(19) Europäisches Patentamt / European Patent Office / Office européen des brevets

(11) EP 3 019 072 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
10.06.2020 Bulletin 2020/24

(21) Application number: **14822131.0**

(22) Date of filing: **13.03.2014**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/US2014/026004

(87) International publication number:
WO 2015/005953 (15.01.2015 Gazette 2015/02)

(54) **PURIFICATION OF GLUCOSE CONCENTRATION SIGNAL IN AN IMPLANTABLE FLUORESCENCE BASED GLUCOSE SENSOR**

REINIGUNG EINES BLUTZUCKERKONZENTRATIONSSIGNALS IN EINEM IMPLANTIERBAREN FLUORESZENZBASIERTEN BLUTZUCKERSENSOR

PURIFICATION DE SIGNAL DE CONCENTRATION DE GLUCOSE DANS UN CAPTEUR DE GLUCOSE À BASE DE FLUORESCENCE IMPLANTABLE

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **09.07.2013 US 201313937871**

(43) Date of publication of application:
18.05.2016 Bulletin 2016/20

(73) Proprietor: **Senseonics, Incorporated**
Germantown, MD 20876 (US)

(72) Inventors:
- **COLVIN, Arthur, E.**
  Mt. Airy, MD 21771 (US)
- **WANG, Xiaolin**
  Germantown, MD 20874 (US)
- **MDINGI, Colleen**
  Germantown, MD 20874 (US)
- **DEHENNIS, Andrew**
  Germantown, MD 20876 (US)

(74) Representative: **Elkington and Fife LLP**
Prospect House
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

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EP 3 019 072 B1

Description

BACKGROUND

Field of Invention

[0001] The present invention relates generally to determining a concentration of glucose in interstitial fluid of a living animal using an optical sensor implanted in the living animal. Specifically, the present invention relates to purification of a raw signal including a glucose-modulated component to remove noise (*e.g.,* offset and/or distortion) and converting the processed signal to a glucose concentration.

Discussion of the Background

[0002] A sensor may be implanted within a living animal (*e.g.*, a human) used to measure the concentration of glucose in a medium (*e.g.*, interstitial fluid (ISF) or blood) within the living animal. The sensor may include a light source (*e.g.,* a light-emitting diode (LED) or other light emitting element), indicator molecules, and a photodetector (*e.g.*, a photodiode, phototransistor, photoresistor or other photosensitive element). Examples of implantable sensors employing indicator molecules to measure the concentration of an analyte are described in U.S. Pat. Nos. 5,517,313 and 5,512,246.

[0003] Broadly speaking, in the context of the field of the present invention, indicator molecules are molecules having one or more optical characteristics that is or are affected by the local presence of an analyte such as glucose. The indicator molecules may be fluorescent indicator molecules, and the fluorescence of the indicator molecules may be modulated, *i.e.,* attenuated or enhanced, by the local presence of glucose.

[0004] The implantable sensor may be configured such that fluorescent light emitted by the indicator molecules impacts the photodetector, which generates a raw electrical signal based on the amount of light received thereby. The generated raw electrical signal may be indicative of the concentration of glucose in the medium surrounding the indicator molecules, but the raw signal may also include noise (*e.g.,* offset and/or distortion) that affects the accuracy of the glucose concentration measurement produced from the raw signal.

[0005] There is presently a need in the art for a more accurate sensor capable of measuring glucose concentration in a medium of a living animal.

[0006] WO 2013/149129 A1 is prior art under Article 54(3) EPC. It discloses a method of determining a concentration of glucose in a medium of a living animal using an optical sensor implanted in the animal. The optical sensor generates a raw signal, adjusts the raw signal, and converts the adjusted signal into a measurement. The measurement is then conveyed using an inductive element of the optical sensor.

SUMMARY

[0007] The invention is defined by the claims. One aspect of the invention may provide a method of determining a concentration of glucose in a medium of a living animal using an optical sensor implanted in the living animal and a sensor reader external to the living animal, according to claim 1.

[0008] Another aspect of the invention may provide a system for determining a concentration of glucose in a medium of a living animal, according to claim 9.

[0009] The method may include measuring, using a temperature sensor of the optical sensor, a temperature of the optical sensor. The method may include conveying, using an inductive element of the optical sensor, the raw signal and measured temperature. The method may include receiving, using an inductive element of the sensor reader, the conveyed raw signal and the conveyed temperature. The method may include temperature correcting, using circuitry of the sensor reader, the received raw signal to compensate for temperature sensitivity of the light source based on the received measured temperature. The method may include offset adjusting, using the circuitry of the sensor reader, the temperature corrected raw signal to compensate for offset based on the tracked cumulative emission time. The method may include distortion adjusting, using the circuitry of the sensor reader, the offset adjusted raw signal to compensate for distortion based on the tracked cumulative emission time and the tracked implant time. The method may include normalizing, using the circuitry of the sensor reader, the distortion adjusted raw signal to a normalized raw signal that would be equal to one at zero glucose concentration based on the measured temperature, the tracked cumulative emission time, and the tracked implant time. The method may include converting, using the circuitry of the sensor reader, the normalized raw signal into a measurement of glucose concentration in the medium of the living animal.

[0010] Further variations encompassed within the systems and methods are described in the detailed description of the invention below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The accompanying drawings, which are incorporated herein and form part of the specification, illustrate various, non-limiting embodiments of the present invention. In the drawings, like reference numbers indicate identical or functionally similar elements.

FIG. 1 is a schematic view illustrating a sensor system embodying aspects of the present invention.
FIG. 2 illustrates a raw signal purification and conversion process that may be performed by the circuitry of an optical sensor in accordance with an embodiment of the present invention.
FIG. 3 illustrates the components of the excitation light received by the photodetector that contribute to the offset in the raw signal in accordance with an embodiment of the present invention.
FIG. 4 illustrates the reactions and kinetics of the related species of the indicator molecules in accordance with an embodiment of the present invention.
FIG. 5 illustrates the relationship between normalized glucose-modulated fluorescence (I/I_0) and glucose concentration in accordance with an embodiment of the present invention.
FIG. 6 illustrates a circuit diagram that may be used in accordance with one embodiment of the present invention.
FIG. 7 illustrates a Clarke error grid showing the experimental results of 18 sensors embodying aspects of the present invention and implanted in Type I diabetic subjects.
FIG. 8 illustrates experimental results of a sensor embodying aspects of the present invention during six read sessions.
FIG. 9 is a schematic view illustrating a sensor reader embodying aspects of the present invention.
FIG. 10 illustrates a raw signal purification and conversion process that may be performed by the circuitry of a sensor reader in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0012] FIG. 1 is a schematic view of a sensor system embodying aspects of the present invention. In one non-limiting embodiment, the system includes a sensor 100 and an external sensor reader 101. In the embodiment shown in FIG. 1, the sensor 100 may be implanted in a living animal (e.g., a living human). The sensor 100 may be implanted, for example, in a living animal's arm, wrist, leg, abdomen, or other region of the living animal suitable for sensor implantation. For example, in one non-limiting embodiment, the sensor 100 may be implanted between the skin and subcutaneous tissues. In some embodiments, the sensor 100 may be an optical sensor (*e.g.,* a fluorometer). In some embodiments, the sensor 100 may be a chemical or biochemical sensor.

[0013] A sensor reader 101 may be an electronic device that communicates with the sensor 100 to power the sensor 100 and/or obtain ahalyte (*e.g.,* glucose) readings from the sensor 100. In non-limiting embodiments, the reader 101 may be a handheld reader, a wristwatch, an armband, or other device placed in close proximity to the sensor 100. In one embodiment, positioning (*i.e.,* hovering or swiping/waiving/passing) the reader 101 within range over the sensor implant site (*i.e.,* within proximity of the sensor 100) will cause the reader 101 to automatically convey a measurement command to the sensor 100 and receive a reading from the sensor 100.

[0014] In some embodiments, the sensor reader 101 may include an inductive element 103, such as, for example, a coil. The sensor reader 101 may generate an electromagnetic wave or electrodynamic field (*e.g.,* by using a coil) to induce a current in an inductive element 114 of the sensor 100, which powers the sensor 100. The sensor reader 101 may also convey data (*e.g.,* commands) to the sensor 100. For example, in a non-limiting embodiment, the sensor reader 101 may convey data by modulating the electromagnetic wave used to power the sensor 100 (*e.g.,* by modulating the current flowing through a coil 103 of the sensor reader 101). The modulation in the electromagnetic wave generated by the reader 101 may be detected/extracted by the sensor 100. Moreover, the sensor reader 101 may receive data (*e.g.,* measurement information) from the sensor 100. For example, in a non-limiting embodiment, the sensor reader 101 may receive data by detecting modulations in the electromagnetic wave generated by the sensor 100, *e.g.,* by detecting modulations in the current flowing through the coil 103 of the sensor reader 101.

[0015] The inductive element 103 of the sensor reader 101 and the inductive element 114 of the sensor 100 may be in any configuration that permits adequate field strength to be achieved when the two inductive elements are brought within adequate physical proximity.

[0016] FIG. 9 is a schematic view of a sensor reader 101 according to a non-limiting embodiment. In some embodiments, the sensor reader 101 may have a connector 902, such as, for example, a Micro-Universal Serial Bus (USB) connector. The connector 902 may enable a wired connection to an external device, such as a personal computer or smart phone. The sensor reader 101 may exchange data to and from the external device through the connector 902 and/or may receive power through the connector 902. The sensor reader 101 may include a connector integrated circuit (IC) 904, such as, for example, a USB-IC, which may control transmission and receipt of data through the connector 902. The sensor reader 101 may also include a charger IC 906, which may receive power via the connector 902 and charge a battery 908.

[0017] In some embodiments, the sensor reader 101 may have a wireless communication IC 910, which enables wireless communication with an external device, such as, for example, a personal computer or smart phone. In one non-limiting embodiment, the communication IC 910 may employ a standard, such as, for example, a Buetooth Low Energy (BLE) standard (e.g., BLE 4.0), to wirelessly transmit and receive data to and from an external device.

[0018] In some embodiments, the sensor reader 101 may include voltage regulators 912 and/or a voltage booster 914. The battery 908 may supply power (via voltage booster 914) to radio-frequency identification (RFID) reader IC 916, which uses the inductive element 103 to convey information (*e.g.,* commands) to the sensor 101 and receive information (*e.g.,* measurement information) from the sensor 100. In the illustrated embodiment, the inductive element is a flat antenna. However, as noted above, the inductive element 103 of the sensor reader 101 may be in any configuration that permits adequate field strength to be achieved when brought within adequate physical proximity to the inductive element 114 of the sensor 100. In some embodiments, the sensor reader 101 may include a power amplifier 918 to amplify the signal to be conveyed by the inductive element 103 to the sensor 100.

[0019] The sensor reader 101 may include a peripheral interface controller (PIC) microcontroller 920 and memory 922 (*e.g.*, Flash memory), which may be non-volatile and/or capable of being electronically erased and/or rewritten. The PIC microcontroller 920 may control the overall operation of the sensor reader 101. For example, the PIC microcontroller 920 may control the connector IC 904 or wireless communication IC 910 to transmit data and/or control the RFID reader IC 916 to convey data via the inductive element 103. The PIC microcontroller 920 may also control processing of data received via the inductive element 103, connector 902, or wireless communication IC 910.

[0020] In some embodiments, the sensor reader 101 may include a display 924 (*e.g.,* liquid crystal display), which PIC microcontroller 920 may control to display data (*e.g.*, glucose concentration values). In some embodiments, the sensor reader 101 may include a speaker 926 (*e.g.,* a beeper) and/or vibration motor 928, which may be activated, for example, in the event that an alarm condition (*e.g.*, detection of a hypoglycemic or hyperglycemic condition) is met. The sensor reader 101 may also include one or more additional sensors 930, which may include an accelerometer and/or temperature sensor, that may be used in the processing performed by the PIC microcontroller 920.

[0021] In one non-limiting embodiment, as illustrated in FIG. 1, sensor 100 includes a sensor housing 102 (*i.e.,* body, shell, capsule, or encasement), which may be rigid and biocompatible. In exemplary embodiments, sensor housing 102 may be formed from a suitable, optically transmissive polymer material, such as, for example, acrylic polymers (*e.g.*, polymethylmethacrylate (PMMA)).

[0022] In some embodiments, the sensor 100 includes indicator molecules 104. Indicator molecules 104 may be fluorescent indicator molecules (*e.g.*, Trimethyltrifluromethylsilane (TFM) fluorescent indicator molecules) or absorption indicator molecules. In some embodiments, the indicator molecules 104 may reversibly bind glucose. When an indicator molecule 104 has bound glucose, the indicator molecule may become fluorescent, in which case the indicator molecule 104 is capable of absorbing (or being excited by) excitation light 329 and emitting light 331. In one non-limiting embodiment, the excitation light 329 may have a wavelength of approximately 378 nm, and the emission light 331 may have a wavelength in the range of 400 to 500 nm. When no glucose is bound, the indicator molecule 104 may be only weakly fluorescent.

[0023] In some non-limiting embodiments, sensor 100 may include a polymer graft 106 coated, diffused, adhered, or embedded on at least a portion of the exterior surface of the sensor housing 102, with the indicator molecules 104 distributed throughout the polymer graft 106. In some embodiments, the polymer graft 106 may be a fluorescent glucose indicating polymer. In one non-limiting embodiment, the polymer is biocompatible and stable, grafted onto the surface of sensor housing 102, designed to allow for the direct measurement of interstitial fluid (ISF) glucose after subcutaneous implantation of the sensor 100.

[0024] In some non-limiting embodiments, the polymer graft 106 may include three monomers: the TFM fluorescent indicator, hydroxyethylmethacrylate (HEMA), and polyethylene glycol methacrylate (PEG-methacrylate). In one embodiment, the polymer graft 106 may include the three monomers in specific molar ratios, with the fluorescent indicator comprising 0.1 molar percent, HEMA comprising 94.3 molar percent, and PEG-methacrylate comprising 5.6 molar percent. The PEG-methacrylate may act as a cross-linker and be what creates a sponge-like matrix. Conventional free radical polymerization may be used to synthesize the polymer that is grafted onto the sensor 100.

[0025] In some embodiments, the sensor 100 may include a light source 108, which may be, for example, a light emitting diode (LED) or other light source, that emits radiation, including radiation over a range of wavelengths that interact with the indicator molecules 104. In other words, the light source 108 may emit the excitation light 329 that is absorbed by the indicator molecules in the matrix layer/polymer 104. As noted above, in one non-limiting embodiment, the light source 108 may emit excitation light 329 at a wavelength of approximately 378 nm.

[0026] In some embodiments, the sensor 100 may also include one or more photodetectors (*e.g.*, photodiodes, phototransistors, photoresistors or other photosensitive elements). For example, in the embodiment illustrated in FIG. 1, sensor 100 has a first photodetector 224 and a second photodetector 226. However, this is not required, and, in some alternative embodiments, the sensor 100 may only include the first photodetector 224.

[0027] Some part of the excitation light 329 emitted by the light source 108 may be reflected from the polymer graft 106 back into the sensor 100 as reflection light 331, and some part of the absorbed excitation light may be emitted as emitted (fluoresced) light 331. In one non-limiting embodiment, the emitted light 331 may have a higher wavelength than the wavelength of the excitation light 329. The reflected light 333 and emitted (fluoresced) light 331 may be absorbed by the one or more photodetectors (*e.g.*, first and second photodetectors 224 and 226) within the body of the sensor 100.

[0028] Each of the one or more photodetectors may be covered by a filter 112 (see FIG. 3) that allows only a certain subset of wavelengths of light to pass through. In some embodiments, the one or more filters 112 may be thin glass filters. In some embodiments, the one or more filters 112 may be thin film (dichroic) filters deposited on the glass and may pass only a narrow band of wavelengths and otherwise reflect most of the light. In one non-limiting embodiment, the second (reference) photodetector 226 may be covered by a reference photodiode filter that passes light at the same wavelength as is emitted from the light source 108 (*e.g.,* 378 nm). The first (signal) photodetector 224 may detect the amount of fluoresced light 331 that is emitted from the molecules 104 in the graft 106. In one non-limiting embodiment, the peak emission of the indicator molecules 104 may occur around 435 nm, and the first photodetector 224 may be covered by a signal filter that passes light in the range of about 400 nm to 500 nm. In some embodiments, higher glucose levels/concentrations correspond to a greater amount of fluorescence of the molecules 104 in the graft 106, and, therefore, a greater number of photons striking the first photodetector 224.

