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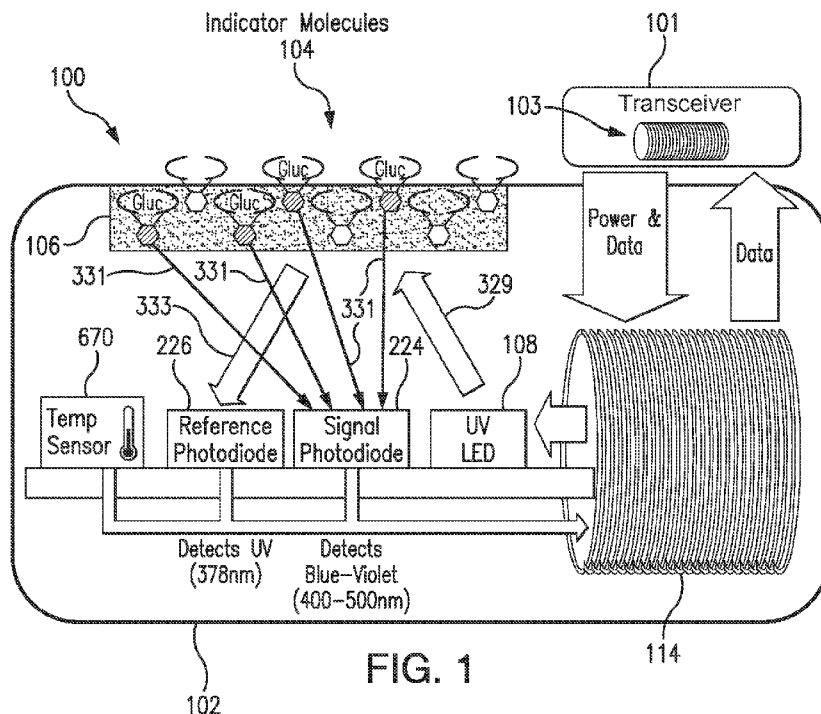


FIG. 1

(57) Abstract: A sensor (e.g., an optical sensor) that may be implanted within a living animal (e.g., a human) and may be used to measure an analyte (e.g., glucose or oxygen) in a medium (e.g., interstitial fluid, blood, or intraperitoneal fluid) within the animal. The sensor may include a sensor housing, an analyte indicator covering at least a portion of the sensor housing, and one or more compounds containing boronate or boronic acid moieties that reduce degradation of the analyte indicator.



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SPECIFICATION

MEDIATION OF *IN VIVO* ANALYTE SIGNAL DEGRADATION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit of priority to U.S. Provisional Application Serial No. 63/237,396, filed on August 26, 2021, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Field of Invention

[0003] The present invention relates generally to continuous reduction of *in vivo* degradation of analyte sensor moieties when measuring an analyte in a medium of a living animal using a system including a sensor implanted (partially or fully) or inserted into the living animal. Specifically, the present invention relates to a sensor that utilizes one or more additives, which may be incorporated within an analyte indicator, and/or a material covering at least a portion of the analyte indicator.

[0004] Discussion of the Background

[0005] A sensor may be implanted (partially or fully) within a living animal (*e.g.*, a human) and used to measure an analyte (*e.g.*, glucose, oxygen, cardiac markers, low-density lipoprotein (LDL), high-density lipoprotein (HDL), or triglycerides) in a medium (*e.g.*, interstitial fluid (ISF), blood, or intraperitoneal fluid) 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 an

analyte are described in U.S. Pat. Nos. 5,517,313 and 5,512,246, which are incorporated herein by reference in their entirety.

[0006] A sensor may include an analyte indicator, which may be in the form of indicator molecules embedded in a graft (*i.e.*, layer or matrix). For example, in an implantable fluorescence-based glucose sensor, fluorescent indicator molecules may reversibly bind glucose and, when irradiated with excitation light (*e.g.*, light having a wavelength of approximately 378 nm), emit an amount of light (*e.g.*, light in the range of 400 to 500 nm) that depends on whether glucose is bound to the indicator molecule.

[0007] If a sensor is implanted in the body of a living animal, the animal's immune system may begin to attack the sensor. For instance, if a sensor is implanted in a human, white blood cells may attack the sensor as a foreign body, and, in the initial immune system onslaught, neutrophils may be the primary white blood cells attacking the sensor. The defense mechanism of neutrophils includes the release of highly caustic substances known as reactive oxygen species. The reactive oxygen species include, for example, hydrogen peroxide.

