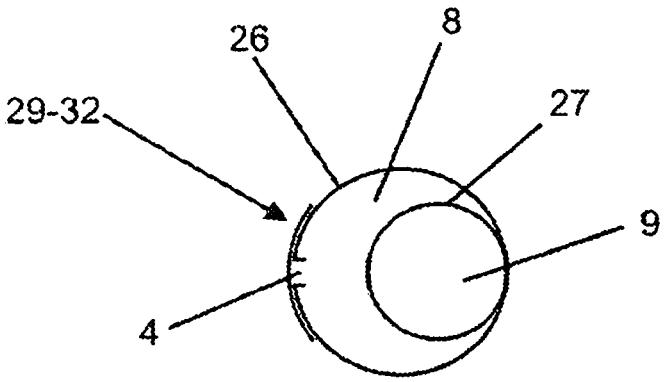

Fig. 2d

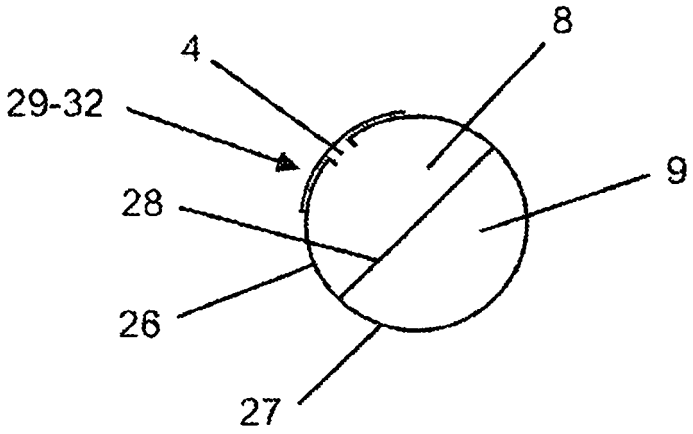

Fig. 2e

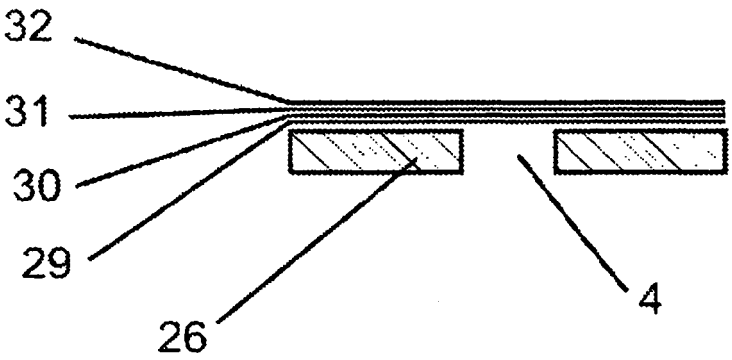

Fig. 3

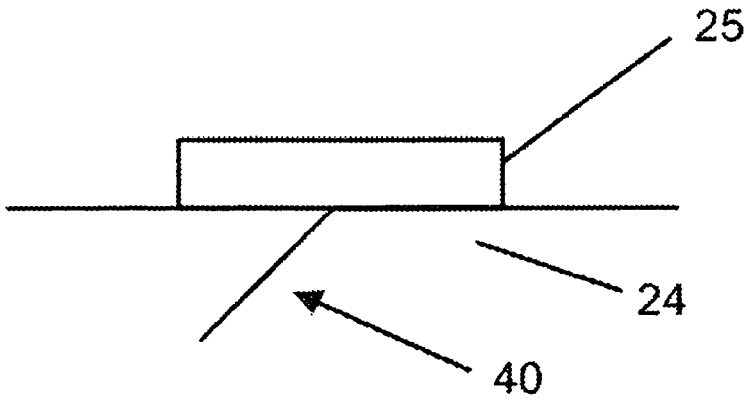

Fig. 4a

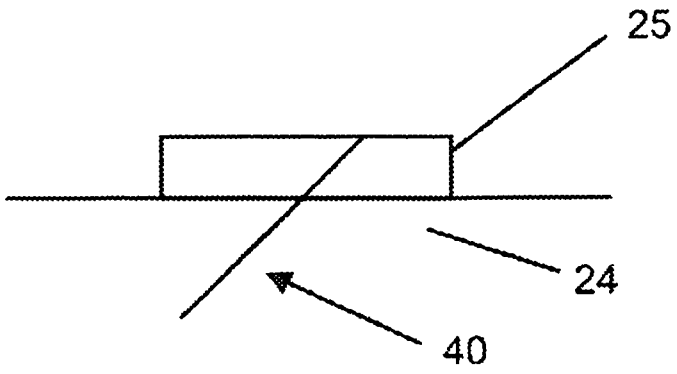

Fig. 4b

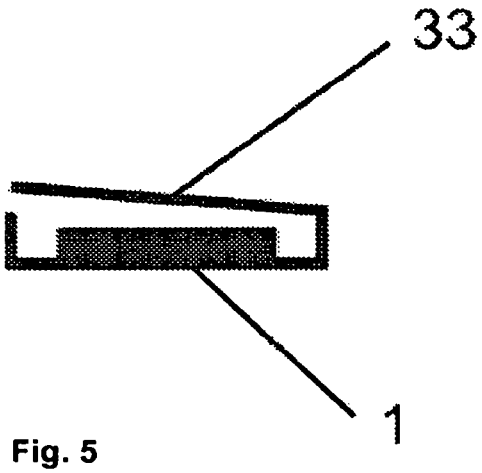

Fig. 5

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	植入式生物传感器，具有自动校准功能		
公开(公告)号	EP2228004B1	公开(公告)日	2013-09-18
申请号	EP2010155995	申请日	2010-03-09
[标]申请(专利权)人(译)	TSOUKALIS ACHILLEAS		
申请(专利权)人(译)	TSOUKALIS，ACHILLEAS		
当前申请(专利权)人(译)	TSOUKALIS，ACHILLEAS		
[标]发明人	TSOUKALIS ACHILLEAS		
发明人	TSOUKALIS, ACHILLEAS		
IPC分类号	A61B5/00		
CPC分类号	A61B5/14865 A61B5/14528 A61B5/14532 A61B5/1495 A61B5/685 A61B5/686 A61B2560/0223 A61B2562/028		
代理机构(译)	EISENFÜHR，SPEISER＆PARTNER		
优先权	20090100135 2009-03-09 GR		
其他公开文献	EP2228004A1		
外部链接	Espacenet		

摘要(译)

可植入的自校准生物传感器皮下或体内植入的生物传感器，其特征在于具有校准流体的闭合微流体回路，其通过后向微透析逻辑与所述回路的外部连通，打开并与组织和组织间液工作电极接触，用于自我校准。一个或多个工作电极可以位于来自EAP的可打开盒子内，并且在测量期间打开并且在测量之后立即关闭，因为它们的灵敏度降低。

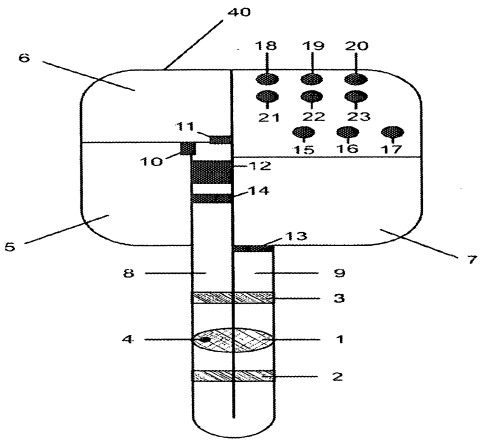

Fig. 1a/b