[0029] In some embodiments, sensor 100 may include a substrate 116. In some non-limiting embodiments, the substrate 116 may be a semiconductor substrate and circuitry may be fabricated in the semiconductor substrate 116. The circuitry may include analog and/or digital circuitry. Also, although in some preferred embodiments the circuitry is fabricated in the semiconductor substrate 116, in alternative embodiments, a portion or all of the circuitry may be mounted or otherwise attached to the semiconductor substrate 116. In other words, in alternative embodiments, a portion or all of the circuitry, which may include discrete circuit elements, an integrated circuit (*e.g.*, an application specific integrated circuit (ASIC)) and/or other electronic components, may be fabricated in the semiconductor substrate 116 with the remainder of the circuitry is secured to the semiconductor substrate 116, which may provide communication paths between the various secured components. In some embodiments, circuitry of the sensor 100 may have the structure described in US 2013/0241745 A1, with reference to FIG. 11D.

[0030] FIG. 6 is block diagram illustrating the functional blocks of the circuitry of sensor 100 according to a non-limiting embodiment in which the circuitry is fabricated in the semiconductor substrate 116. As shown in the embodiment of FIG. 6, in some embodiments, an input/output (I/O) frontend block 536 may be connected to the external inductive element 114, which may be in the form of a coil 220, through coil contacts 428a and 428b. The I/O frontend block 536 may include a rectifier 640, a data extractor 642, a clock extractor 644, clamp/modulator 646 and/or frequency divider 648. Data extractor 642, clock extractor 644 and clamp/modulator 646 may each be connected to external coil 220 through coil contacts 428a and 428b. The rectifier 640 may convert an alternating current produced by coil 220 to a direct current that may be used to power the sensor 100. For instance, the direct current may be used to produce one or more voltages, such as, for example, voltage VDD_A, which may be used to power the one or more photodetectors (*e.g.*, photodetectors 224 and 226). In one non-limiting embodiment, the rectifier 640 may be a Schottky diode; however, other types of rectifiers may be used in other embodiments. The data extractor 642 may extract data from the alternating current produced by coil 220. The clock extractor 644 may extract a signal having a frequency (*e.g.*, 13.56MHz) from the alternating current produced by coil 220. The frequency divider 648 may divide the frequency of the signal output by the clock extractor 644. For example, in a non-limiting embodiment, the frequency divider 648 may be a 4:1 frequency divider that receives a signal having a frequency (*e.g.*, 13.56MHz) as an input and outputs a signal having a frequency (*e.g.*, 3.39MHz) equal to one fourth the frequency of the input signal. The outputs of rectifier 640 may be connected to one or more external capacitors 118 (*e.g.*, one or more regulation capacitors) through contacts 428h and 428i.

[0031] In some embodiments, an I/O controller 538 may include a decoder/serializer 650, command decoder/data encoder 652, data and control bus 654, data serializer 656 and/or encoder 658. The decoder/serializer 650 may decode and serialize the data extracted by the data extractor 642 from the alternating current produced by coil 220. The command decoder/data encoder 652 may receive the data decoded and serialized by the decoder/serializer 650 and may decode commands therefrom. The data and control bus 654 may receive commands decoded by the command decoder/data encoder 652 and transfer the decoded commands to the measurement controller 532. The data and control bus 654 may also receive data, such as measurement information, from the measurement controller 532 and may transfer the received data to the command decoder/data encoder 652. The command decoder/data encoder 652 may encode the data received from the data and control bus 654. The data serializer 656 may receive encoded data from the command decoder/data encoder 652 and may serialize the received encoded data. The encoder 658 may receive serialized data from the data serializer 656 and may encode the serialized data. In a non-limiting embodiment, the encoder 658 may be a Manchester encoder that applies Manchester encoding (*i.e.,* phase encoding) to the serialized data. However, in other embodiments, other types of encoders may alternatively be used for the encoder 658, such as, for example, an encoder that applies 8B/10B encoding to the serialized data.

[0032] The clamp/modulator 646 of the I/O frontend block 536 may receive the data encoded by the encoder 658 and may modulate the current flowing through the inductive element 114 (*e.g.,* coil 220) as a function of the encoded data. In this way, the encoded data may be conveyed wirelessly by the inductive element 114 as a modulated electromagnetic wave. The conveyed data may be detected by an external reading device by, for example, measuring the current induced by the modulated electromagnetic wave in a coil of the external reading device. Furthermore, by modulating the current flowing through the coil 220 as a function of the encoded data, the encoded data may be conveyed wirelessly by the coil 220 as a modulated electromagnetic wave even while the coil 220 is being used to produce operating power for the sensor 100. See, for example, U.S. Pat. Nos. 6,330,464 and 8,073,548, which describe a coil used to provide operative power to an optical sensor and to wirelessly convey data from the optical sensor. In some embodiments, the encoded data is conveyed by the sensor 100 using the clamp/modulator 646 at times when data (*e.g*., commands) are not being received by the sensor 100 and extracted by the data extractor 642. For example, in one non-limiting embodiment, all commands may be initiated by an external sensor reader (*e.g.,* reader 101 of FIG. 1) and then responded to by the sensor 100 (*e.g.,* after or as part of executing the command). In some embodiments, the communications received by the inductive element 114 and/or the communications conveyed by the inductive element 114 may be radio frequency (RF) communications. Although, in the illustrated embodiments, the sensor 100 includes a single coil 220, alternative embodiments of the sensor 100 may include two or more coils (*e.g.,* one coil for data transmission and one coil for power and data reception).

[0033] In an embodiment, the I/O controller 538 may also include a nonvolatile storage medium 660. In a non-limiting embodiment, the nonvolatile storage medium 660 may be an electrically erasable programmable read only memory (EEPROM). However, in other embodiments, other types of nonvolatile storage media, such as flash memory, may be used. The nonvolatile storage medium 660 may receive write data (*i.e.,* data to be written to the nonvolatile storage medium 660) from the data and control bus 654 and may supply read data (*i.e.,* data read from the nonvolatile storage medium 660) to the data and control bus 654. In some embodiments, the nonvolatile storage medium 660 may have an integrated charge pump and/or may be connected to an external charge pump. In some embodiments, the nonvolatile storage medium 660 may store identification information (*i.e.,* traceability or tracking information), measurement information and/or setup parameters (*i.e.,* calibration information). In one embodiment, the identification information may uniquely identify the sensor 100. The unique identification information may, for example, enable full traceability of the sensor 100 through its production and subsequent use. In one embodiment, the nonvolatile storage medium 660 may store calibration information for each of the various sensor measurements.

[0034] In some embodiments, the analog interface 534 may include a light source driver 662, analog to digital converter (ADC) 664, a signal multiplexer (MUX) 666 and/or comparator 668. In a non-limiting embodiment, the comparator 668 may be a transimpedance amplifier, in other embodiments, different comparators may be used. The analog interface 534 may also include light source 108, one or more photodetectors (*e.g*., first and second photodetectors 224 and 226), and/or a temperature sensor 670 (*e.g*., temperature transducer).

[0035] In some embodiments, the one or more photodetectors (*e.g*., photodetectors 224 and 226) may be mounted on the semiconductor substrate 116, but, in some preferred embodiments, the one or more photodetectors 110 may be fabricated in the semiconductor substrate 116. In some embodiments, the light source 108 may be mounted on the semiconductor substrate 116. For example, in a non-limiting embodiment, the light source 108 may be flip-chip mounted on the semiconductor substrate 116. However, in some embodiments, the light source 108 may be fabricated in the semiconductor substrate 116.

[0036] In a non-limiting, exemplary embodiment, the temperature transducer 670 may be a band-gap based temperature transducer. However, in alternative embodiments, different types of temperature transducers may be used, such as, for example, thermistors or resistance temperature detectors. Furthermore, like the light source 108 and one or more photodetectors, in one or more alternative embodiments, the temperature transducer 670 may be mounted on semiconductor substrate 116 instead of being fabricated in semiconductor substrate 116.

[0037] The light source driver 662 may receive a signal from the measurement controller 532 indicating the light source current at which the light source 108 is to be driven, and the light source driver 662 may drive the light source 108 accordingly. The light source 108 may emit radiation from an emission point in accordance with a drive signal from the light source driver 662. The radiation may excite indicator molecules 104 distributed throughout the graft 106. The one or more photodetectors (e.g., first and second photodetectors 224 and 226) may each output an analog light measurement signal indicative of the amount of light received by the photodetector. For instance, in the embodiment illustrated in FIG. 6, the first photodetector 224 may output a first analog light measurement signal indicative of the amount of light received by the first photodetector 224, and the second photodetector 226 may output a first analog light measurement signal indicative of the amount of light received by the second photodetector 226. The comparator 668 may receive the first and second analog light measurement signals from the first and second photodetectors 224 and 226, respectively, and output an analog light difference measurement signal indicative of the difference between the first and second analog light measurement signals. The temperature transducer 670 may output an analog temperature measurement signal indicative of the temperature of the sensor 100. The signal MUX 666 may select one of the analog temperature measurement signal, the first analog light measurement signal, the second analog light measurement signal and the analog light difference measurement signal and may output the selected signal to the ADC 664. The ADC 664 may convert the selected analog signal received from the signal MUX 666 to a digital signal and supply the digital signal to the measurement controller 532. In this way, the ADC 664 may convert the analog temperature measurement signal, the first analog light measurement signal, the second analog light measurement signal, and the analog light difference measurement signal to a digital temperature measurement signal, a first digital light measurement signal, a second digital light measurement signal, and a digital light difference measurement signal, respectively, and may supply the digital signals, one at a time, to the measurement controller 532.

[0038] In some embodiments, the measurement controller 532 may receive one or more digital measurements and generate measurement information, which may be indicative of the presence and/or concentration of an analyte (*e.g.,* glucose) in a medium in which the sensor 100 is implanted. In some embodiments, the generation of the measurement information may include conversion of a digitized raw signal (*e.g.*, the first digital light measurement signal) into a glucose concentration. For accurate conversion, the measurement controller 532 may take into consideration the optics, electronics, and chemistry of the sensor 100. Further, in some embodiments, the measurement controller 532 may be used to obtain a purified signal of glucose concentration by eliminating noise (*e.g.*, offset and distortions) that is present in the raw signals (*e.g.*, the first digital light measurement signals).

[0039] In some embodiments, the circuitry of sensor 100 fabricated in the semiconductor substrate 116 may additionally include a clock generator 671. The clock generator 671 may receive, as an input, the output of the frequency divider 648 and generate a clock signal CLK. The clock signal CLK may be used by one or more components of one or more of the I/O frontend block 536, I/O controller 538, measurement controller 532, and analog interface 534.

[0040] In a non-limiting embodiment, data (*e.g.*, decoded commands from the command decoder/data encoder 652 and/or read data from the nonvolatile storage medium 660) may be transferred from the data and control bus 654 of the I/O controller 538 to the measurement controller 532 via transfer registers and/or data (*e.g.*, write data and/or measurement information) may be transferred from the measurement controller 532 to the data and control bus 654 of the I/O controller 538 via the transfer registers.

[0041] In some embodiments, the circuitry of sensor 100 may include a field strength measurement circuit. In embodiments, the field strength measurement circuit may be part of the I/O front end block 536, I/O controller 538, or the measurement controller 532 or may be a separate functional component. The field strength measurement circuit may measure the received (*i.e.,* coupled) power (*e.g.,* in mWatts). The field strength measurement circuit of the sensor 100 may produce a coupling value proportional to the strength of coupling between the inductive element 114 (*e.g.,* coil 220) of the sensor 100 and the inductive element of the external reader 101. For example, in non-limiting embodiments, the coupling value may be a current or frequency proportional to the strength of coupling. In some embodiments, the field strength measurement circuit may additionally determine whether the strength of coupling/received power is sufficient to perform an analyte concentration measurement and convey the results thereof to the external sensor reader 101. For example, in some non-limiting embodiments, the field strength measurement circuit may detect whether the received power is sufficient to produce a certain voltage and/or current. In one non-limiting embodiment, the field strength measurement circuit may detect whether the received power produces a voltage of at least approximately 3V and a current of at least approximately 0.5mA. However, other embodiments may detect that the received power produces at least a different voltage and/or at least a different current. In one non-limiting embodiment, the field strength measurement circuit may compare the coupling value field strength sufficiency threshold.

[0042] In the illustrated embodiment, the clamp/modulator 646 of the I/O circuit 536 acts as the field strength measurement circuit by providing a value (*e.g.*, I_{couple}) proportional to the field strength. The field strength value I_{couple} may be provided as an input to the signal MUX 666. When selected, the MUX 666 may output the field strength value I_{couple} to the ADC 664. The ADC 664 may convert the field strength value I_{couple} received from the signal MUX 666 to a digital field strength value signal and supply the digital field strength signal to the measurement controller 532. In this way, the field strength measurement may be made available to the measurement controller 532 and may be used in initiating an analyte measurement command trigger based on dynamic field alignment. However, in an alternative embodiment, the field strength measurement circuit may instead be an analog oscillator in the sensor 100 that sends a frequency corresponding to the voltage level on a rectifier 640 back to the reader 101.

[0043] In some embodiments, the sensor 100 may be used to obtain accurate ISF glucose readings in patients, and the circuitry of the sensor 100 (which may, for example, include measurement controller 532) may convert the raw signal generated by the photodetector 224 into a glucose concentration. For accurate conversion, the circuitry of the sensor 100 may take into consideration the optics, electronics, and chemistry of the sensor 100. Further, in some embodiments, the circuitry may be used to obtain a purified signal of glucose concentration by eliminating noise (*e.g.,* offset and distortions) that are present in raw signals from the sensor 100.

[0044] In some embodiments, the circuitry may use parameters measured during manufacturing of the sensor 100 and parameters characterized as a result of *in vitro* and *in vivo* tests to convert the raw signals generated by the sensor 100 into glucose concentrations. In some embodiments, the intermediate steps performed by the circuitry of the sensor

100 in determining a glucose concentration from a raw signal may be: (i) purifying the raw signal, (ii) normalizing the purified signal to produce a normalized signal Sn that is directly proportional to glucose concentration, and (iii) converting the normalized signal Sn into a glucose concentration.

[0045] The purification may involve compensating for/removing impurities, such as an offset produced by the excitation light 329 and distortion produced by non-glucose modulated light emitted by the indicator molecules 104. In some embodiments, the purification may also involve correcting the raw signal for temperature sensitivity. Accordingly, the purified signal may be proportional to the glucose modulated indicator fluorescence emitted by the indicator molecules 104.

[0046] The raw signals from the sensor 100, as captured by the photodetector 224, may contain noise (*e.g.*, offset and distortions), which are not related to actual glucose modulation of the indicator molecules 104. The fluorescent amplitude of the light 331 emitted by the indicator molecules 104, as well as some elements of the electronic circuitry within the sensor 100, may be temperature sensitive. The circuitry may, therefore, purify the raw signal by removing the non-glucose-modulated offset/distortion of the raw signal and correcting for temperature sensitivity before normalizing the signal and converting the normalized signal to a glucose concentration.

[0047] FIG. 2 illustrates an exemplary raw signal purification and conversion process 200 that may be performed by the circuitry of optical sensor 100, which may be, for example, implanted within a living animal (*e.g.*, a living human), in accordance with an embodiment of the present invention. The process 200 may include a step S202 of tracking the amount of time t_i that has elapsed since the optical sensor was implanted in the living animal. Because oxidation and thermal degradation begins when the sensor 100 is implanted, the implant time t_i may be equivalent to the oxidation time t_{ox} and the thermal degradation time t_{th}.