[0008] Hydrogen peroxide and other reactive species such as reactive oxygen and nitrogen species may degrade the indicator molecules of an analyte indicator. For instance, in indicator molecules having a boronate group, hydrogen peroxide may degrade the indicator molecules by oxidizing the boronate group, thus disabling the ability of the indicator molecule to bind glucose.

[0009] There is presently a need in the art for improvements in reducing analyte indicator degradation. There is also a need in the art for continuous analyte sensors having increased longevity.

SUMMARY

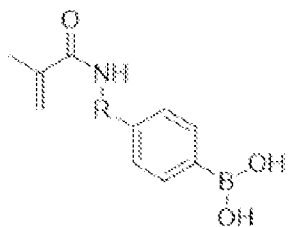
[0010] The present invention overcomes the disadvantages of prior systems by providing, among other advantages, reduced analyte indicator degradation.

[0011] One aspect of the present invention provides a sensor that may be for implantation or insertion within a living animal and measurement of an analyte in a medium within the living animal. The sensor may include a sensor housing, an analyte indicator covering at least a portion of the sensor housing, and one or more additives that reduce deterioration of the analyte indicator.

[0012] In some embodiments, the sensor may include at least one additive-containing polymer graft, and the one or more additives may be co-polymerized with or dispersed within the additive-containing polymer graft. In some embodiments, the additive-containing polymer graft may cover at least a portion of the sensor housing. In some embodiments, the additive-containing polymer graft may be within the sensor housing.

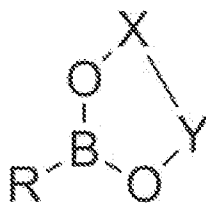
[0013] In some embodiments, the one or more additives may be incorporated with the analyte indicator, e.g., as a co-monomer. In some embodiments, the sensor may include a material, e.g., a membrane, covering at least a portion of the analyte indicator, and the one or more additives are incorporated within the material.

[0014] Another aspect of the present invention provides a sensor for measurement of an analyte in a medium within a living animal. The sensor may include a sensor housing, an analyte indicator covering at least a portion of the sensor housing, and one or more compounds containing boronate or boronic acid moieties that reduce degradation of the analyte indicator. The one or more compounds containing boronic acid containing moieties maybe a compound of Formula I:



[Formula I], wherein R = methylene or an alkyl group, an aryl group, a

heteroaryl group, a cyclic group, a multicyclic group, a polyalkylene glycol group, a polyethylene glycol (PEG) group, a linear or substituted polyalkylene glycol or PEG group, or a combination thereof, or a compound of Formula I wherein the boronic acid is substituted with a



boronate group of Formula II:

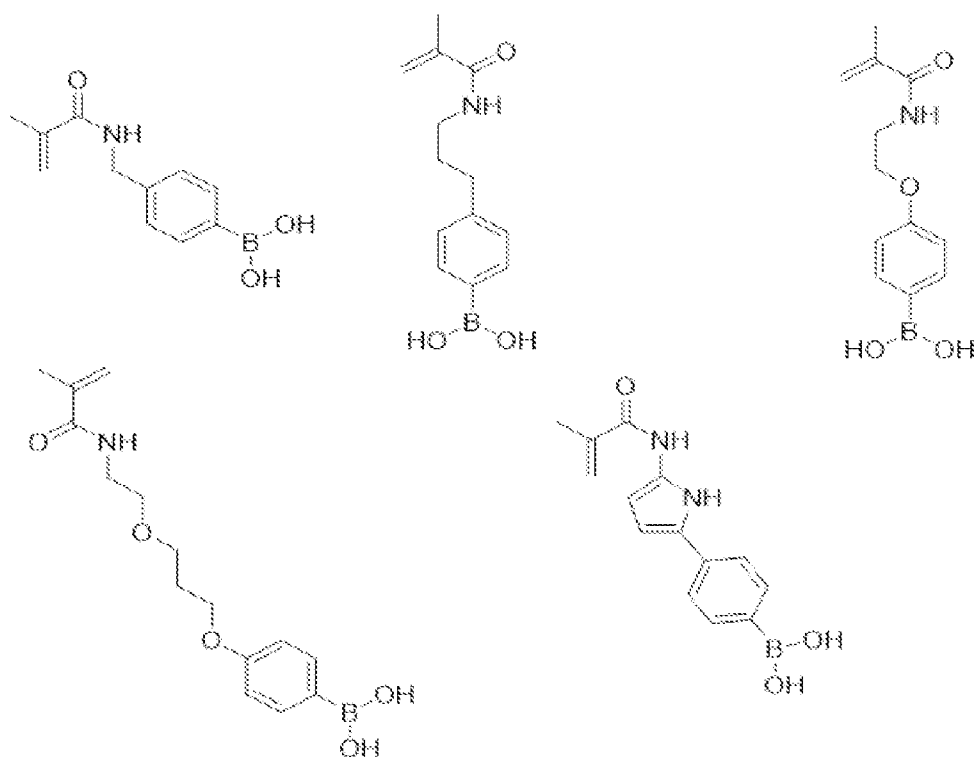
[Formula II], wherein X and Y = alkyl.

