(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 August 2012 (16.08.2012)

(10) International Publication Number
WO 2012/106972 Al

(51) International Patent Classification:
G01N 33/66 (2006.01) *G01N 27/30* (2006.01) *G01N 33/487* (2006.01)

(21) International Application Number: PCT/CN201 1/084292

(22) International Filing Date: 20 December 201 1 (20. 12.201 1)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/440,394 8 February 201 1 (08.02.201 1) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: BLOOD GLUCOSE SENSOR

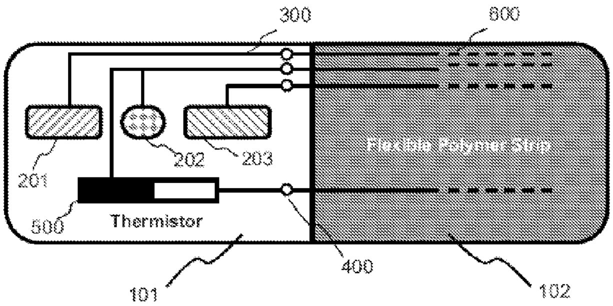

FIG. 2

(57) Abstract: A glucose sensor for monitoring a person's blood glucose level comprises a biocompatible base (101) and a working electrode (201), a reference electrode (202) and a thermistor disposed on the base. A method of using the body temperature measured by thermistor to assist monitoring blood glucose levels especially hypoglycemia events is also provided.

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Blood Glucose Sensor

BACKGROUND OF THE DISCLOSURE

[0001] The disclosure relates to systems and methods for monitoring a person's blood glucose level.

[0002] According to the American Diabetes Association, 23.7 million people in the United States have diabetes; and, with 1.6 million newly diagnosed cases each year, diabetes, already one of the most prevalent chronic diseases in the US, is on the rise.

[0003] An estimated 5-10% of diabetics have Type I diabetes, previously known as juvenile diabetes. In this particularly severe form, the body does not produce insulin, and Type I diabetes is fatal without insulin treatment. Intensive insulin therapy is key to managing this condition, and studies have shown that it significantly delays and prevents the progression of microvascular diseases such as retinopathy and microalbuminuria.

[0004] However, incidences of hypoglycemia pose a substantial hurdle to effective and safe intensive insulin therapy. One study shows that an attempt to achieve a near-normal glycemic profile led to a threefold increase in hypoglycemia. Therefore, frequent monitoring of blood glucose levels is a critical measure to reduce hypoglycemia incidences.

[0005] An additional benefit of frequent blood glucose measurements is that they provide critical data for determining the appropriate insulin dosage, and many algorithms that attempt to use continuously monitored glucose data to determine insulin dosage have been developed thus far, and these algorithm invariably relies on near-continuous glucose concentration data. Therefore, a sensor that is capable of providing frequent, near-continuous monitoring of glucose concentration is necessary for improving diabetes management, especially for those with Type I diabetes. It has been well established that concentration of subcutaneous interstitial fluid closely follows the glucose concentration in the blood; therefore, a minimally invasive, subcutaneous glucose sensor can be used as a continuous glucose monitoring modality.

[0006] Currently there are three major subcutaneous continuous glucose monitoring systems (CGMS) each marketed by Medtronic Inc, Abbott Laboratories and Dexcom inc. The duration of each sensor is between 3 and 7 days, and the price of each sensor is between $40 and $60, with the initial cost of the system between $1,000 and $1,339.

[0007] in addition to potentially prohibitive costs, the existing systems on the market are often inaccurate. A recent study found that half of hypoglycemia events, a potentially life-threatening condition, are missed by these systems, which imposes a substantial limitation on their efficacy.

[0008] in summary, there is an unmet need for a high-accuracy, low-cost alternative to current CGMS on the market.

SUMMARY OF THE DISCLOSURE

[0009] It is discovered herein that the body temperature of a subject is influenced by the subject's blood glucose level, especially when the subject is suffering hypoglycemia or hyperglycemia. Accordingly, body temperature provides additional valuable information about a subject's blood glucose level, in particular when monitoring of such level is the most criticaL Based on this discovery, the present disclosure provides a design of a glucose sensor that includes electrodes like used in a conventional glucose sensor and a thermistor for measuring the body temperature of a subject.

[0010] in a conventional glucose sensor, the sensor tip is made of polymers, which makes the manufacturing expensive. Each sensor typically costs more than $30 to make. Further, polymer-made sensors require a long run in time, typically ranging from one or two hours to 10 hours or more. Still further, it is difficult or even infeasible to manufacture a sensor with a build in thermistor. Thus, one embodiment of the present disclosure provides a glucose sensor made of silicon, such as a silicon on insulator (SOI) wafer.