[0048] In some embodiments, the circuitry of sensor 100 may include an implant timer circuit that is started when the sensor is implanted. For example, in one non-limiting embodiment, the implant timer circuit may be a counter that increments with each passing of a unit of time (*e.g.*, one or more milliseconds, one more seconds, one or more minutes, one or more hours, or one or more days, etc.). However, this is not required, and, in some alternative embodiments, the circuitry of the sensor 100 may track the implant time t_i by storing the time at which the sensor was implanted (*e.g.*, in nonvolatile storage medium 660) and comparing the stored time with the current time, which may, for example, be received from the external reader 101 (*e.g.,* with an measurement command from the external reader 101). In other alternative embodiments, the sensor 100 may store the time at which the sensor was implanted, *i.e.,* the implant time t_i (*e.g.,* in nonvolatile storage medium 660), which may then be read by an external unit (*e.g.*, sensor reader 101) for calculation of the implant time t_i. As explained in detail below, the tracked implant time t_i may be used in compensating for distortion in the raw signal, normalizing the raw signal, and/or converting the normalized signal Sn to a glucose concentration.

[0049] The process 200 may include a step S204 of tracking the cumulative amount of time t_e that the light source 108 has emitted the excitation light 329. Because the indicator molecules 104 are irradiated with the excitation light 329, the cumulative emission time t_e may be equivalent to the photobleaching time t_{pb}.

[0050] In some embodiments, the circuitry of sensor 100 includes an emission timer circuit that is advanced while the light source 108 emits excitation light 329. For example, in one non-limiting embodiment, the emission timer circuit may be a counter that increments with each passing of a unit of time (*e.g.*, one or more milliseconds, one more seconds, one or more minutes, one or more hours, or one or more days, etc.) while the light source 108 emits excitation light 329. However, this is not required. For example, in some alternative embodiments, the light source 108 may emit excitation light 329 for a set amount of time for each measurement, and the counter may increment once for each measurement taken by the sensor 100. As explained in detail below, the tracked cumulative emission time t_e may be used in compensating for offset in the raw signal, compensating for distortion in the raw signal, normalizing the raw signal, and/or converting the normalized signal Sn to a glucose concentration.

[0051] The process 200 may include a step S206 of emitting excitation light 329. The excitation light 329 may be emitted by light source 108. In some embodiments, step S206 may be carried out in response to a measurement command from the external sensor reader 101 (*e.g.,* under the control of a measurement controller). Execution of step S206 may cause incrementing of the tracked cumulative emission time t_e, which may be equivalent to the photobleaching time t_{pb}.

[0052] The process 200 may include a step S208 of generating a raw signal indicative of the amount of light received by a photodetector (*e.g.*, first photodetector 224). In some embodiments, the raw signal may be generated by the first (signal) photodetector 224. In some non-limiting embodiments, the raw signal may be digitized by the ADC 664.

[0053] As shown in equation 3, the raw signal may contain an offset Z and distortion $I_{distortion}$.

$$Signal = I + Z + I_{distortion} \quad (3)$$

where *Signal* is the raw signal generated by the photodetector, *I* is the glucose-modulated fluorescence from the indicator molecules 104, Z is an offset, and $I_{distortion}$ is distortion produced by the indicator molecules 104 (*e.g.*, distortion produced by photo, thermal, and/or oxidative decay species of). In order to accurately calculate the glucose-modulated fluorescence I emitted by the indicator molecules 104, the raw signal may be purified by removing the offset Z and the distortion $I_{distortion}$ from the raw signal. In addition, for accurate calculation of the fluorescence from the glucose indicator I, the raw signal may be corrected for temperature sensitivity. Accordingly, the process 200 may include steps S210, S212, S214, and/or S216 of measuring temperature, correcting for temperature sensitivity, compensating for offset Z, and compensating for distortion $I_{distortion}$, respectively.

[0054] In step S210, the temperature T of the optical sensor 100 may be measured. In some embodiments, the temperature may be measured by the temperature sensor 670. As explained below, in some embodiments, the measured temperature T may be used for correcting the raw signal for temperature sensitivity.

[0055] In step S212, the circuitry of sensor 100 may temperature correct the raw signal based on the temperature T of the sensor 100, which may be measured in step S210. In particular, in some non-limiting embodiments, the measurement controller 532 may perform the temperature correction. As noted above, the fluorescent amplitude of the light 331 emitted by the indicator molecules 104, as well as some elements of the circuitry within the sensor 100 (*e.g.,* light source 108), may be temperature sensitive. In one non-limiting embodiment, the circuitry (*e.g.*, measurement controller 532) may correct for the temperature sensitivity as shown in equation 4:

$$[Signal]_T = Signal\left(1 + (T - 37)c_z\right) \qquad (4)$$

wherein the *Signal* is the raw signal generated by the photodetector (*e.g.,* photodetector 224), $[Signal]_T$ is the temperature corrected raw signal, and c_z is the temperature sensitivity of the optical sensor. In one non-limiting embodiment, the temperature sensitivity may simply be the temperature sensitivity of the light source 108.

[0056] In step S214, the circuitry of sensor 100 may compensate for the offset Z present in the raw signal. In some embodiments, the offset Z may be hardware based. For example, in some embodiments, the offset Z may be related at least in part to the peak wavelength of the excitation light 329 emitted by the particular light source 108 used in sensor 100 and/or the tolerance of the particular optical band-pass filter 112 used in sensor 100.

[0057] The offset Z present in the raw signal may result from excitation light 329 emitted from light source 108 that reaches the photodetector (*e.g.*, first (signal) photodetector 224). The excitation light 329 that reaches the photodetector is convoluted in the total light that reaches photodetector, and, thus, produces an offset in the raw signal generated by the photodetector.

[0058] As illustrated in FIG. 3, the excitation light 329 emitted from light source 108 that reaches the photodetector may include (i) a reflection light component 335 that is reflected from the graft 106 (*e.g.,* gel) before reaching the photodetector and (ii) a bleed light component 337 that reaches the photodetector without encountering the graft 106. The reflection light component 335 may produce a reflection component Z_{gel} of the offset Z, and the bleed light component 337 may produce a bleed component Z_{bleed} of the offset Z.

[0059] In some embodiments, the offset Z may be measured during the manufacturing of the sensor 100. However, the offset Z may increase due to photobleaching of the indicator molecules 104. In particular, as indicator molecules 104 become photo-bleached, the overall absorbance of the graft/gel 106 decreases, which increases the reflectance of the graft/gel 106, the amount of excitation light 329 reflected from the graft/gel 106, and the intensity of the reflection light component 335. Accordingly, in some embodiments, in order to compensate for the offset in the raw signal, the circuitry of the sensor 100 may dynamically track the offset (*e.g.,* by using the tracked cumulative emission time t_e).

[0060] In some embodiments, the circuitry of sensor 100 (*e.g.,* measurement controller 532) may compensate for the offset Z present in the raw signal by calculating the offset Z and removing (*e.g.*, subtracting) the offset Z from the raw signal. For example, in embodiments where the raw signal is temperature corrected, the calculated offset Z may be removed from the raw signal by subtracting the calculated offset Z from the temperature corrected raw signal $[Signal]_T$.

[0061] In one non-limiting embodiment, the circuitry of the sensor 100 *(e.g.,* measurement controller 532) may calculate the offset Z as shown in equation 5:

$$[Z] = Z_{gel}\left(1 + \phi_Z\left(1 - e^{-k_{pb}t_{pb}}\right)\right) + Z_{bleed} \qquad (5)$$

where Z_{gel} is the component of the offset Z produced by the reflection light component 335 (*i.e.,* the excitation light 329 spillover component that is reflected from the graft 106 (*e.g.,* gel) and received by the photodetector), ϕ_z is the percent increase of Z_{gel} when the indicator is fully photo-bleached, k_{pb} is the rate of photobleaching, t_{pb} is the photobleaching time, and z_{bleed} is the component of the offset Z produced by the bleed light component 337 (*i.e.,* the portion of the excitation light 329 received by the photodetector that reaches the photodetector without encountering the graft 106). In some embodiments, the circuitry (*e.g.*, measurement controller 532) may use the tracked cumulative emission time t_e for the photobleaching time t_{pb}.

[0062] In step S216, the circuitry of sensor 100 may compensate for the distortion $I_{distortion}$ present in the raw signal. In particular, in some embodiments, the measurement controller 532 may perform the distortion compensation. The distortion $I_{distortion}$ may be chemistry (photochemistry) and kinetics based. The distortion $I_{distortion}$ may be any non-glucose-modulated light in the emission light 331 arriving at the photodetector from the indicator molecules 104. For example, photo, thermal, and oxidative decay species of the indicator molecules 104 may emit fluorescent light that is not modulated by glucose. In fact, most of the distortion $I_{distortion}$ may be due to various matrix species kinetically related to the parent indicator BA (*i.e.,* the active indicator species) as shown in FIG. 4.

[0063] In some embodiments, the glucose indicator molecule BA, within an in-vivo environment, may undergo a steady loss of signal amplitude over time. The glucose indicator molecule BA may be temperature sensitive. In some embodiments, oxidation, thermal degradation, and photobleaching may be the dominant mechanisms of the signal degradation. In some embodiments, the oxidation, thermal degradation, and photobleaching may all be chronic and predictable under a first order decay function on the loss of signal amplitude. This decay may establish the end of useful life for the overall sensor product. In some embodiments, the glucose indicator BA may be degraded by the three decay mechanisms (*i.e.,* oxidation, thermal degradation, and photobleaching).

[0064] In regard to oxidative decay species Ox, in some non-limiting embodiments, under in-vivo conditions, oxidation pressure from ambient and normal reactive oxidation species (ROS), the glucose indicator BA may progressively undergo a highly specific oxidative deboronation. This reaction may remove the boronate recognition moiety of the indicator molecule BA. The resulting deboronated indicator (*i.e.,* oxidized indicator Ox) may be fluorescent (*e.g.,* at a lower quantum efficiency than the glucose indicator BA) and may not modulate. Moreover, the oxidized species Ox may be temperature sensitive and may decay due to photo activation, photobleaching, and/or thermal degradation.

[0065] In regard to photo-activated decay species PA, when the oxidized indicator Ox is photo activated, it may produce a major product (*i.e.,* photo-activated oxidated species PA). Photo-activated oxidated species PA may be fluorescent (*e.g.*, at a higher quantum efficiency than oxidized species Ox) and may not modulate. Similar to the oxidized species Ox, the photo-activated oxidated species PA may be temperature sensitive and may decay due to photobleaching and/or thermal degradation.

[0066] In regard to thermal degradation product species Th, the glucose indicator BA, the oxidized indicator Ox, and the photo-activated decay species PA, may all thermally degrade. Similar to the oxidized species Ox and the photo-activated oxidated species PA, the resulting thermally degraded indicator Th may be fluorescent (*e.g.*, at a lower quantum efficiency than the glucose indicator BA) and does not modulate. The thermal degradation product species Th may be temperature sensitive and may decay due to photobleaching.

[0067] The oxidated species Ox, photo-activated oxidated species PA, and thermal degradation product species Th illustrated in FIG. 4 are fluorescent derivatives of the base glucose-indicator BA. However, only the base glucose-indicator BA of the indicator molecules 104 is a glucose modulated species. Therefore, to obtain the most accurate measurement of glucose concentration based on the emission light 331 received by the photodetector, the fluorescence I produced by the base glucose-indicator BA, which carries glucose concentration information, may be de-convoluted from the emission light 331, which also include fluorescence from the oxidated species Ox, photo-activated oxidated species PA, and thermal degradation product species Th. In other words, the oxidated species Ox, photo-activated oxidated species PA, and thermal degradation product species Th are distortion-producing species, and the non-glucose-modulated light $I_{distortion}$ from these species may be removed from the raw signal. Accordingly, the circuitry of the sensor 100 may track each of the distortion-producing species and remove them from the final signal that is converted to a glucose concentration measurement.

[0068] As shown in FIG. 4, the matrix species also include completely oxidated (*i.e.,* lights out) species LO. This species LO, which is a derivative of the base glucose-indicator BA, has been photobleached and may not emit fluorescence.

[0069] The fluorescence [$I_{distortion}$] from all the distortion-producing species is:

$$[I_{distortion}] = [Ox] + [Th] + [PA] \qquad (8)$$

where [Ox], [PA], and [Th] are fluorescence from the oxidated species Ox, photo-activated oxidated species PA, and thermal degradation product species Th, respectively.

[0070] When the sensor is new (*e.g.*, at manufacturing), the distortion producing subspecies (*e.g.*, Ox, Th, and PA) of the indicator molecules 104 have not yet formed and may contribute nothing significant to the initial raw signal at turn-on. However, the distortion $I_{distortion}$ may increase from the time the sensor 100 is inserted *in vivo.* In particular, once the sensor 100 is inserted in vivo, the distortion producing subspecies (*e.g.*, Ox, Th, and PA) may form progressively. Accordingly, in some embodiments, the circuitry of the sensor 100 may kinetically track the distortion-producing species (*e.g.*, by using the tracked implant time t_i).

[0071] In some embodiments, the circuitry of sensor 100 (*e.g.*, measurement controller 532) may compensate for the distortion $I_{distortion}$ present in the raw signal by calculating the fluorescence emitted from one or more of the distortion producing species (*e.g.*, Ox, Th, and PA) and removing (*e.g.,* subtracting) the non-glucose modulated fluorescence $I_{distortion}$ from the raw signal. For example, in embodiments where the raw signal is temperature corrected, the calculated non-glucose modulated fluorescence $I_{distortion}$ may be removed from the raw signal by subtracting the calculated distortion $I_{distortion}$ from the temperature corrected raw signal $[Signal]_T$.

[0072] In one non-limiting embodiment, the circuitry of the sensor 100 (*e.g.,* measurement controller 532) may calculate the fluorescence emitted from one or more of the distortion producing species (*e.g.*, oxidated species Ox, photo-activated oxidated species PA, and thermal degradation product species Th) as shown in equations 9-11:

$$[OX] = I_{0,QC}\,\%F_{Ox}\left[\left(1-e^{-k_{ox}t_{ox}}\right)e^{-k_{th}t_{th}}e^{-k_{pb}t_{pb}}e^{-k_{pa}t_{pb}}\right]\left[1-(T-37)c_{OX}\right] \tag{9}$$

$$[Th] = I_{0,QC}\,\%F_{Th}\left[\left(1-e^{-k_{th}t_{th}}\right)e^{-k_{pb}t_{pb}}\right]\left[1-(T-37)c_{Th}\right] \tag{10}$$

$$[PA] = I_{0,QC}\,\%F_{PA}\left[\left(1-e^{-k_{ox}t_{ox}}\right)e^{-k_{th}t_{th}}e^{-k_{pb}t_{pb}}\left(1-e^{-k_{pa}t_{pb}}\right)\right]\left[1-(T-37)c_{PA}\right] \tag{11}$$

where $I_{0,QC}$ is the fluorescence intensity of the base glucose indicator at zero glucose concentration I_0 obtained from manufacturing quality control (QC); $\%F_{Ox}$, $\%F_{Th}$, and $\%F_{PA}$ are the relative quantum efficiencies of Ox, Th, and PA, respectively, to the base glucose indicator BA; k_{ox}, k_{th}, and k_{pb} are rates for oxidation, thermal degradation, and photobleaching, respectively; t_{ox}, t_{th}, and t_{pb} are oxidation time, thermal degradation time, and photobleaching time, respectively; and c_{Ox}, c_{Th}, and c_{PA} are the temperature correction coefficients of Ox, Th and PA, respectively. In some embodiments, the circuitry of the sensor 100 (*e.g.,* measurement controller 532) may use the tracked cumulative emission time t_e for the photobleaching time t_{pb}. In some embodiments, the circuitry of the sensor 100 may use the tracked implant time t_i for the oxidation time t_{ox} and thermal degradation time t_{th}.

[0073] The process 200 may include a step S218 of normalizing the raw signal, which in some embodiments may have be temperature corrected, offset compensated, and/or distortion compensated, into a normalized signal Sn. In some embodiments, the normalized signal Sn may be directly proportional to glucose concentration.

[0074] In its simplest form, the normalized signal Sn may be represented by the following equation:

$$Sn = \frac{I}{I_0} \tag{12}$$

where I is the glucose-modulated fluorescence from the indicator molecules 104 and I_0 is baseline glucose-modulated fluorescence at zero glucose concentration.