[0015] In some embodiments, the sensor may be implantable within a living animal. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be co-monomers with the analyte indicator. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be co-monomers with the analyte indicator in a hydrogel. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be entrapped in a hydrogel covering at least a portion of the sensor housing.

[0016] In some embodiments, the one or more compounds containing boronate or boronic acid moieties may reduce chemical degradation and/or oxidation of the analyte indicator. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may reduce a degradation rate of the analyte indicator. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may bind to degradative species. In

some embodiments, the one or more compounds containing boronic acid containing moieties may sequester degradative species so as to reduce, and/or prevent degradation of the analyte indicator by the degradative species.

[0017] In some embodiments, the compound containing boronate or boronic acid moieties may be selected from

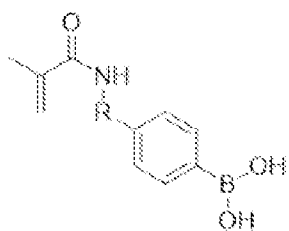


[0018] In some embodiments, the analyte indicator covering at least a portion of the sensor housing may include a polymer comprising co-monomers of four monomers according to Formula II: $A_xB_yC_zD_w$ [Formula II], A may be an analyte indicator monomer, B may be a methacrylate monomer, C may be a polyethylene glycol monomer, D may be a compound or monomer containing boronate or boronic acid moieties, A may be 0.01 to 10 % by weight, B may be 1 to 99 % by weight, C may be 1 to 99 % by weight, and D may be 0.01 to 99% by weight of the total polymer. In some embodiments, the one or more compounds containing

boronate or boronic acid moieties may be provided at a molar ratio of 0.1 to 100 to the analyte indicator monomer.

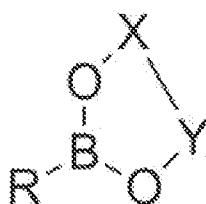
[0019] In some embodiments, the sensor may include at least one drug eluting polymer matrix that covers a portion of the sensor housing.

[0020] Yet another aspect of the present invention provides a method of fabricating a sensor for measurement of an analyte in a medium within a living animal. The method may include applying an analyte indicator to a sensor housing of the sensor such that the applied analyte indicator covers at least a portion of the sensor housing, and the analyte indicator may include one or more compounds containing boronate or boronic acid moieties that reduce degradation of the analyte indicator. The one or more compounds containing boronic acid containing moieties may be selected from: a compound of Formula I:



[Formula I], wherein R = methylene or an alkyl group, an aryl group, a

heteroaryl group, a cyclic group, a multicyclic group, a polyalkylene glycol group, a polyethylene glycol (PEG) group, a linear or substituted polyalkylene glycol or PEG group, or a combination thereof, or a compound of Formula I wherein the boronic acid is substituted with a



boronate group of Formula II:

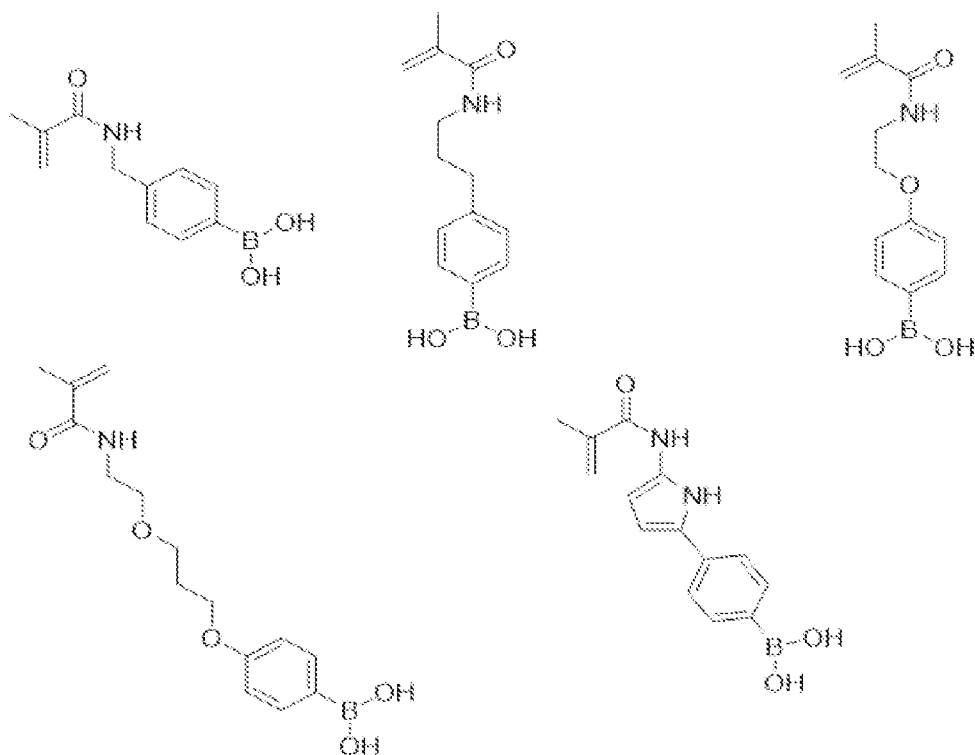
[Formula II], wherein X and Y = alkyl.

[0021] In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be co-monomers with the analyte indicator. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be co-monomers with the analyte indicator in a hydrogel. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be entrapped in a hydrogel covering at least a portion of the sensor housing.

[0022] In some embodiments, the one or more compounds containing boronate or boronic acid moieties may reduce chemical degradation and/or oxidation of the analyte indicator. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may reduce a degradation rate of the analyte indicator.

[0023] In some embodiments, the one or more compounds containing boronate or boronic acid moieties may interact or react with a degradative species without compromising signal integrity or performance of the sensor device, and the degradative species may be hydrogen peroxide, a reactive oxygen species, a reactive nitrogen species, enzymes, free radical or metal ions. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may bind to the degradative species. In some embodiments, the one or more compounds containing boronate or boronic acid moieties may sequester the degradative species so as to reduce, and/or prevent degradation of the analyte indicator by the degradative species.

[0024] In some embodiments, the compound boronate or boronic acid moieties may be selected from



[0025] In some embodiments, the analyte indicator covering at least a portion of the sensor housing may include a polymer comprising co-monomers of four monomers according to Formula III: ABCD [Formula III], A may be an analyte indicator monomer, B may be a methacrylate monomer, C maybe a polyethylene glycol monomer, D may be a compound or monomer containing boronate or boronic acid moieties, A may be 0.01 to 10 % by weight, B may be 1 to 99 % by weight, C may be 1 to 99 % by weight, and D may be 0.01 to 99% by weight of the total polymer.

[0026] In some embodiments, the one or more compounds containing boronate or boronic acid moieties may be provided at a molar ratio of 0.1 to 100 to the analyte indicator monomer.

[0027] Further variations encompassed within the systems and methods are described in the detailed description of the invention below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] 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.

[0029] FIG. 1 is a schematic view illustrating a sensor system embodying aspects of the present invention.

[0030] FIG. 2 illustrates a perspective view of a sensor embodying aspects of the present invention.

[0031] FIG. 3 illustrates an exploded view of a sensor embodying aspects of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0032] FIG. 1 is a schematic view of a sensor system embodying aspects of the present invention. In some non-limiting embodiment, as shown in FIG. 1, the system may include a sensor 100 and an external transceiver 101. In some embodiments, the sensor 100 may be an implantable sensor configured to be fully or partially 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, peritoneum, or other region of the living animal suitable for sensor implantation. For example, in some non-limiting embodiments, the sensor 100 may be implanted beneath the skin (*i.e.*, in the subcutaneous or peritoneal tissues). However, this is not required, and, in some alternative embodiments, the sensor 100 may be a transcutaneous sensor.