[0011] Thus, on embodiment of the present disclosure provides a glucose sensor comprising a biocompatible base; and a working electrode, a reference electrode and a thermistor disposed on the base. in one aspect, the glucose sensor further comprises a counter electrode disposed on the base. in another aspect, the glucose sensor further comprises glucose oxidase disposed on the base.

[0012] The base of the glucose sensor, in some aspects, is electrically insulating. In one aspect, the base is made of a material comprising silicon.

[0013] In one aspect, the working electrode comprises platinum black. In one aspect, the reference electrode comprises silver chloride. In another aspect, the counter electrode comprises platinum black.

[0014] In one embodiment, the base has a substantially flat surface, which is from about 0.05 mm to about 2 mm wide. In another embodiment, the base is from about 0.01 mm to about 1 mm thick.

[0015] In certain embodiments, each of the electrodes and the thermistor is connected to a controller. In yet other embodiments, the controller comprises a microprocessor. The controller, in some aspects, comprises an electrical data storage unit. Still in some aspects, the controller is connected to a wireless transmitter.

[0016] One embodiment of the present disclosure provides sensor that further comprises a polymer connector. The polymer connector, either and the side or the external end (the end closer to the skin), can make the sensor more flexible and thus more durable and comfortable to use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] The foregoing advantages and features of the disclosure will become apparent upon reference to the following detailed description and the accompanying drawings, of which:

[0018] FIG. 1 illustrates one embodiment of the glucose sensor of the present disclosure, which includes three electrodes on the sensor; and

[0019] FIG. 2 illustrates another embodiment of the glucose sensor of the present disclosure, which includes two electrodes on the sensor.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0020] Various embodiments of the disclosure will be described in detail below, with reference to the accompanying drawings.

[0021] With reference to FIG. 1 and FIG. 2, a glucose sensor is provided, including a base 101, which is optionally connected to a flexible polymer strip 102 for connecting the base 101 to a controller and/or to facilitate insertion or retrieval.

[0022] In one embodiment, with reference to FIG. 1, the glucose sensor includes two electrodes, a working electrode 201 and a reference electrode 202. In another embodiment, with reference to FIG. 2, the glucose sensor includes three electrodes. In addition to the working electrode 201 and reference electrode 202, the glucose sensor in this embodiment further includes a counter electrode 203. A two-electrode sensor consists of a working electrode, typically made of catalytic material such as platinum, and a counter electrode, typically made of silver/silver chloride or iridium/iridium oxide; a three-electrode system consists of a working electrode, typically made of a catalytic material such as platinum, and reference electrode, typically made of a silver and silver chloride or iridium and iridium Oxide, and a counter electrode, typically made of a catalytic material. Despite the additional complexity, an advantage for a three-electrode sensor is that there is no current flow through the reference electrode, on which electrochemical corrosion occurs over time.

[0023] Methods of preparing working electrodes and placing them on a solid base are well known in the art. In one embodiment, the working electrode 201 is made of platinum black. The counter electrode 204 can also be made of platinum black when included on the glucose sensor. in some embodiments, the reference electrode 202 is made of silver and/or silver chloride or iridium/iridium oxide. Any of all of the electrodes can be simply printed on the base or disposed on the based on other means known to the skilled artisan.

[0024] In one embodiment, the base has a substantially flat surface, which can be from about 0.05 mm to about 5 mm wide, or alternatively from about 0.1 mm to about 2 mm wide, or alternatively from about 0.5 mm to about 2 mm, or yet alternatively from about 1 mm to about 2 mm wide. In another embodiment, the base is from about 0.01 mm to about 2 mm thick, or alternatively from about 0.05 to about 1 mm think, or alternatively from about 0.1 mm to about 0.5 mm thick.

[0025] In certain embodiments, each of the electrodes and the thermistor is connected to a controller. In yet other embodiments, the controller comprises a microprocessor. The controller, in some aspects, comprises an electrical data storage unit. Still in some aspects, the controller is connected to a wireless transmitter. The wireless transmitter can be used to transmit raw electric signal or processed measurement data to a wireless receiver such as a wireless monitor or a smart cell phone.

[0026] Also referring to FIG. 1 and FIG. 2, in one embodiment, the glucose sensor further includes a component for measuring body temperature. In some aspects, such a component is a thermistor. It is to be understood that the component for measuring body temperature does not have to be a thermistor. A thermistor is a type of resistor whose resistance varies with temperature. Other samples of components for measuring body temperature include silicon bandgap temperature sensors which are widely used in silicon integrated circuit at very low cost. The typical accuracy for these bandgap temperature sensors is around ~2 mV/°C.