[0075] As explained above, only the glucose-modulated fluorescence I carries glucose concentration information, but the raw signal generated by the photodetector affected by temperature sensitivity and additionally contains an offset Z and a non-glucose modulated signal $I_{distortion}$. The raw signal may be corrected for temperature sensitivity and the offset Z and a non-glucose modulated signal $I_{distortion}$ may be removed, and, accordingly, the normalized signal Sn is may be represented by the following equation:

$$Sn = \frac{[Signal]_T - Z - I_{distortion}}{I_0} \quad (13)$$

where $[Signal]_T$ is the temperature corrected raw signal.

[0076] The circuitry of the sensor 100 (*e.g.*, measurement controller 532) may remove noise from the raw signal and normalize it so that the normalized signal Sn may have a constant value at infinite glucose concentration. In other words, the normalized signal at infinite glucose concentration (Sn_{max}) may not change even the indicator molecules 104 are photobleached, oxidate, and thermally degrade. If the noise were not removed, the noise may compress the modulation shown in FIG. 5 (*i.e.,* the Y-axis displacement from zero to infinite glucose), and the extent to which the modulation were compressed may change based on the extent to which the indicator molecules 104 were photobleached, oxidated, and/or thermally degraded.

[0077] In some embodiments, the circuitry of sensor 100 (*e.g.,* measurement controller 532) may normalize the glucose-modulated fluorescence I by calculating the baseline glucose-modulated fluorescence at zero glucose concentration (*i.e.,* I_0) and dividing the glucose-modulated fluorescence I by the calculated I_0.

[0078] In one non-limiting embodiment, the circuitry of the sensor 100 may calculate the baseline glucose-modulated fluorescence at zero glucose concentration I_0 according to the following equation:

$$I_0 = I_{0,QC} e^{-k_{ox}t_{ox}} e^{-k_{th}t_{th}} e^{-k_{pb}t_{pb}} \left[1 - (T - 37)c_f\right] \quad (14)$$

where $I_{0,QC}$ is the I_0 obtained from manufacturing quality control (QC); $e^{-k_{ox}t_{ox}}e^{-k_{th}t_{th}}e^{-k_{pb}t_{pb}}$ is the glucose indicator decay due to the superimposition of oxidation, thermal degradation, and photobleaching; k_{ox}, k_{th}, and k_{pb} are rates for oxidation, thermal degradation and photobleaching, respectively; t_{ox}, t_{th}, and t_{pb} are oxidation time, thermal degradation time, and photobleaching time, respectively; c_f is the temperature correction coefficient of the glucose indicator; and T is the temperature of the optical sensor 100, which may be measured by the temperature sensor 670 in step S210. In some embodiments, the circuitry of the sensor 100 may use the tracked cumulative emission time t_e for the photobleaching time t_{pb}. In some embodiments, the circuitry of the sensor 100 (*e.g.,* measurement controller 532) may use the tracked implant time t_i for the oxidation time t_{ox} and thermal degradation time t_{th}. The circuitry of the sensor 100 may be configured to kinetically track the first order decay loss of signal that occurs over time (*e.g.*, by using the tracked cumulative emission time t_e and tracked implant time t_i).

[0079] The process 200 may include a step S220 of converting the normalized signal Sn to a glucose concentration. The conversion of the normalized signal Sn into a glucose concentration may be based on the relationship between percent modulation and glucose as shown in FIG. 5. As described above, the percent modulation I/I_0 versus glucose concentration may be constant throughout the life of the glucose sensor 100. The end of life of the glucose sensor 100 may arise when the signal to noise ratio declines over time to a point where the error specification can no longer be maintained.

[0080] In some embodiments, the circuitry may use an interpretive algorithm to convert the normalized signal Sn into glucose concentration. The interpretive algorithm may be derived through a standard curve based on the following reaction:

$$A + B \longleftrightarrow BA \quad (15)$$

where *A* is glucose indicator, *B* is glucose, and *BA* is glucose-indicator complex. The fluorescence of the indicator increases upon binding glucose.

[0081] The equilibrium expression for the dissociation defining Sn_{max} (*i.e.,* the normalized signal Ns at infinite glucose concentration) is

$$K_d = \frac{[A][B]}{[AB]} \quad (16)$$

[0082] The glucose concentration [A] is

$$[A] = K_d \frac{[AB]}{[B]} \qquad (17)$$

where K_d is constant, and [*AB*] and [*B*] terms must be determined from measurement. The following derivation illustrates how the glucose concentration [*A*] may be calculated at any one measurement (*e.g.*, for any normalized signal Sn) based on the relationship shown in equations 16 and 17.

[0083] The total fluorescence *F* emitted by the indicator molecules 104 is:

$$F = F_B + F_{AB} \qquad (18)$$

where F_B is the fluorescence from the unbound indicator, and F_{AB} is the fluorescence from the glucose indicator complex.

[0084] According to Beer's law:

$$F = I_e ebc\phi \qquad (19)$$

where *F* is fluorescence of the species, I_e is excitation light, *e* is molar extinction coefficient, *b* is path length, *c* is concentration of the fluorescer, and Φ is quantum efficiency.

[0085] By substituting specifically for the concentration terms for each of the glucose indicator *A* and the glucose-indicator complex *AB,* the fluorescence *F* is:

$$F = I_0 eb[B]\phi_B + I_0 eb[AB]\phi_{AB} \qquad (20)$$

[0086] By defining:

$$q_B = \phi_B([B] + [AB]) \qquad (21)$$

$$q_{AB} = \phi_{AB}([B] + [AB]) \qquad (22)$$

$$f_B = \frac{[B]}{[B] + [AB]} \qquad (23)$$

$$f_{AB} = \frac{[AB]}{[B] + [AB]} \qquad (24)$$

equation (20) becomes:

$$F = I_e eb(f_B q_B + f_{AB} q_{AB}) \qquad (25)$$

[0087] The fluorescent signal value at zero glucose concentration F_{min}, which is the lowest fluorescent signal value from the sensor, is:

$$F_{\min} = I_e ebq_B \qquad (26)$$

[0088] The opposite boundary condition occurs when glucose concentration is very high, almost all (*e.g.,* 99.99%) of fluorescence signal is from the glucose indicator complex *AB,* and almost none (*e.g.,* approaching zero) of the fluorescence signal is from unbound indicator *B.* The fluorescent signal value at glucose saturation F_{max}, which is the highest possible value of fluorescence, is:

$$F_{\max} = I_e ebq_{AB} \qquad (27)$$

[0089] By incorporating the equations for F_{min} and F_{max} (*i.e.,* equations 26 and 27) into equation 25, equation 25 becomes

$$F = F_{\min} f_B + F_{\max} f_{AB} = F_{\min} f_B + F_{\max}(1 - f_B) \qquad (28)$$

[0090] Therefore,

$$f_B = \frac{F_{\max} - F}{F_{\max} - F_{\min}} \qquad (29)$$

and

$$f_{AB} = 1 - f_B = \frac{F - F_{\min}}{F_{\max} - F_{\min}} \qquad (30)$$

[0091] The glucose concentration [A] is:

$$[A] = K_d \frac{[AB]}{[B]} = K_d \frac{f_{AB}}{f_B} = K_d \frac{F - F_{\min}}{F_{\max} - F} \qquad (31)$$

[0092] By substituting the normalized fluorescence Sn determined by the circuitry of the sensor 100 for the fluorescence *F,* the glucose concentration [*A*] becomes:

$$[A] = K_d \frac{Sn - Sn_{\min}}{Sn_{\max} - Sn} \qquad (32)$$

where the dissociation constant K_d and normalized signal at glucose saturation Sn_{max} may be determined during manufacturing, the normalized signal Sn is generated by the circuitry of the sensor 100 by processing the raw signal generated by the photodetector of the sensor 100, and Sn_{min} (*i.e.,* I_0/I_0) is equal to one.

[0093] The process 200 may include the step S222 of conveying the glucose concentration to the external sensor reader 101. In some embodiments, the glucose concentration may be conveyed using the inductive element 114 of the sensor 100.

[0094] According to some embodiments of the invention, during sensor manufacturing, one or more sensors 100 may be cycled through a computer automated quality control measurement system. This system may measure parameters (*e.g.,* c_z, K_d, Sn_{max}, Z_{gel}, Z_{bleed}). The cycle may include operating newly manufactured sensor 100 at two different temperatures (*e.g.,* 32°C and 37°C) at three different glucose concentrations (*e.g.*, 0mM, 4.0mM, and 18.0mM glucose). The automated system may track the performance of each sensor 100 under these changing conditions and make specific measurements for each sequential temperature and concentration test. In some embodiments, other parameters (*e.g.,* K_{pb}, K_{pa}, K_{th}, ϕ_z, c_f, c_{Th}, c_{ox}, c_{PA}, $\%F_{Ox}$, $\%F_{PA}$ and $\%F_{Th}$) may be developed from designed and controlled *in vitro* experiments, and still other parameters (*e.g.,* K_{Ox}) may be developed from *in vivo* tests. One or more parameter values may be determined for each manufactured sensor 100 and used by the circuitry of the sensor 100 in processing a raw signal and converting the normalized signal Sn to a glucose concentration (*e.g.,* according to the corresponding serial number of the sensor 100).

[0095] In a non-limiting example of sensors that may be used to determine a concentration of glucose in a medium, experimental results were obtained using eighteen sensors incorporating one or more aspects of the present invention and implanted into type-I diabetic subjects. Data was collected during 6 in-clinic sessions to determine the sensor performance and the accuracy of the algorithm *in vivo.* The sensors were removed 28 days after insertion. The Mean Absolute Relative Difference (MARD) for all the 18 sensors from day 3 data collection through day 28 is 13.7%. Day 0 data collection was excluded as, in some embodiments, the sensor may not be fully responsive to glucose during a heal-up period. A total of 3,466 paired data points were obtained to evaluate sensor performance, and blood glucose measured by YSI machine was used as a reference. FIG. 7 is a Clarke error grid showing the 3,466 paired data points with 3328 data points (96.02%) in either the A range (*i.e.,* values within 20% of the reference sensor) or the B range (*i.e.,* values outside of 20% range but that may not lead to inappropriate treatment). FIG. 8 illustrates experimental results of a sensor embodying aspects of the present invention during six read sessions. FIG. 8 shows the performance of one of the implanted sensors during the six read sessions and shows that the sensor tracks the blood glucose well. The MARD for this sensor is 13%. Other embodiments of the sensor may be used to produce different results.

[0096] In some embodiments, as described above, the circuitry of the sensor 100 (which may, for example, include measurement controller 532) may eliminate noise (*e.g.*, offset and distortions) present in the raw signal generated by the photodetector 224 and convert the purified raw signal into a glucose concentration, and the sensor 100 may convey the glucose concentration to the sensor reader 101. However, this is not required, and, in alternative embodiments, the sensor 100 may convey the raw signal generated by the photodetector 224 to the sensor reader 101, and circuitry of the sensor reader 101 (which may, for example, include PIC microcontroller 920) may eliminate noise present in the raw signal generated by the photodetector 224 and convert the purified raw signal into a glucose concentration. For example, in some embodiments, the circuitry of the sensor reader 101 may (i) purify the raw signal, (ii) normalize the purified signal to produce a normalized signal Sn that is directly proportional to glucose concentration, and (iii) convert the normalized signal Sn into a glucose concentration.

[0097] FIG. 10 illustrates an exemplary raw signal purification and conversion process 1000 that may be performed by a system including the sensor 100, which may be, for example, implanted within a living animal (*e.g.*, a living human), and a sensor reader 101, which may be external to the living animal but in the proximity of the sensor 100 (*e.g.,* on an armband or wristband attached to the living animal), in accordance with an embodiment of the present invention. The process 1000 may include a step S1002 of tracking the amount of time t_i that has elapsed since the optical sensor 100 was implanted in the living animal. As noted above, because oxidation and thermal degradation begins when the sensor 100 is implanted, the implant time t_i may be equivalent to the oxidation time t_{ox} and the thermal degradation time t_{th}.

[0098] In some embodiments, the circuitry of sensor reader 101 may include an implant timer circuit that is started when the sensor 100 is implanted. For example, in one non-limiting embodiment, the implant timer circuit may be a counter that increments with each passing of a unit of time (*e.g.*, one or more milliseconds, one more seconds, one or more minutes, one or more hours, or one or more days, etc.). However, this is not required, and, in some alternative embodiments, the circuitry of the sensor reader 101 may track the implant time t_i by storing the time at which the sensor 100 was implanted (*e.g.,* in memory 922) and comparing the stored time with the current time. In other alternative embodiments, the sensor 100 may receive the time at which the sensor was implanted, *i.e.,* the implant time t_i, from the sensor reader 101 (*e.g.,* when the sensor 100 and sensor reader 101 are first linked together) and store the received implant time t_i (*e.g.,* in nonvolatile storage medium 660). The sensor reader 101 may receive the time at which sensor 100 was implanted from the sensor 100 for calculation of the implant time t_i. The tracked implant time t_i may be used in compensating for distortion in the raw signal, normalizing the raw signal, and/or converting the normalized signal Sn to a glucose concentration.

[0099] The process 1000 may include a step S1004 of tracking the cumulative amount of time t_e that the light source 108 has emitted the excitation light 329. Because the indicator molecules 104 are irradiated with the excitation light 329, the cumulative emission time t_e may be equivalent to the photobleaching time t_{pb}.

[0100] In some embodiments, the circuitry of sensor 100 may include an emission timer circuit that is advanced while the light source 108 emits excitation light 329. For example, in one non-limiting embodiment, the emission timer circuit may be a counter that increments with each passing of a unit of time (*e.g.*, one or more milliseconds, one more seconds, one or more minutes, one or more hours, or one or more days, etc.) while the light source 108 emits excitation light 329. The count may be conveyed by the sensor 100 to the sensor reader 101. However, this is not required. For example, in some alternative embodiments, the light source 108 may emit excitation light 329 for a set amount of time for each measurement, and the counter may increment once for each measurement taken by the sensor 100. Here again, the count may be conveyed by the sensor 100 to the sensor reader 101. In another alternative embodiment, the light source 108 may emit excitation light 329 for a set amount of time for each measurement, and the circuitry of the sensor reader 101 may include an emission timer circuit that is incremented once for each measurement command issued by the sensor reader 101 to the sensor 100 or for each measurement received by the sensor reader 101 from the sensor 100. The tracked cumulative emission time t_e may be used in compensating for offset in the raw signal, compensating for distortion in the raw signal, normalizing the raw signal, and/or converting the normalized signal Sn to a glucose concentration.

[0101] The process 1000 may include a step S1006 of emitting excitation light 329, a step S208 of generating a raw signal indicative of the amount of light received by a photodetector, and/or a step S1010 of measuring the temperature T of the optical sensor 100, which may correspond to steps S206, S208, and S210, respectively, of the process 200 described above with reference to FIG. 2.

[0102] The process 1000 may include a step S1012 of conveying the raw signal indicative of the amount of light received by a photodetector, which may be a digitized raw signal, and/or the measured temperature. In some embodiments, the raw signal and/or measured temperature may be conveyed using the inductive element 114 of the sensor 100. The sensor reader 101 may receive the conveyed raw signal and/or measured temperature (*e.g.*, using the inductive element 103 of the sensor reader 101).

[0103] The process 1000 may include a step S1014 of temperature correcting the raw signal based on the measured temperature of the sensor 100, a step S1016 of compensating for the offset Z present in the raw signal, a step S1018 of compensating for the distortion $I_{distortion}$ present in the raw signal, a step S1020 of normalizing the raw signal, and a step S1022 of converting the normalized signal Sn to a glucose concentration. These steps may correspond to steps S212, S214, S216, S218, and S220, respectively, of the process 200 described above with reference to FIG. 2, except that steps S1014, S1016, S1018, S1020, and S1022 may be performed the circuitry of the sensor reader 101 (*e.g.,* by the PIC microcontroller 920) instead of by the circuitry of the sensor 100 (*e.g.,* by measurement controller 532).