[0033] In some embodiments, a transceiver 101 may be an electronic device that communicates with the sensor 100 to power the sensor 100, provide commands and/or data to the sensor 100, and/or receive data from the sensor 100. In some embodiments, the received data

may include one or more sensor measurements. In some embodiments, the sensor measurements may include, for example and without limitation, one or more light measurements from one or more photodetectors of the sensor 100 and/or one or more temperature measurements from one or more temperature sensors of the sensor 100. In some embodiments, the transceiver 101 may calculate analyte (*e.g.*, glucose) concentrations from the measurement information received from the sensor 100.

[0034] In some non-limiting embodiments, the transceiver 101 may be a handheld device or an on-body/wearable device. For example, in some embodiments where the transceiver 101 is an on-body/wearable device, the transceiver 101 may be held in place by a band (*e.g.*, an armband or wristband) and/or adhesive, and the transceiver 101 may convey (*e.g.*, periodically, such as every two minutes, and/or upon user initiation) measurement commands (*i.e.*, requests for measurement information) to the sensor 100. In some embodiments where the transceiver 101 is a handheld device, positioning (*i.e.*, hovering or swiping/waving/passing) the transceiver 101 within range over the sensor implant site (*i.e.*, within proximity of the sensor 100) may cause the transceiver 101 to automatically convey a measurement command to the sensor 100 and receive a data from the sensor 100.

[0035] In some embodiments, as shown in FIG. 1, the transceiver 101 may include an inductive element 103, such as, for example, a coil. In some embodiments, the transceiver 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. In some non-limiting embodiments, the sensor 100 may use the current induced in the inductive element 114 to power the sensor 100. However, this is not required, and, in some alternative embodiments, the sensor 100 may be powered by an internal power source (*e.g.*, a battery).

[0036] In some embodiments, the transceiver 101 may convey data (*e.g.*, commands) to the sensor 100. For example, in some non-limiting embodiments, the transceiver 101 may convey data by modulating the electromagnetic wave generated by the inductive element 103 (*e.g.*, by modulating the current flowing through the inductive element 103 of the transceiver 101). In some embodiments, the sensor 100 may detect/extract the modulation in the electromagnetic wave generated by the transceiver 101. Moreover, the transceiver 101 may receive data (*e.g.*, one or more sensor measurements) from the sensor 100. For example, in some non-limiting embodiments, the transceiver 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 inductive element 103 of the transceiver 101.

[0037] In some embodiments, as shown in FIG. 1, the sensor 100 may include 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)).

[0038] In some embodiments, as shown in FIG. 1, the sensor 100 may include an analyte indicator 106. In some non-limiting embodiments, the analyte indicator 106 may be a polymer graft coated, diffused, adhered, or embedded on at least a portion of the exterior surface of the sensor housing 102. The analyte indicator 106 (*e.g.*, polymer graft) may cover the entire surface of sensor housing 102 or only one or more portions of the surface of housing 102. As an alternative to coating the analyte indicator 106 on the outer surface of sensor housing 102, the analyte indicator 106 may be disposed on the outer surface of the sensor housing 102 in other ways, such as by deposition or adhesion. In some embodiments, the analyte indicator 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 glucose in interstitial fluid (ISF), blood, or intraperitoneal fluid after implantation of the sensor 100. In some embodiments, the analyte indicator 106 may be a hydrogel.

[0039] In some embodiments, the analyte indicator 106 (*e.g.*, polymer graft) of the sensor 100 may include indicator molecules 104. The indicator molecules 104 may be distributed throughout the entire analyte indicator 106 or only throughout one or more portions of the analyte indicator 106. The indicator molecules 104 may have a boronate group. The indicator molecules 104 may be fluorescent indicator molecules (*e.g.*, TFM having the chemical name 9-[N-[6-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolano)-3-(trifluoromethyl)benzyl]-N-[3-(methacrylamido)propylamino]methyl]-10-[N-[6-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolano)-3-(trifluoromethyl)benzyl]-N-[2-(carboxyethyl)amino]methyl]anthracene sodium salt) or light absorbing, non-fluorescent indicator molecules. In some embodiments, the indicator molecules 104 may reversibly bind an analyte (*e.g.*, glucose, oxygen, cardiac markers, low-density lipoprotein (LDL), high-density lipoprotein (HDL), or triglycerides). When an indicator molecule 104 has bound an analyte, 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 analyte is bound, the indicator molecule 104 may be only weakly fluorescent.