[0027] A thermistor can be a positive temperature coefficient (PTC) thermistor, also known as a posistor, or a negative temperature coefficient (NTC) thermistor. Materials and methods of preparing a thermistor is also known in the art. In one aspect, the thermistor is made of a ceramic. in another aspect, the thermistor is made of a polymer.

[0028] Materials and methods for preparing a base for a glucose sensor are commonly known in the art. In one embodiment, the base is made of silicon, such as a silicon on insulator wafer. The glucose sensors currently on the market typically include a polymer base. Compared to polymer made bases, production of a silicon base is less expensive, more uniform and more scalable. Further, as it is more difficult or even practically infeasibie to place a thermistor on a polymer base, a silicon bases is advantageous over a polymer base for preparing a glucose sensor that also includes a thermistor.

[0029] The present inventors discovered that the body temperature of a subject, such as a human patient, varies with the glucose level in the subject. in one embodiment, the body temperature drops when the blood glucose level in the subject decreases.

[0030] Further, the change is the most significant when the subject is suffering hypoglycemia or hyperglycemia. In the case of hypoglycemia, it is well recognized that glucose sensors perform the poorest at low level of blood glucose levels. In this context, even a glucose sensor that can reliably and accurately measure the blood glucose level when the level is above a hypoglycemia level, it may fail to detect a hypoglycemia event. Unfortunately, hypoglycemia is the most dangerous condition a diabetic patient may experience. Therefore, any information that can help increase the detection rate, or conversely decreasing the "missing rate" for hypoglycemia is valuable.

[0031] For the purpose of illustration only, the algorithm for integrating body temperature measurement in glucose sensing can be as follows. Let A denote a hypoglycemia event, B denote glucose > G_hypo mg/dL (G__hypo is a predefined glucose level used to trigger hypoglycemia alarms), C denote temperature > T__hypo (T__hypo is a predefined body temperature threshold used to trigger hypoglycemia alarms). For glucose sensing only CGMs: the total probability of hypoglycemia event is:

P(A) = P(A and B) + P(A and ^B) (1)

Thus, the percentage of missed hypoglycemia event will be:

Miss_1= P(A and B) / P(A) = P(A|B) (2)

[0032] It is noted that in some marketed CGM product, Miss_1 = P(A|B) = 50%.

[0033] With the combined sensing CGM (using both low glucose level and low temperature to trigger alarms), Equation (1) can be rewritten as:

P(A) = P(A and B and C) + P(A and B and ^C) + P(A and ^B) (3)

[0034] Then, the percentage of missed hypoglycemia event will be:

Miss_2= P(A and B and C)/P(A) = P(A and B) * P(C|A and B)/P(A) = Miss_1 * P(C|A and B) <= Miss_1

[0035] Therefore the combined CGM should always have less miss.

[0036] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0037] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0038] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, *etc.* As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, *etc.* As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 particles refers to groups having 1, 2, or 3 particles. Similarly, a group having 1-5 particles refers to groups having 1, 2, 3, 4, or 5 particles, and so forth.

[0039] While various aspects and embodiments have been disclosed herein, other aspects and embodiments will be apparent to those skilled in the art. The various aspects and embodiments disclosed herein are for purposes of illustration and are not intended to be limiting, with the true scope and spirit being indicated by the following claims.

[0040] All references cited herein are incorporated by reference in their entireties and for all purposes to the same extent as if each individual publication, patent, or patent application was specifically and individually incorporated by reference in its entirety for all purposes.

WHAT IS CLAIMED IS:

1. A glucose sensor comprising:

   a biocompatible base; and

   a working electrode, a reference electrode and a thermistor disposed on the base.

2. The glucose sensor of claim 1, further comprising a counter electrode disposed on the base.

3. The glucose sensor of claim 1 or 2, further comprising glucose oxidase disposed on the base.

4. The glucose sensor of any of the preceding claims, wherein the base is electrically insulating.

5. The glucose sensor of any of the preceding claims, wherein the base is made of a material comprising silicon.

6. The glucose sensor of any of the preceding claims, wherein the working electrode comprises platinum black.

7. The glucose sensor of any of the preceding claims, wherein the reference electrode comprises silver chloride.

8. The glucose sensor of any of claims 2 to 7, wherein the counter electrode comprises platinum black.

9. The glucose sensor of any of the preceding claims, wherein the base has a substantially flat surface, which is from about 0.05 mm to about 2 mm wide.