[0104] In some embodiments, the sensor reader 101 may store (*e.g.,* in memory 922) parameters specific to the sensor 100 and use the parameters during performance of steps S1014, S1016, S1018, S1020, and/or S1022. In some non-limiting embodiments, the sensor reader 101 may download some or all of the parameters specific to the sensor 100 from a web server. In some non-limiting embodiments, the sensor reader 101 may receive some or all of the parameters specific to the sensor 100 from the sensor 100, which may store the parameters (*e.g.*, in nonvolatile storage medium 660) and convey the parameters to the sensor reader 101 (*e.g.,* using inductive element 114). In some embodiments, the parameters specific to the sensor 100 may include static parameters and/or dynamic parameters. For instance, in some non-limiting embodiments, the parameters specific to the sensor 100 may include static sensor parameters (*e.g.,* K_{pb}, K_{pa}, K_{th}, ϕ_z, c_f, c_{Th}, c_{ox}, c_{PA}, $\%F_{Ox}$, $\%F_{PA}$ and/or $\%F_{Th}$) developed from controlled *in vitro* experiments and/or static sensor parameters (*e.g.,* K_{Ox}) developed from *in vivo* tests. In some non-limiting embodiments, the sensor reader 101 may store parameters for only one sensor 100 at a time and be paired to a particular sensor 100 after receiving the sensor's parameters (*e.g.,* by downloading them from a web server or receiving them from the sensor 100). However, in alternative embodiments, the sensor reader 101 may store parameters for more than one sensor 100. For example, in one non-limiting embodiment, the sensor reader 101 may store parameters for all of the sensors 100 with which the sensor reader 101 may be used.

[0105] In another alternative embodiment, the circuitry of the sensor 100 (which may, for example, include measurement controller 532) may eliminate noise (*e.g.*, temperature sensitivity, offset, and distortions) present in the raw signal generated by the photodetector 224, the sensor 100 may convey the purified raw signal to the sensor reader 101, and the sensor reader 101 may convert the purified raw signal into a glucose concentration.

[0106] Embodiments of the present invention have been fully described above with reference to the drawing figures. Although the invention has been described based upon these preferred embodiments, it would be apparent to those of skill in the art that certain modifications, variations, and alternative constructions could be made to the described embodiments within the scope of the claims. For example, the circuitry of the sensor 100 and/or the sensor reader 101 may be implemented in hardware, software, or a combination of hardware and software. The software may be implemented as computer executable instructions that, when executed by a processor, cause the processor to perform one or more functions.

Claims

1. A method of determining a concentration of glucose in a medium of a living animal using an optical sensor (100)

adapted to be implanted in the living animal and a sensor reader (101) external to the living animal, the method comprising:

emitting, using a light source (108) of the optical sensor, excitation light to indicator molecules (104) of the optical sensor, the indicator molecules having an optical characteristic responsive to the concentration of glucose;
generating, using a photodetector (224) of the optical sensor, a raw signal indicative of the amount of light received by the photodetector, wherein the light received by the photodetector includes glucose-modulated light emitted by the indicator molecules and at least one of excitation light emitted by the light source and non-glucose modulated light emitted by the indicator molecules;
conveying, using an inductive element (114, 220) of the optical sensor, the raw signal;
receiving, using an inductive element (103) of the sensor reader, the conveyed raw signal;
tracking, using circuitry (920) of the sensor reader, the cumulative emission time that the light source has emitted the excitation light;
tracking, using circuitry (920) of the sensor reader, the implant time that has elapsed since the optical sensor was implanted in the living animal;
adjusting, using circuitry (920) of the sensor reader, the received raw signal to compensate for offset and distortion based on the tracked cumulative emission time and the tracked implant time; and
converting, using circuitry (920) of the sensor reader, the adjusted signal into a measurement of glucose concentration in the medium of the living animal.

2. The method of claim 1, further comprising:

measuring, using a temperature sensor (670) of the optical sensor, a temperature of the optical sensor;
conveying, using the inductive element of the optical sensor, the measured temperature of the optical sensor;
receiving, using the inductive element of the sensor reader, the conveyed temperature of the optical sensor;
correcting, using circuitry (920) of the sensor reader, the received raw signal indicative of the amount of light received by the photodetector to compensate for temperature sensitivity of the light source based on the received temperature.

3. The method of claim 1, wherein the offset is hardware based, and adjusting the received raw signal comprises:

calculating the offset based on the tracked cumulative emission time; and
subtracting the calculated offset from the received raw signal.

4. The method of claim 1, wherein the adjusted signal is directly proportional to glucose concentration in the medium.

5. The method of claim 1, further comprising:

measuring, using a temperature sensor (670) of the optical sensor, a temperature of the optical sensor;
conveying, using the inductive element of the optical sensor, the measured temperature;
receiving, using the inductive element of the sensor reader, the conveyed temperature;
wherein adjusting the received raw signal to compensate for offset and distortion based on the tracked cumulative emission time and the tracked implant time comprises:

temperature correcting, using circuitry (920) of the sensor reader, the received raw signal to compensate for temperature sensitivity of the light source based on the received temperature;
offset adjusting, using the circuitry of the sensor reader, the temperature corrected raw signal to compensate for offset based on the tracked cumulative emission time;
distortion adjusting, using the circuitry of the sensor reader, the offset adjusted raw signal to compensate for distortion based on the tracked cumulative emission time and the tracked implant time; and
normalizing, using the circuitry of the sensor reader, the distortion adjusted raw signal to a normalized raw signal that would be equal to one at zero glucose concentration based on the measured temperature, the tracked cumulative emission time, and the tracked implant time; and

wherein converting the adjusted signal into the measurement of glucose concentration in the medium of the living animal comprises converting, using the circuitry of the sensor reader, the normalized raw signal into a measurement of glucose concentration in the medium of the living animal.

6. The method of claim 1, wherein the non-glucose modulated light emitted by the indicator molecules comprises light emitted by distortion producing indicator molecule subspecies;
wherein, preferably, the distortion producing indicator molecule subspecies include one or more of oxidated species, photo-activated oxidated species, and thermal degradation product species, and adjusting the raw signal preferably comprises:

calculating the light emitted by the one or more of the oxidated species, the photo-activated oxidated species, and the thermal degradation product species based on the tracked cumulative emission time and the tracked implant time; and
subtracting the calculated light emitted by the one or more of the oxidated species, the photo-activated oxidated species, and the thermal degradation product species from the raw signal.

7. The method of claim 1, wherein the glucose-modulated light is emitted by active indicator species of the indicator molecules, and adjusting the raw signal preferably comprises normalizing the raw signal to a normalized raw signal that would be equal to one at zero glucose concentration;
wherein normalizing preferably comprises:

calculating the amount of light emitted by the active indicator species at zero glucose concentration based on the tracked cumulative emission time and the tracked implant time; and
dividing the raw signal by the calculated amount of light emitted by the active indicator species at zero glucose concentration;

wherein calculating the amount of light emitted by the active indicator species at zero glucose concentration is preferably based on a measured temperature of the optical sensor, the tracked cumulative emission time, and the tracked implant time.

8. The method of claim 1, wherein the non-glucose modulated light is emitted by oxidated species, photo-activated oxidated species, and/or photo-activated oxidated species of the indicator molecules.

9. A system for determining a concentration of glucose in a medium of a living animal, the system comprising:

(1) an optical sensor (100) adapted to be implanted in the living animal, wherein the optical sensor includes:

(a) indicator molecules (104) having an optical characteristic responsive to the concentration of glucose;
(b) a light source (108) configured to emit excitation light to the indicator molecules;
(c) a photodetector (224) configured to generate a raw signal indicative of the amount of light received by the photodetector, wherein the light received by the photodetector includes glucose-modulated light emitted by the indicator molecules and at least one of excitation light emitted by the light source and non-glucose modulated light emitted by the indicator molecules; and
(d) an inductive element (114, 220) configured to convey the raw signal; and

(2) a sensor reader (101) external to the living animal, the sensor reader including:

(a) an inductive element (103) configured to receive the conveyed raw signal; and
(b) circuitry (920) configured to:

(i) track the cumulative emission time that the light source has emitted the excitation light;
(ii) track the implant time that has elapsed since the optical sensor was implanted in the living animal;
(iii) adjust the received raw signal to compensate for offset and distortion based on the tracked cumulative emission time and the tracked implant time; and
(iv) convert the adjusted signal into a measurement of glucose concentration in the medium of the living animal.

10. The system of claim 9, further comprising a temperature sensor (670) configured to measure a temperature of the optical sensor;
wherein the inductive element of the optical sensor is configured to convey the measured temperature of the optical sensor, the inductive element of the sensor reader is configured to receive the conveyed temperature, and the circuitry of the sensor reader is further configured to correct the received raw signal to compensate for temperature

sensitivity of the light source based on the received temperature.

11. The system of claim 9, wherein the circuitry is further configured to normalize the received raw signal to a normalized raw signal that would be equal to one at zero glucose concentration.

12. The system of claim 9, wherein the optical sensor includes (e) circuitry (664) configured to convert the raw signal into a digital raw signal, and the conveyed raw signal is the digital raw signal.

Patentansprüche

1. Verfahren zur Bestimmung einer Konzentration von Glukose in einem Medium eines lebendigen Tiers unter Verwendung eines optischen Sensors (100), der in das lebendige Tier implantiert werden kann, und einer Sensorlesevorrichtung (101) außerhalb des lebendigen Tiers, wobei das Verfahren folgendes umfasst:

unter Verwendung einer Lichtquelle (108) des optischen Sensors, Emittieren von Erregungslicht auf Indikatormoleküle (104) des optischen Sensors, wobei die Indikatormoleküle eine optische Eigenschaft aufweisen, die auf die Konzentration von Glukose anspricht;
unter Verwendung eines Photodetektors (224) des optischen Sensors, Erzeugen eines Rohsignals, das die von dem Photodetektor empfangene Lichtmenge anzeigt, wobei das von dem Photodetektor empfangene Licht Glukose-moduliertes Licht aufweist, das von den Indikatormolekülen emittiert wird, und mindestens eines der folgenden Lichter: durch die Lichtquelle emittiertes Erregungslicht und/oder durch die Indikatormoleküle emittiertes nicht Glukose-moduliertes Licht;
unter Verwendung eines induktiven Elements (114, 220) des optischen Sensors, Übertragen des Rohsignals;
unter Verwendung eines induktiven Elements (103) der Sensorlesevorrichtung, Empfangen des übertragenen Rohsignals;
unter Verwendung einer Schaltkreisanordnung (920) der Sensorlesevorrichtung, Verfolgen der kumulativen Emissionszeit, über welche die Lichtquelle das Erregungslicht emittiert hat;
unter Verwendung der Schaltkreisanordnung (920) der Sensorlesevorrichtung, Verfolgen der Implantationszeit, die abgelaufen ist, seit der optische Sensor in das lebendige Tier implantiert worden ist;
unter Verwendung der Schaltkreisanordnung (920) der Sensorlesevorrichtung, Anpassen des empfangenen Rohsignals, um auf der Basis der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit einen Versatz und eine Verzerrung zu kompensieren; und
unter Verwendung der Schaltkreisanordnung (920) der Sensorlesevorrichtung, Umwandeln des angepassten Signals in eine Messung der Glukosekonzentration in dem Medium des lebendigen Tiers.

2. Verfahren nach Anspruch 1, ferner umfassend:

unter Verwendung eines Temperatursensors (670) des optischen Sensors, Messen einer Temperatur des optischen Sensors;
unter Verwendung des induktiven Elements des optischen Sensors, Übertragen der gemessenen Temperatur des optischen Sensors;
unter Verwendung des induktiven Elements der Sensorlesevorrichtung, Empfangen der übertragenen Temperatur des optischen Sensors;
unter Verwendung der Schaltkreisanordnung (920) der Sensorlesevorrichtung, Berichtigen des empfangenen Rohsignals, das die von dem Photodetektor empfangene Lichtmenge anzeigt, um eine Temperaturempfindlichkeit der Lichtquelle auf der Basis der empfangenen Temperatur zu kompensieren.

3. Verfahren nach Anspruch 1, wobei der Versatz auf Hardware basiert, und wobei das Anpassen des Rohsignals folgendes umfasst:

Berechnen des Versatzes auf der Basis der verfolgten kumulativen Emissionszeit; und
Subtrahieren des berechneten Versatzes von dem empfangenen Rohsignal.

4. Verfahren nach Anspruch 1, wobei das angepasste Signal direkt proportional zu der Glukosekonzentration in dem Medium ist.

5. Verfahren nach Anspruch 1, ferner umfassend:

unter Verwendung eines Temperatursensors (670) des optischen Sensors, Messen einer Temperatur des optischen Sensors;
unter Verwendung des induktiven Elements des optischen Sensors, Übertragen der gemessenen Temperatur;
unter Verwendung des induktiven Elements der Sensorlesevorrichtung, Empfangen der übertragenen Temperatur;
wobei das Anpassen des empfangenen Rohsignals zur Kompensation eines Versatzes und einer Verzerrung, das auf der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit basiert, folgendes umfasst:

unter Verwendung der Schaltkreisanordnung (920) der Sensorlesevorrichtung, Korrigieren der Temperatur des empfangenen Rohsignals, um die Temperaturempfindlichkeit der Lichtquelle auf der Basis der empfangenen Temperatur zu kompensieren;
unter Verwendung der Schaltkreisanordnung der Sensorlesevorrichtung, Versatzanpassung des Rohsignals mit korrigierter Temperatur, um einen Versatz auf der Basis der verfolgten kumulativen Emissionszeit zu kompensieren;
unter Verwendung der Schaltkreisanordnung der Sensorlesevorrichtung, Verzerrungsanpassung des Rohsignals mit angepasstem Versatz, um eine Verzerrung auf der Basis der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit zu kompensieren; und
unter Verwendung der Schaltkreisanordnung der Sensorlesevorrichtung, Normalisieren des Rohsignals mit angepasster Verzerrung in ein normalisiertes Rohsignal, das auf der Basis der gemessenen Temperatur, der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit bei einer Glukosekonzentration von Null Eins entsprechen würde; und

wobei das Umwandeln des angepassten Signals in die Messung der Glukosekonzentration in dem Medium des lebendigen Tiers unter Verwendung der Schaltkreisanordnung der Sensorlesevorrichtung das Umwandeln des normalisierten Rohsignals in eine Messung der Glukosekonzentration in dem Medium des lebendigen Tiers umfasst.

6. Verfahren nach Anspruch 1, wobei das von den Indikatormolekülen emittierte nicht Glukose-modulierte Licht umfasst, das durch Verzerrung erzeugende Indikatormolekül-Subspezies emittiert wird;
wobei die Verzerrung erzeugenden Indikatormolekül-Subspezies vorzugsweise eines oder mehrere der folgenden aufweisen: oxidierte Spezies, photoaktivierte oxidierte Spezies und thermische Abbauproduktspezies, und wobei das Anpassen des Rohsignals vorzugsweise folgendes umfasst:

Berechnen des durch die eine oder die mehreren der oxidierten Spezies, der photoaktivierten oxidierten Spezies und der thermischen Abbauproduktspezies emittierten Lichts auf der Basis der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit; und
Subtrahieren des berechneten Lichts, das durch die eine oder die mehreren der oxidierten Spezies, der photoaktivierten oxidierten Spezies und der thermischen Abbauproduktspezies emittiert wird, von dem Rohsignal.

7. Verfahren nach Anspruch 1, wobei das Glukose-modulierte Licht durch aktive Indikatorspezies der Indikatormoleküle emittiert wird, und wobei das Anpassen des Rohsignals vorzugsweise das Normalisieren des Rohsignals in ein normalisiertes Rohsignal umfasst, das bei einer Glukosekonzentration von Null Eins entsprechen würde;
wobei das Normalisieren vorzugsweise folgendes umfasst:

Berechnen der durch die aktiven Indikatorspezies bei einer Glukosekonzentration von Null emittierten Lichtmenge auf der Basis der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit; und
Dividieren des Rohsignals durch die durch die aktiven Indikatorspezies bei einer Glukosekonzentration von Null berechnete emittierte Lichtmenge;

wobei das Berechnen der durch die aktiven Indikatorspezies bei einer Glukosekonzentration von Null emittierten Lichtmenge vorzugsweise auf einer gemessenen Temperatur des optischen Sensors, der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit basiert.

8. Verfahren nach Anspruch 1, wobei das nicht Glukose-modulierte Licht durch oxidierte Spezies, photoaktivierte oxidierte Spezies und/oder photoaktivierte oxidierte Spezies der Indikatormoleküle emittiert wird.