[0040] 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.

[0041] 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. In the case of a fluorescence-based sensor, the one or more photodetectors may be sensitive to fluorescent light emitted by the indicator molecules 104 such that a signal is generated by a photodetector (*e.g.*, photodetector 224) in response thereto that is indicative of the level of fluorescence of the indicator molecules and, thus, the amount of analyte of interest (*e.g.*, glucose).

[0042] Some part of the excitation light 329 emitted by the light source 108 may be reflected from the analyte indicator 106 back into the sensor 100 as reflection light 333, 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 different 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.

[0043] 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 (*e.g.*, dichroic) filters deposited on the glass and may pass only a narrow band of wavelengths and otherwise reflect most of the received light. In some embodiments, the filters may be thin film (dichroic) filters deposited directly onto the photodetectors and may pass only a narrow band of wavelengths and otherwise reflect most of the light received thereby. The filters 112 may be identical (*e.g.*, both filters 112 may allow signals to pass) or different (*e.g.*, one filter 112 may be a reference filter and another filter 112 may be a signal filter).

[0044] 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 analyte indicator 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 analyte indicator 106, and, therefore, a greater number of photons striking the first photodetector 224.

[0045] In some embodiments, as shown in FIG. 1, the sensor 100 may include a substrate 116. In some embodiments, the substrate 116 may be a circuit board (*e.g.*, a printed circuit board (PCB) or flexible PCB) on which circuit components (*e.g.*, analog and/or digital circuit

components) may be mounted or otherwise attached. However, in some alternative embodiments, the substrate 116 may be a semiconductor substrate having circuitry fabricated therein. The circuitry may include analog and/or digital circuitry. Also, in some semiconductor substrate embodiments, in addition to the circuitry fabricated in the semiconductor substrate, circuitry may be mounted or otherwise attached to the semiconductor substrate 116. In other words, in some semiconductor substrate 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.

[0046] In some embodiments, the one or more of the sensor housing 102, analyte indicator 106, indicator molecules 104, light source 108, photodetectors 224, 226, temperature transducer 670, substrate 116, and inductive element 114 of sensor 100 may include some or all of the features described in one or more of U.S. Application Serial No. 13/761,839, filed on February 7, 2013, U.S. Application Serial No. 13/937,871, filed on July 9, 2013, and U.S. Application Serial No. 13/650,016, filed on October 11, 2012, all of which are incorporated by reference in their entireties. Similarly, the structure and/or function of the sensor 100 and/or transceiver 101 may be as described in one or more of U.S. Application Serial Nos. 13/761,839, 13/937,871, and 13/650,016.

[0047] In some embodiments, the sensor 100 may include a transceiver interface device, and the transceiver 101 may include a sensor interface device. In some embodiments where the sensor 100 and transceiver 101 include an antenna or antennas (*e.g.*, inductive elements 103 and

114), the transceiver interface device may include the inductive element 114 of the sensor 100, and the sensor interface device may include the inductive element 103 of the transceiver 101. In some of the transcutaneous embodiments where there exists a wired connection between the sensor 100 and the transceiver 101, the transceiver interface device and sensor interface device may include the wired connection.

[0048] FIGS. 2 and 3 illustrate a non-limiting embodiment of a sensor 100 embodying aspects of the present invention that may be used in the sensor system illustrated in FIG. 1. FIGS. 2 and 3 illustrate perspective and exploded views, respectively, of the non-limiting embodiment of the sensor 100.

[0049] In some embodiments, as illustrated in FIG. 3, the sensor housing 102 may include an end cap 113. In some embodiments, the sensor 100 may include one or more capacitors 118. The one or more capacitors 118 may be, for example, one or more tuning capacitors and/or one or more regulation capacitors. The one or more capacitors 118 may be too large for fabrication in the semiconductor substrate 116 to be practical. Further, the one or more capacitors 118 may be in addition to one or more capacitors fabricated in the semiconductor substrate 116.