10. The glucose sensor of claim 6, wherein the base is from about 0.01 mm to about 1 mm thick.

11. The glucose sensor of any of the preceding claims, wherein each of the electrodes and the thermistor is connected to a controller.

12. The glucose sensor of claim 11, wherein the controller comprises a microprocessor.

13. The glucose sensor of claim 11 or 12, wherein the controller comprises an electrical data storage unit.

14. The glucose sensor of any of claims 11 to 13, wherein the controller is connected to a wireless transmitter.

15. The glucose sensor of any of claims 11 to 14, further comprising a polymer connector.

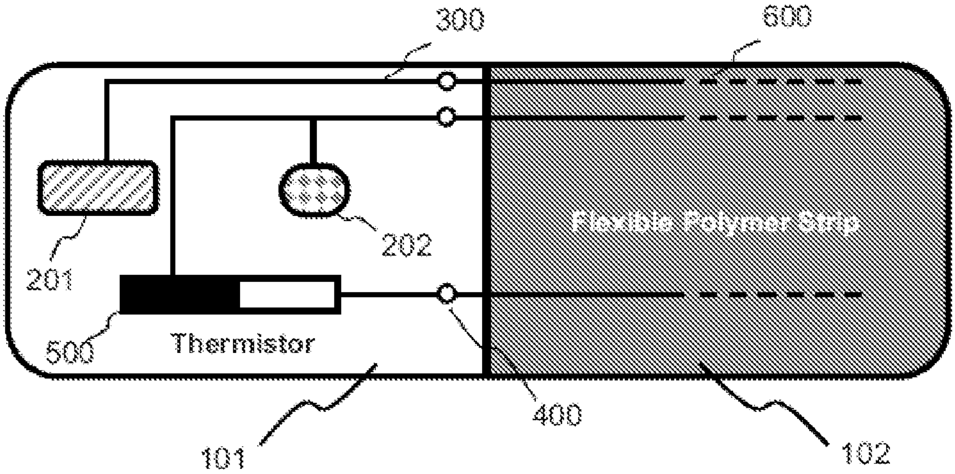
300
600
201
202
Flexible Polymer Strip
500
Thermistor
400
101
102

FIG. 1

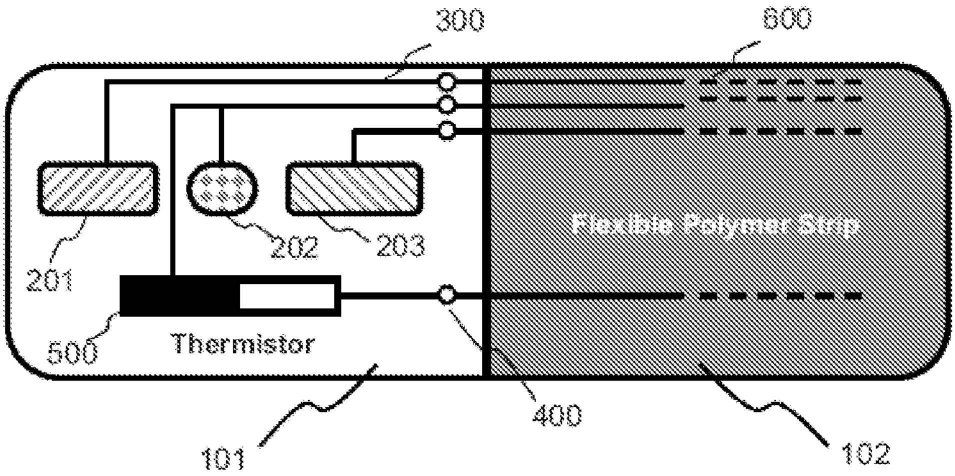
300
600
201
202
203
Flexible Polymer Strip
500
Thermistor
400
101
102

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2011/084292

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: G01N33, G01N27

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

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

CNPAT,CNKI, WPI, EPODOC : glucose, temperature, thermistor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP1909097A1 (NIKKISO COMPANY LIMITED) 09 Apr. 2008(09.04.2008), see paragraph 0017-0027, Fig. 1.	1-15
X	CN1839313A (HOFFMANN LAROCHE & CO AG F) 27 Sep. 2006 (27.09.2006), see the description, page 9, line 13 to page 14, line 30, and Fig. 1-15	1-15
A	WO2007123178A (MATSUSHITAELECTRIC IND CO LTD) 01 Nov. 2007 (01.11.2007), see the whole document	1-15

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 Mar. 2012 (19.03.2012)	**29 Mar. 2012 (29.03.2012)**

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2011/084292

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2011/084292

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

G01N33/66 (2006.01) i

G01N33/487 (2006.01) i

G01N27/30 (2006.01) i