9. System zur Bestimmung einer Konzentration von Glukose in einem Medium eines lebendigen Tiers, wobei das

System folgendes umfasst:

(1) einen optischen Sensor (100), der in das lebendige Tier implantiert werden kann, wobei der optische Sensor folgendes aufweist:

(a) Indikatormoleküle (104) mit einer optischen Eigenschaft, die auf die Konzentration von Glukose reagiert;
(b) eine Lichtquelle (108), die so gestaltet ist, dass sie Erregungslicht der Indikatormoleküle emittiert;
(c) einen Photodektor (224), der so gestaltet ist, dass ein Rohsignal erzeugt, das die durch den Photodetektor empfangene Lichtmenge anzeigt, wobei das durch den Photodetektor empfangene Licht durch die Indikatormoleküle emittiertes Glukose-moduliertes Licht aufweist und mindestens eines der folgenden Lichter: durch die Lichtquelle emittiertes Erregungslicht und/oder durch die Indikatormoleküle emittiertes nicht Glukose-moduliertes Licht; und
(d) ein induktives Element (114, 220), das für eine Übertragung des Rohsignals gestaltet ist; und

(2) eine Sensorlesevorrichtung (101) außerhalb des lebendigen Tiers, wobei die Sensorlesevorrichtung folgendes aufweist:

(a) ein induktives Element (103), das für den Empfang des übertragenen Rohsignals gestaltet ist; und
(b) eine Schaltkreisanordnung (920), die für folgende Zwecke gestaltet ist:

(i) Verfolgen der kumulativen Emissionszeit, über welche die Lichtquelle das Erregungslicht emittiert hat;
(ii) Verfolgen der Implantationszeit, die abgelaufen ist, seit der optische Sensor in das lebendige Tier implantiert worden ist;
(iii) Anpassen des empfangenen Rohsignals, um auf der Basis der verfolgten kumulativen Emissionszeit und der verfolgten Implantationszeit einen Versatz und eine Verzerrung zu kompensieren; und
(iv) Umwandeln des angepassten Signals in eine Messung der Glukosekonzentration in dem Medium des lebendigen Tiers.

10. System nach Anspruch 9, das ferner einen Temperatursensor (670) umfasst, der zum Messen einer Temperatur des optischen Sensors gestaltet ist;
wobei das induktive Element des optischen Sensors so gestaltet ist, dass es die gemessene Temperatur des optischen Sensors überträgt, wobei das induktive Element der Sensorlesevorrichtung für den Empfang der übertragenen Temperatur gestaltet ist, und wobei die Schaltkreisanordnung der Sensorlesevorrichtung ferner für eine Korrektur des empfangenen Rohsignals gestaltet ist, um eine Temperaturempfindlichkeit der Lichtquelle auf der Basis der empfangenen Temperatur zu kompensieren.

11. System nach Anspruch 9, wobei die Schaltkreisanordnung ferner für eine Normalisierung des empfangenen Rohsignals in ein normalisiertes Rohsignal gestaltet ist, das bei einer Glukosekonzentration von Null Eins entsprechen würde.

12. System nach Anspruch 9, wobei der optische Sensor (e) eine Schaltkreisanordnung (664) aufweist, die für eine Umwandlung des Rohsignals in ein digitales Rohsignal gestaltet ist, und wobei das übertragene Rohsignal das digitale Rohsignal ist.

Revendications

1. Procédé de détermination d'une concentration de glucose dans un milieu d'un animal vivant à l'aide d'un capteur optique (100) conçu pour être implanté dans l'animal vivant et un lecteur de capteur (101) externe à l'animal vivant, le procédé comprenant les étapes consistant à :

émettre, à l'aide d'une source de lumière (108) du capteur optique, une lumière d'excitation aux molécules indicatrices (104) du capteur optique, les molécules indicatrices ayant une caractéristique optique sensible à la concentration de glucose ;
générer, à l'aide d'un photodétecteur (224) du capteur optique, un signal brut indiquant la quantité de lumière reçue par le photodétecteur, la lumière reçue par le photodétecteur comprenant une lumière modulée par le glucose émise par les molécules indicatrices et une lumière d'excitation émise par la source de lumière et/ou une lumière modulée par une substance autre que le glucose émise par les molécules indicatrices ;

transmettre, à l'aide d'un élément inductif (114, 220) du capteur optique, le signal brut ;
recevoir, à l'aide d'un élément inductif (103) du lecteur de capteur, le signal brut transmis ;
suivre, à l'aide des circuits (920) du lecteur de capteur, le temps d'émission cumulé pendant lequel la source de lumière a émis la lumière d'excitation ;
suivre, à l'aide des circuits (920) du lecteur du capteur, le temps d'implantation qui s'est écoulé depuis que le capteur optique a été implanté dans l'animal vivant ;
ajuster, à l'aide des circuits (920) du lecteur de capteur, le signal brut reçu pour compenser le décalage et la distorsion en fonction du temps d'émission cumulé suivi et du temps d'implantation suivi ; et
convertir, à l'aide des circuits (920) du lecteur de capteur, le signal ajusté en une mesure de la concentration de glucose dans le milieu de l'animal vivant.

2. Procédé selon la revendication 1, comprenant en outre les étapes consistant à :

mesurer, à l'aide d'un capteur de température (670) du capteur optique, une température du capteur optique ;
transmettre, à l'aide de l'élément inductif du capteur optique, la température mesurée du capteur optique ;
recevoir, à l'aide de l'élément inductif du lecteur de capteur, la température transmise du capteur optique ;
corriger, à l'aide des circuits (920) du lecteur de capteur, le signal brut reçu indiquant la quantité de lumière reçue par le photodétecteur pour compenser la sensibilité à la température de la source de lumière à la température en fonction de la température reçue.

3. Procédé selon la revendication 1, le décalage étant basé sur matériel, et l'ajustement du signal brut reçu comprenant les étapes consistant à :

calculer le décalage sur la base du temps d'émission cumulé suivi ; et
soustraire le décalage calculé du signal brut reçu.

4. Procédé selon la revendication 1, le signal ajusté étant directement proportionnel à la concentration de glucose dans le milieu.

5. Procédé selon la revendication 1, comprenant en outre les étapes consistant à :

mesurer, à l'aide d'un capteur de température (670) du capteur optique, une température du capteur optique ;
transmettre, à l'aide de l'élément inductif du capteur optique, la température mesurée ;
recevoir, à l'aide de l'élément inductif du lecteur, la température transmise ;
l'ajustement du signal brut reçu pour compenser le décalage et la distorsion en fonction du temps d'émission cumulé suivi et du temps d'implantation suivi comprenant les étapes consistant à :

corriger la température, à l'aide des circuits (920) du lecteur de capteur, du signal brut reçu pour compenser la sensibilité à la température de la source de lumière en fonction de la température reçue ;
ajuster en décalage, à l'aide des circuits du lecteur de capteur, le signal brut corrigé en température pour compenser le décalage basé sur le temps d'émission cumulé suivi ;
ajuster en distorsion, à l'aide des circuits du lecteur de capteur, le signal brut ajusté pour compenser la distorsion sur la base du temps d'émission cumulé suivi et du temps d'implantation suivi ; et
normaliser, à l'aide des circuits du lecteur de capteur, le signal brut ajusté à la distorsion en un signal brut normalisé qui serait égal à un à une concentration de glucose nulle, en fonction de la température mesurée, du temps d'émission cumulé suivi et du temps d'implantation suivi ; et
la conversion du signal ajusté en une mesure de la concentration de glucose dans le milieu de l'animal vivant comprenant l'étape consistant à convertir, à l'aide des circuits du lecteur de capteur, le signal brut normalisé en une mesure de la concentration de glucose dans le milieu de l'animal vivant.

6. Procédé de la revendication 1, la lumière non modulée par le glucose émise par les molécules indicatrices comprenant la lumière émise par la sous-espèce de molécule indicatrice produisant une distorsion ;
de préférence, les sous-espèces de molécules indicatrices produisant des distorsions comprenant des espèces oxydées, des espèces oxydées photo-activées et/ou des espèces de produits de dégradation thermique, et l'ajustement du signal brut comprenant de préférence les étapes consistant à :

calculer la lumière émise par les espèces oxydées, les espèces oxydées photo-activées et/ou les espèces de produits de dégradation thermique sur la base du temps d'émission cumulé suivi et du temps d'implantation

suivi ; et
soustraire le signal brut la lumière calculée émise par les espèces oxydées, les espèces oxydées photo-activées et/ou les espèces de produits de dégradation thermique.

7. Procédé selon la revendication 1, la lumière modulée par le glucose étant émise par des espèces indicatrices actives des molécules indicatrices et l'ajustement du signal brut comprenant de préférence l'étape consistant à normaliser le signal brut à un signal brut normalisé qui serait égal à un à une concentration de glucose nulle ;
la normalisation comprenant de préférence les étapes consistant à :

calculer la quantité de lumière émise par l'espèce indicatrice active à une concentration de glucose nulle, sur la base du temps d'émission cumulé suivi et du temps d'implantation suivi ; et
diviser le signal brut par la quantité calculée de lumière émise par l'espèce indicatrice active à une concentration de glucose nulle ;

le calcul de la quantité de lumière émise par l'espèce indicatrice active à une concentration de glucose nulle étant de préférence basé sur une température mesurée du capteur optique, le temps d'émission cumulé suivi et le temps d'implantation suivi.

8. Procédé selon la revendication 1, la lumière non modulée par le glucose étant émise par des espèces oxydées, des espèces oxydées photo-activées et/ou des espèces oxydées photo-activées des molécules indicatrices.

9. Système permettant de déterminer une concentration de glucose dans un milieu d'un animal vivant, le système comprenant :

(1) un capteur optique (100) conçu pour être implanté dans l'animal vivant, le capteur optique comprenant :

(a) des molécules indicatrices (104) ayant une caractéristique optique sensible à la concentration de glucose ;
(b) une source de lumière (108) conçue pour émettre une lumière d'excitation aux molécules indicatrices ;
(c) un photodétecteur (224) conçu pour générer un signal brut indiquant la quantité de lumière reçue par le photodétecteur, la lumière reçue par le photodétecteur comprenant une lumière modulée par le glucose émise par les molécules indicatrices et au moins une lumière d'excitation émise par la source de lumière et une lumière non modulée par le glucose émise par les molécules indicatrices ; et
(d) un élément inductif (114, 220) conçu pour transmettre le signal brut ; et

(2) un lecteur de capteur (101) externe à l'animal vivant, le lecteur de capteur comprenant :

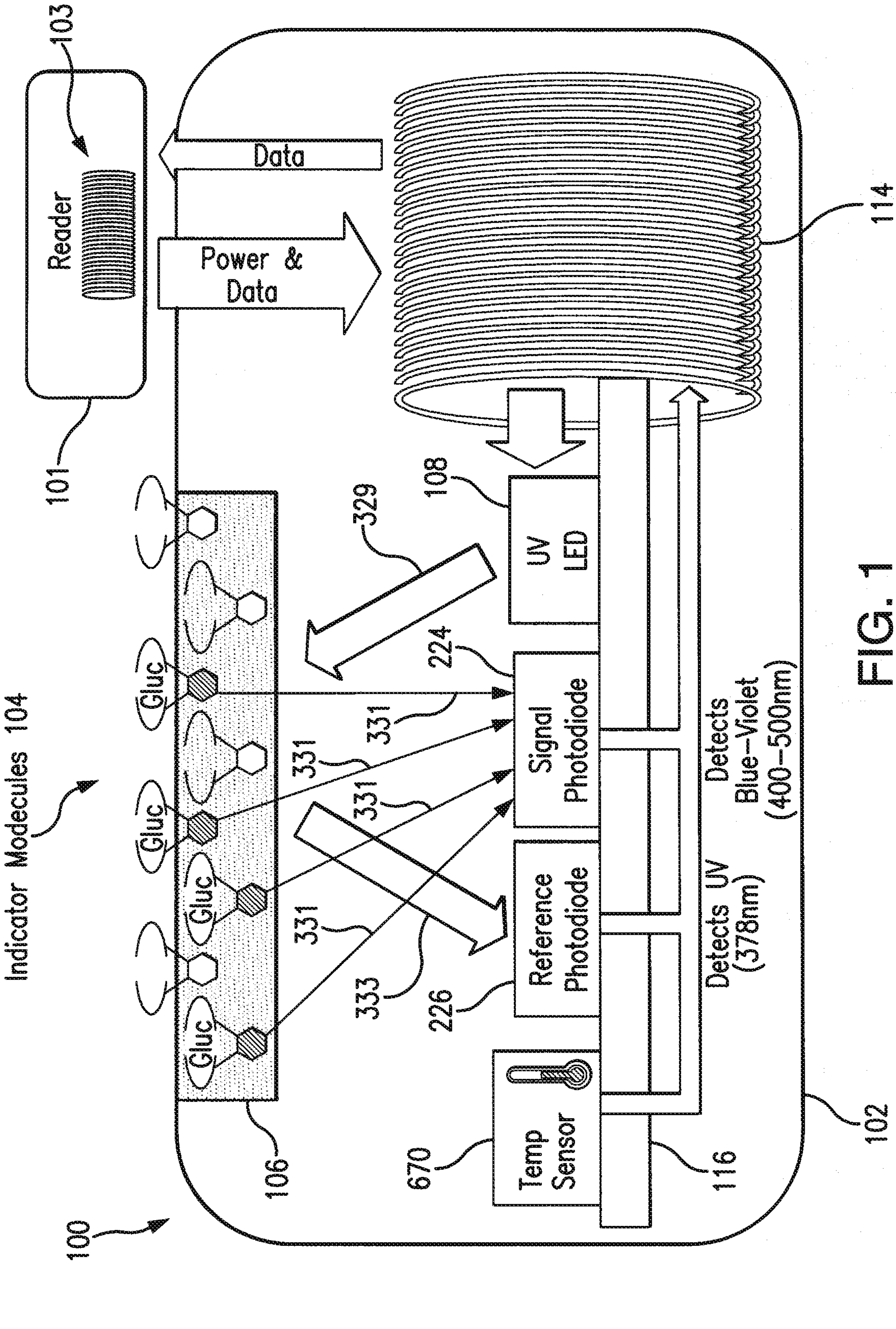
(a) un élément inductif (103) conçu pour recevoir le signal brut transmis ; et
(b) des circuits (920) conçus pour :

(i) suivre le temps d'émission cumulé pendant lequel la source de lumière a émis la lumière d'excitation ;
(ii) suivre le temps écoulé depuis que le capteur optique a été implanté dans l'animal vivant ;
(iii) ajuster le signal brut reçu pour compenser le décalage et la distorsion sur la base du temps d'émission cumulé suivi et du temps d'implantation suivi ; et
(iv) convertir le signal ajusté en une mesure de la concentration de glucose dans le milieu de l'animal vivant.

10. Système selon la revendication 9, comprenant en outre un capteur de température (670) conçu pour mesurer une température du capteur optique ;
l'élément inductif du capteur optique étant conçu pour transmettre la température mesurée du capteur optique, l'élément inductif du lecteur de capteur étant conçu pour recevoir la température transmise, et les circuits du lecteur de capteur étant en outre conçus pour corriger le signal brut reçu afin de compenser la sensibilité à la température de la source de lumière en fonction de la température reçue.

11. Système selon la revendication 9, les circuits étant en outre conçus pour normaliser le signal brut reçu en un signal brut normalisé qui serait égal à un à une concentration de glucose nulle.

12. Système selon la revendication 9, le capteur optique comprenant (e) des circuits (664) conçus pour convertir le signal brut en un signal brut numérique, et le signal brut transmis étant le signal brut numérique.