[0050] In some embodiments, as illustrated in FIG. 3, the sensor 100 may include a reflector 119 (*i.e.*, mirror). Reflector 119 may be attached to the semiconductor substrate 116 at an end thereof. In a non-limiting embodiment, reflector 119 may be attached to the semiconductor substrate 116 so that a face portion 121 of reflector 119 is generally perpendicular to a top side of the semiconductor substrate 116 (*i.e.*, the side of semiconductor substrate 116 on or in which the light source 108 and one or more photodetectors 110 are mounted or fabricated) and faces the light source 108. The face 121 of the reflector 119 may reflect radiation emitted by light source

108. In other words, the reflector 119 may block radiation emitted by light source 108 from exiting the axial end of the sensor 100.

[0051] According to one aspect of the invention, an application for which the sensor 100 was developed (although by no means the only application for which it is suitable) is measuring various biological analytes in the living body of an animal (including a human). For example, sensor 100 may be used to measure glucose, oxygen, toxins, pharmaceuticals or other drugs, hormones, and other metabolic analytes in, for example, the human body.

[0052] In some embodiments, the specific composition of the analyte indicator 106 and the indicator molecules 104 may vary depending on the particular analyte the sensor is to be used to detect and/or where the sensor is to be used to detect the analyte (*e.g.*, in the in subcutaneous tissues, blood, or peritoneum). In some embodiments, the analyte indicator 106 facilitates exposure of the indicator molecules 104 to the analyte. In some embodiments, the indicator molecules 104 may exhibit a characteristic (*e.g.*, emit an amount of fluorescence light) that is a function of the concentration of the specific analyte to which the indicator molecules 104 are exposed.

[0053] In some embodiments, the sensor 100 may include at least one drug eluting polymer matrix and/or a layer of catalyst and/or one or more therapeutic agents that may be provided on, incorporated in, or dispersed within the analyte indicator or sensor housing as described in U.S. Pat. No. 9,931,068 (Huffstetler et al.), which is incorporated herein by reference in its entirety. In some embodiments, the one or more therapeutic agents may be incorporated in the analyte indicator 106. In some embodiments, the sensor 100 may include a membrane covering at least a portion of the analyte indicator 106, and the one or more therapeutic agents may be incorporated within the membrane. In some embodiments, the one or more therapeutic agents include

dexamethasone, triamcinolone, betamethasone, methylprednisolone, beclometasone, fludrocortisone, derivatives thereof, and analogs thereof, a glucocorticoid, an anti-inflammatory drug, e.g., a non-steroidal anti-inflammatory drug including but not limited to acetylsalicylic acid, isobutylphenylpropanoic acid.

[0054] The implantation or insertion of a medical device, such as a bio-sensor, into a user/patient's body can cause the body to exhibit adverse physiological reactions that are detrimental to the functioning of the device. The reactions may range from infections due to implantation surgery to the immunological response of a foreign object implanted in the body. That is, the performance of the implantable bio-sensor can be hindered or permanently damaged *in vivo* via the immunological response to an infection or the device itself. In particular, the performance of the analyte indicator 106 may be deteriorated by the immunological response of the body into which the sensor 100 is implanted. For example, as explained above, white blood cells, including neutrophils, may attack an implanted sensor 100. The neutrophils release, *inter alia*, hydrogen peroxide, which may degrade indicator molecules 104 (e.g., by oxidizing a boronate group of an indicator molecule 104 and disabling the ability of the indicator molecule 104 to bind glucose).

[0055] In some embodiments, the analyte indicator 106 may include one or more additives that interact or react with one or more degradative species without compromising signal integrity or performance of the sensor device. In some embodiments, the additive may be incorporated into the analyte indicator 106 that may cover at least a portion of the sensor housing 102. The degradative species may include one or more of hydrogen peroxide, a reactive oxygen species, a reactive nitrogen species, a free radical, enzymes, and a metal ion. In some embodiments, the additive may be copolymerized with the indicator molecule 104. In some embodiments, the one

or more additives may be provided in the analyte indicator 106 (e.g., polymer graft). In some embodiments, the one or more additives may interact and/or react with degradative species. In some embodiments, the one or more additives may neutralize the degradative species. In some embodiments, the one or more additives may bind to the degradative species. In some embodiments, the one or more additives may sequester the degradative species so as to inhibit, reduce, and/or prevent degradation of the analyte indicator by the degradative species.

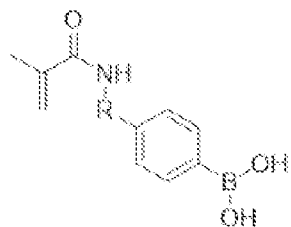
Accordingly, in some embodiments, the one or more additives reduce degradation of the analyte indicator 106.