Indicator Modecules 104
103
Reader
101
Data
Power & Data
114
Gluc
Gluc
Gluc
Gluc
329
108
UV LED
224
331
331
331
331
333
Signal Photodiode
Reference Photodiode
226
106
670
Temp Sensor
116
Detects UV (378nm)
Detects Blue–Violet (400–500nm)
102
100

FIG. 1

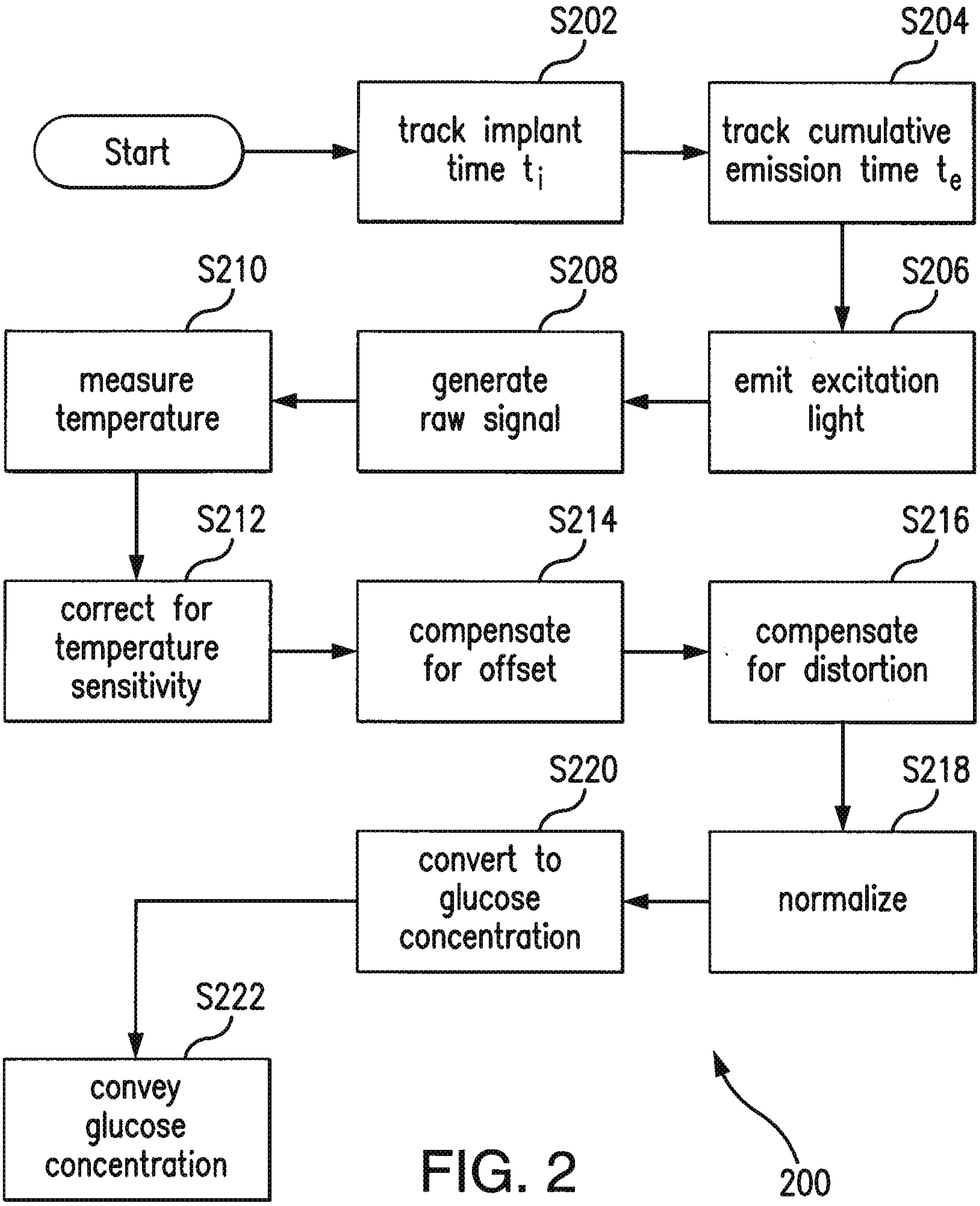

Start
S202
track implant time t_i
S204
track cumulative emission time t_e
S206
emit excitation light
S208
generate raw signal
S210
measure temperature
S212
correct for temperature sensitivity
S214
compensate for offset
S216
compensate for distortion
S218
normalize
S220
convert to glucose concentration
S222
convey glucose concentration
200

FIG. 2

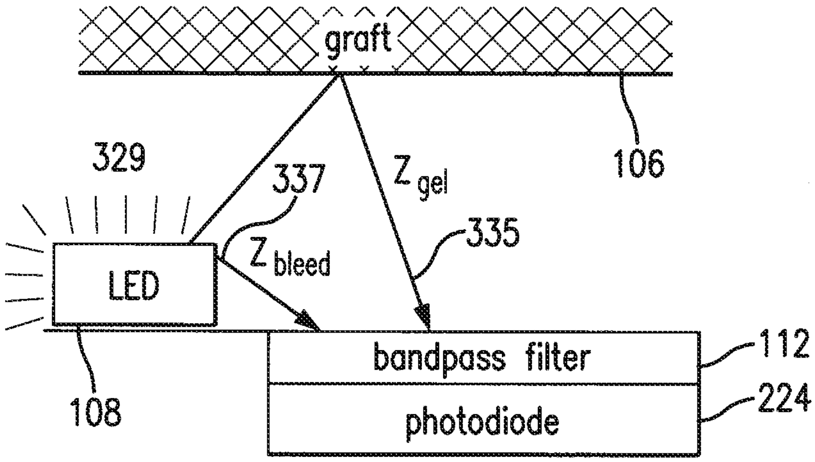

graft
329
337
Z gel
106
335
LED
Z bleed
bandpass filter
112
photodiode
224
108

FIG. 3

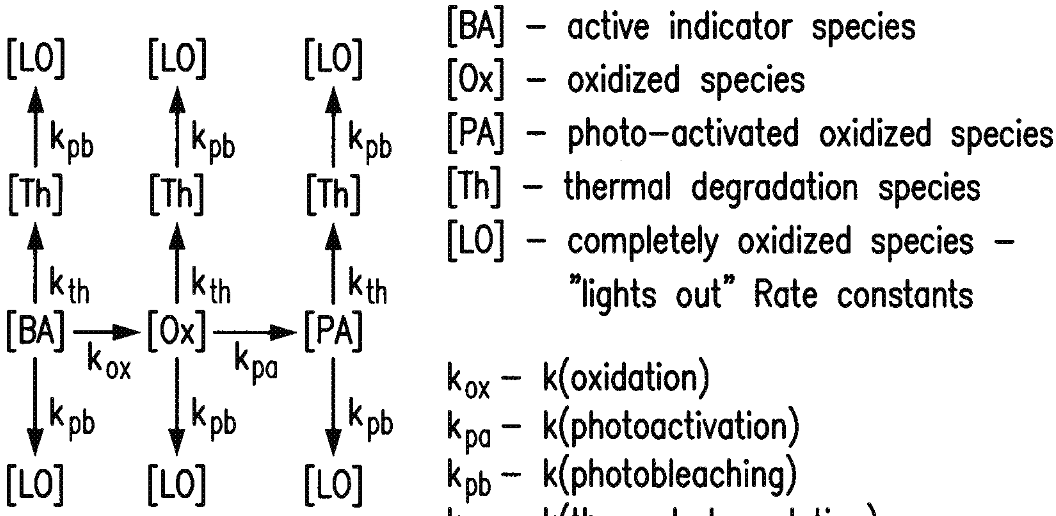

[LO]
kpb
[Th]
kth
[BA]
kox
[Ox]
kpa
[PA]
[BA] – active indicator species
[Ox] – oxidized species
[PA] – photo–activated oxidized species
[Th] – thermal degradation species
[LO] – completely oxidized species – "lights out" Rate constants
kox – k(oxidation)
kpa – k(photoactivation)
kpb – k(photobleaching)
kth – k(thermal degradation)

FIG. 4

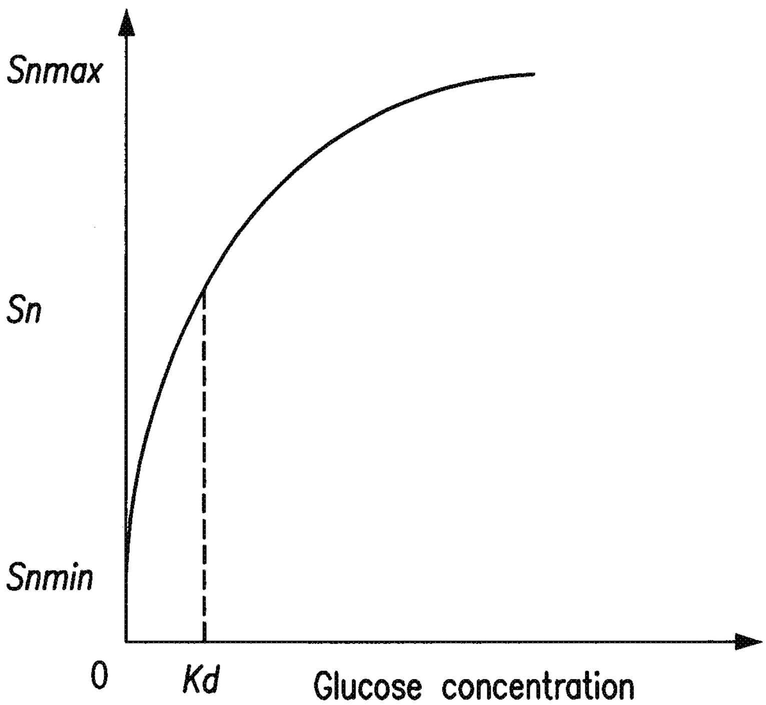
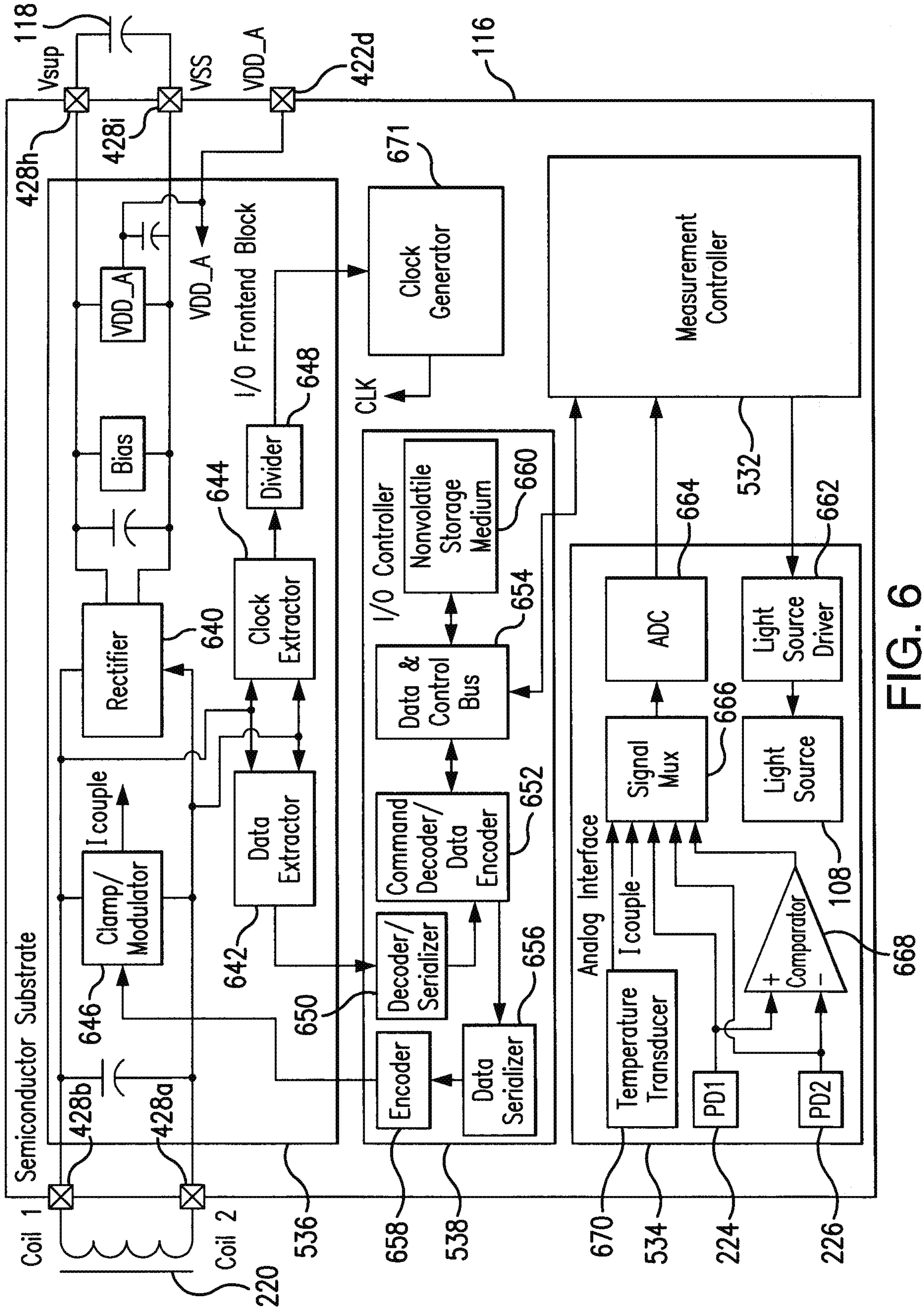


FIG. 5



Semiconductor Substrate
I/O Frontend Block
Rectifier
Bias
VDD_A
Clamp/Modulator
I couple
Clock Extractor
Data Extractor
Divider
Clock Generator
CLK
I/O Controller
Nonvolatile Storage Medium
Data & Control Bus
Command Decoder/ Data Encoder
Decoder/ Serializer
Encoder
Data Serializer
Measurement Controller
Analog Interface
ADC
Light Source Driver
Signal Mux
Light Source
Temperature Transducer
I couple
Comparator
PD1
PD2
Coil 1
Coil 2
Vsup
VSS
VDD_A
118
116
428h
428i
422d
671
644
648
640
642
646
650
652
654
656
658
660
662
664
666
668
670
532
534
536
538
108
224
226
220
428a
428b

FIG. 6

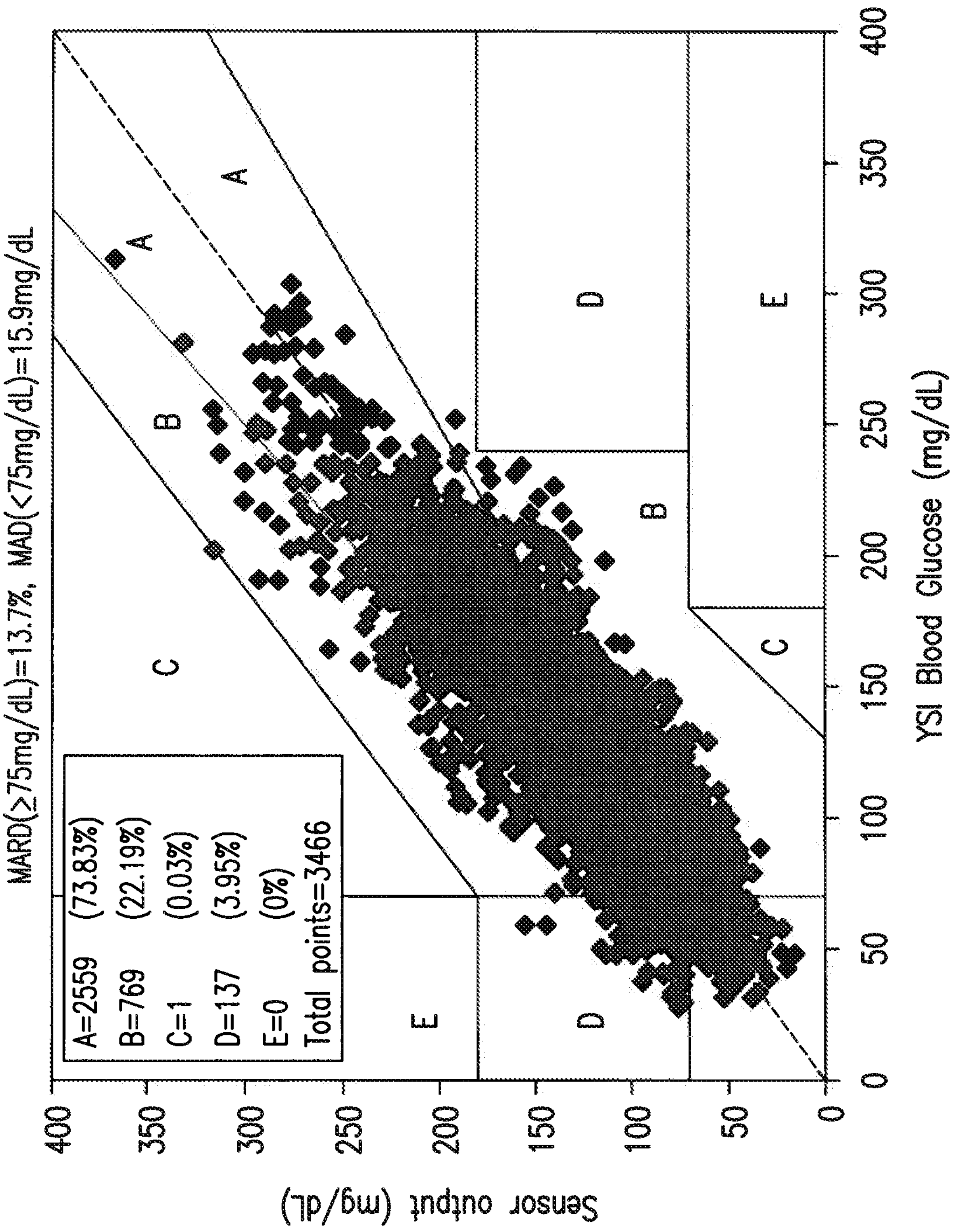

Clarke Error Grid
MARD(≥75mg/dL)=13.7%, MAD(<75mg/dL)=15.9mg/dL
A=2559 (73.83%)
B=769 (22.19%)
C=1 (0.03%)
D=137 (3.95%)
E=0 (0%)
Total points=3466
A
A
B
B
C
C
D
D
E
E
Sensor output (mg/dL)
YSI Blood Glucose (mg/dL)
0
50
100
150
200
250
300
350
400

FIG. 7

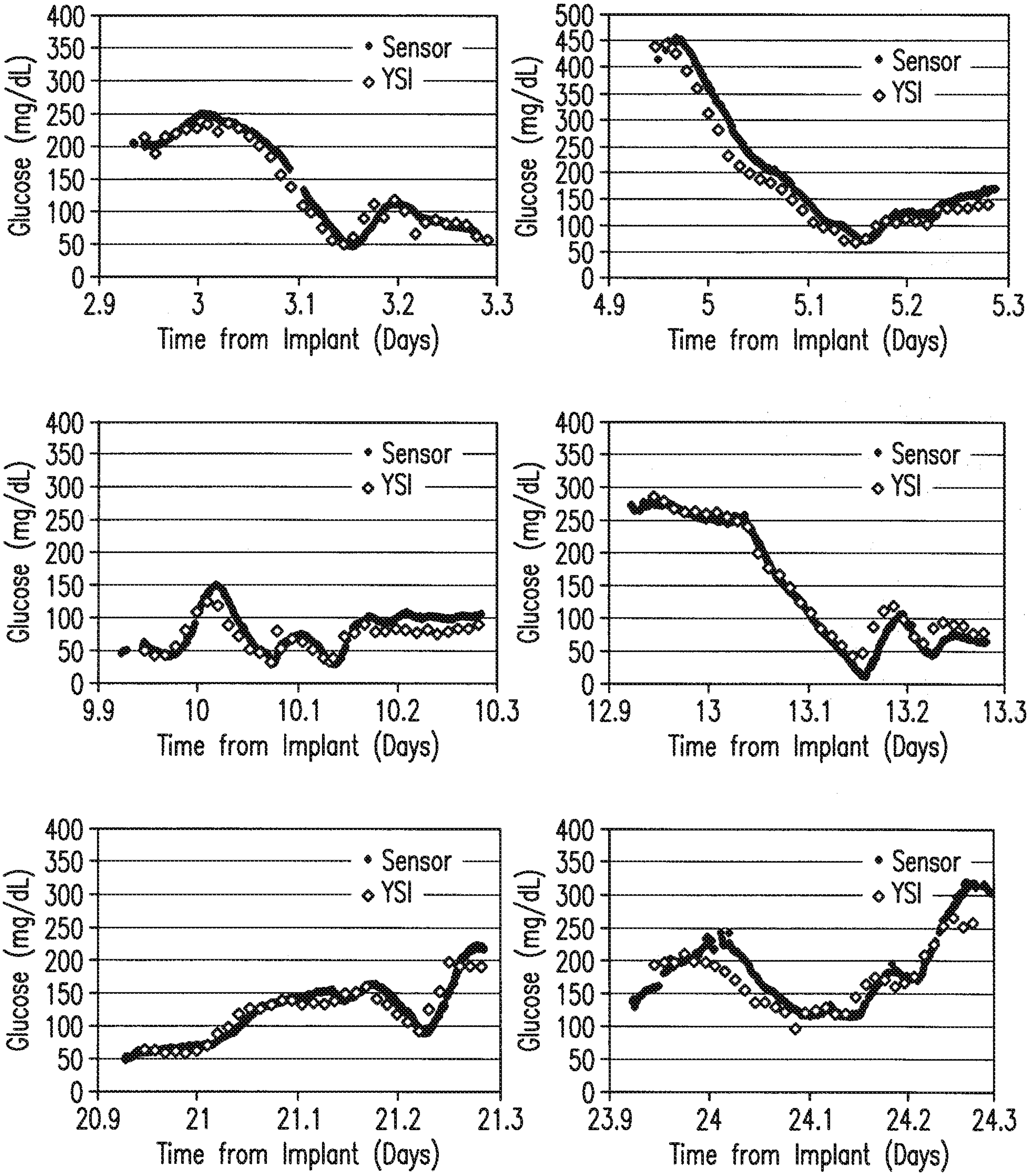

Glucose (mg/dL)
Time from Implant (Days)
Sensor
YSI
400
350
300
250
200
150
100
50
0
2.9
3
3.1
3.2
3.3
500
450
4.9
5
5.1
5.2
5.3
9.9
10
10.1
10.2
10.3
12.9
13
13.1
13.2
13.3
20.9
21
21.1
21.2
21.3
23.9
24
24.1
24.2
24.3

FIG. 8

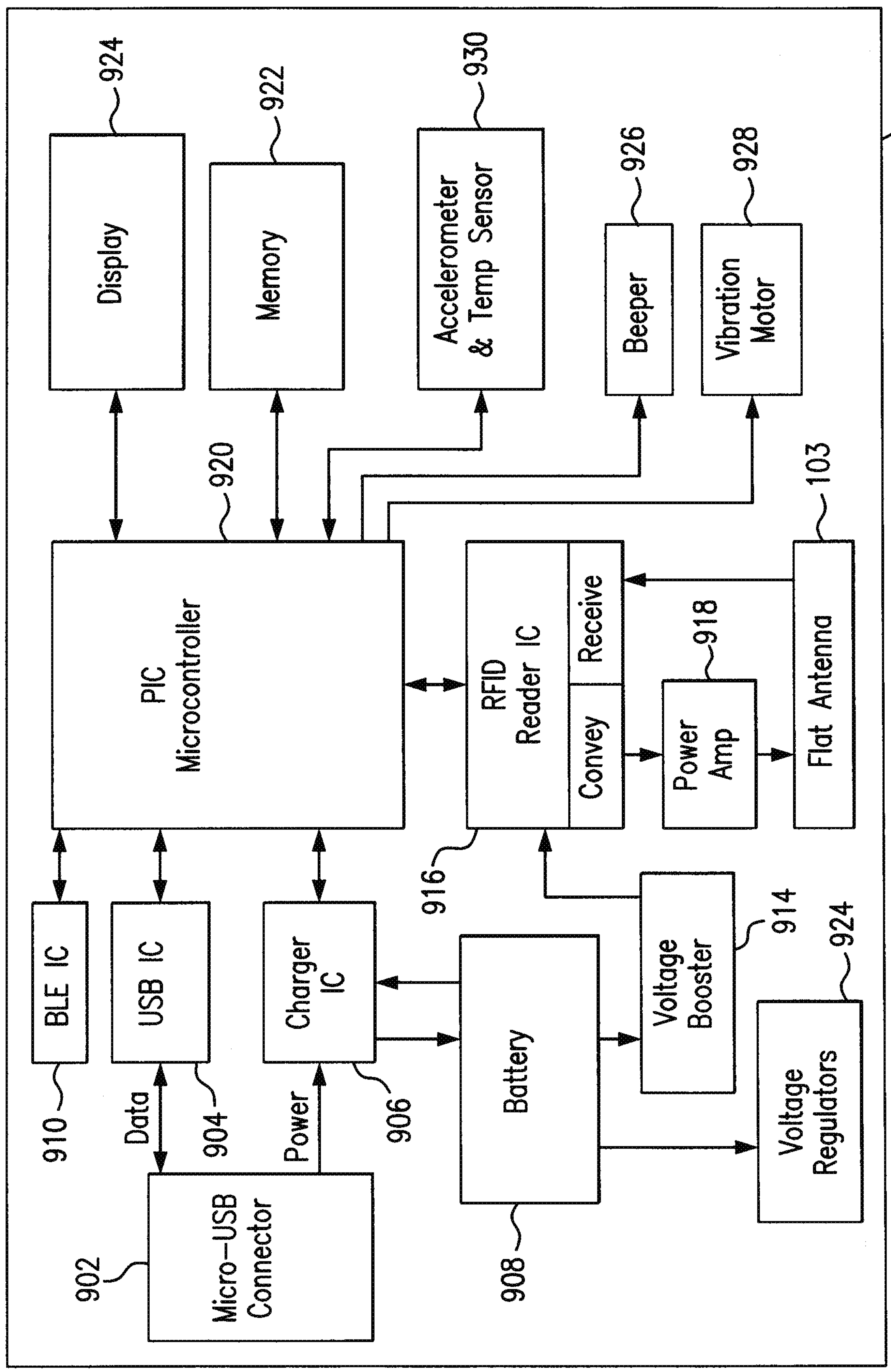

Display
924
Memory
922
Accelerometer & Temp Sensor
930
Beeper
926
Vibration Motor
928
101
PIC Microcontroller
920
RFID Reader IC
Receive
Convey
916
Power Amp
918
Flat Antenna
103
BLE IC
910
USB IC
904
Data
Charger IC
906
Power
Micro-USB Connector
902
Battery
908
Voltage Booster
914
Voltage Regulators
924

FIG. 9

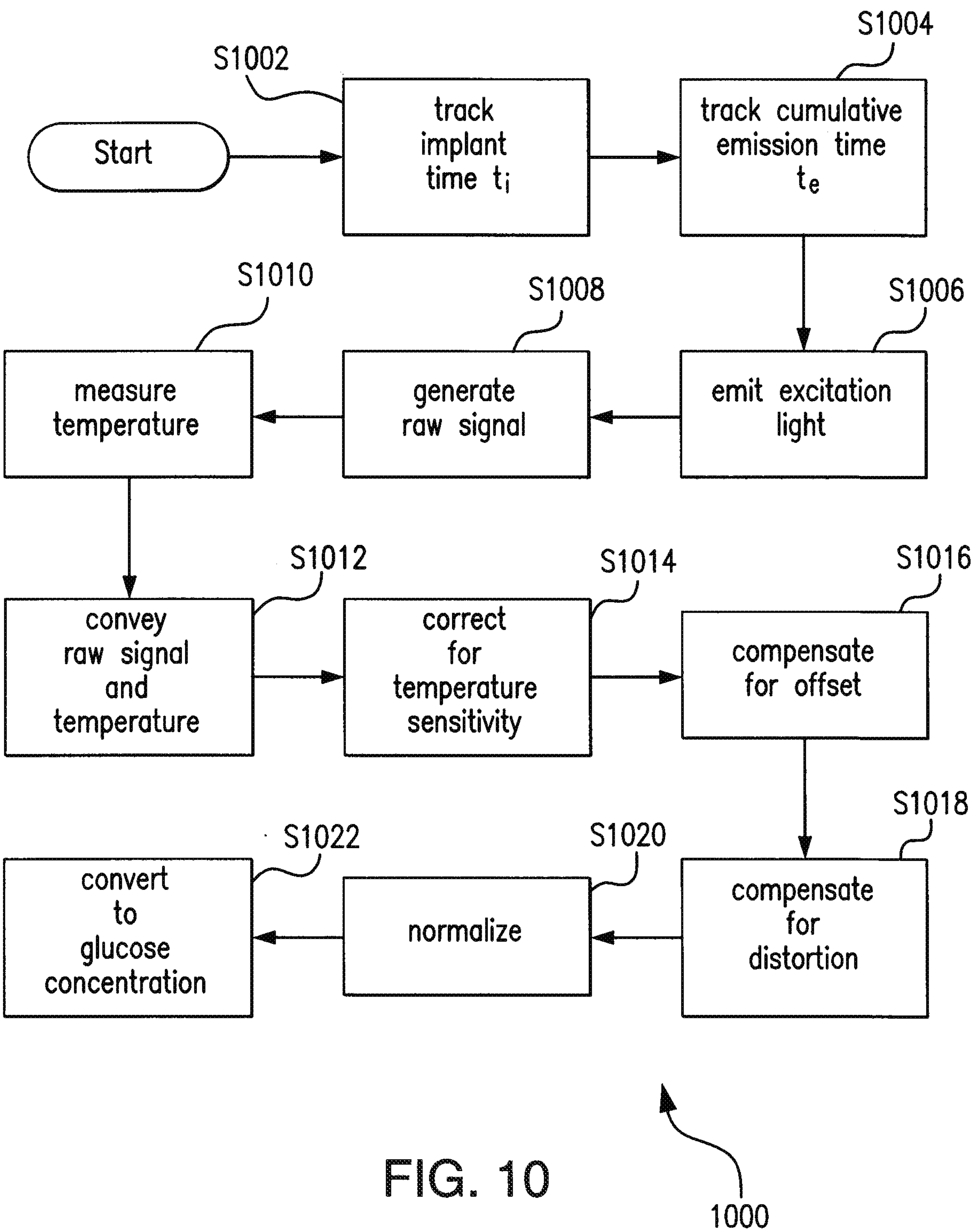

Start
S1002
track implant time t_i
S1004
track cumulative emission time t_e
S1006
emit excitation light
S1008
generate raw signal
S1010
measure temperature
S1012
convey raw signal and temperature
S1014
correct for temperature sensitivity
S1016
compensate for offset
S1018
compensate for distortion
S1020
normalize
S1022
convert to glucose concentration
1000

FIG. 10

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5517313 A **[0002]**
- US 5512246 A **[0002]**
- WO 2013149129 A1 **[0006]**
- US 20130241745 A1 **[0029]**
- US 6330464 B **[0032]**
- US 8073548 B **[0032]**

patsnap

专利名称(译)	在可植入荧光的葡萄糖传感器中纯化葡萄糖浓度信号		
公开(公告)号	EP3019072A1	公开(公告)日	2016-05-18
申请号	EP2014822131	申请日	2014-03-13
申请(专利权)人(译)	SENSEONICS注册成立		
当前申请(专利权)人(译)	SENSEONICS注册成立		
[标]发明人	COLVIN ARTHUR E WANG XIAOLIN MDINGI COLLEEN DEHENNIS ANDREW		
发明人	COLVIN, ARTHUR, E. WANG, XIAOLIN MDINGI, COLLEEN DEHENNIS, ANDREW		
IPC分类号	A61B5/00		
CPC分类号	A61B5/0071 A61B5/14532 A61B5/1459 A61B5/7203 A61B2560/0252		
代理机构(译)	泽吉尔斯达，ROBERT WIEBO JOHAN		
优先权	13/937871 2013-07-09 US		
其他公开文献	EP3019072A4 EP3019072B1		
外部链接	Espacenet		

摘要(译)

公开了用于确定活动物的培养基中的葡萄糖浓度的方法，传感器和系统。 确定葡萄糖浓度可以包括：将激发光从光源发射到指示剂分子；产生指示由光电检测器接收的光量的原始信号；纯化和归一化该原始信号；以及将归一化的信号转换为葡萄糖浓度。 纯化可涉及从原始信号中去除噪声（例如，偏移和/或失真）。 纯化和归一化可以涉及跟踪光源已经发射激发光的累积发射时间以及跟踪自光学传感器被植入以来已经过去的植入时间。 纯化和归一化可能涉及测量传感器的温度。 纯化，标准化和转化可涉及使用在制造，体外测试和/或体内测试期间确定的参数。