[0056] In some non-limiting embodiments, the one or more additives may be boronates and boronic acid containing moieties compounds that interact with degradative species without compromising signal integrity or performance of the sensor.

[0057] In some non-limiting embodiments, a sensor 100 for measurement of an analyte (e.g., glucose) in a medium (e.g., interstitial fluid) within a living animal (e.g., a human) contains one or more of the following components: a sensor housing 102; a light source 108 within the sensor housing 102 configured to emit excitation light 329; an analyte indicator 106 covering a portion of the sensor housing 102, one or more indicator molecules 104 that are part of the analyte indicator 106, reversibly bind the analyte, are positioned to be irradiated by the excitation light, and are configured to emit light 331 indicative of the amount of the analyte in the medium within the living animal; a photodetector 224 within the sensor housing 102 that is sensitive to light 331 emitted by the one or more indicator molecules 104 and configured to generate a signal indicative of the amount of the analyte in the medium within the living animal; and one or more compounds having boronate and boronic acid containing moieties that interact with degradative species without compromising signal integrity or performance of the sensor 100. In some non-

limiting embodiments, the sensor 100 may include a drug eluting matrix and/or a layer of catalyst provided on or incorporated in the analyte indicator 106.

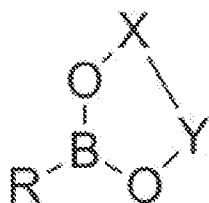
[0058] In some non-limiting embodiments, one or more of the compounds containing boronate or boronic acid containing moieties may be a boronic acid compound of Formula I:



[Formula I], wherein R = methylene or an alkyl group, an aryl group, a

heteroaryl group, a cyclic group, a multicyclic group, a polyalkylene glycol group, a polyethylene glycol (PEG) group, a linear or substituted polyalkylene glycol or PEG group, or a combination thereof. The present inventors have found that the R group in Formula I provides for unexpectedly better incorporation of the compounds into a hydrogel, improved activation, and enhanced sensor longevity.

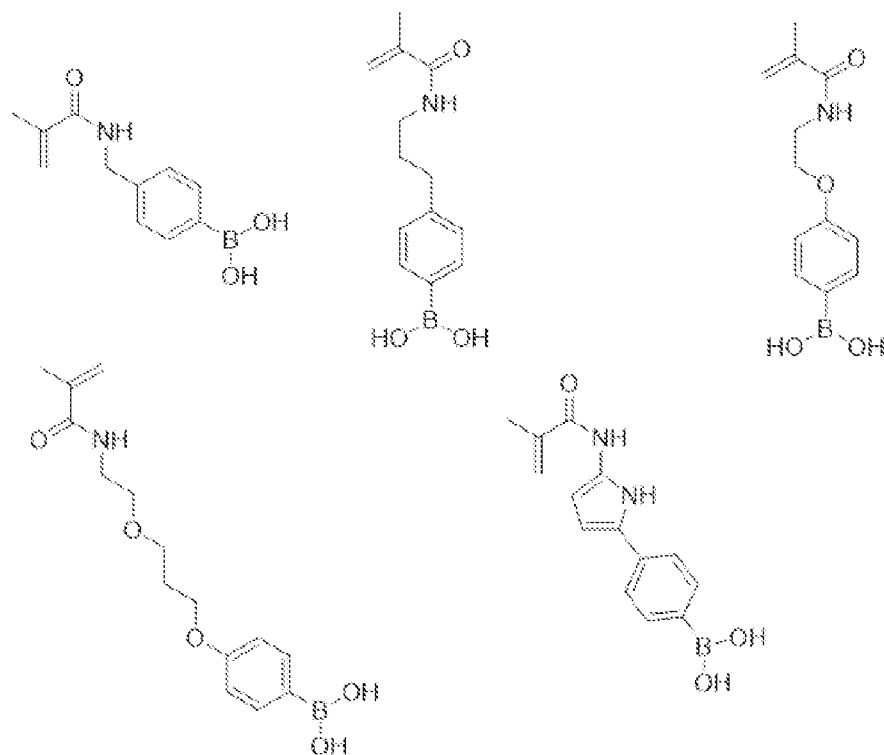
In some aspects, the boronic acid portion of Formula I may be substituted with a boronate group



of Formula II:

[Formula II], wherein X and Y = alkyl.

In some non-limiting examples, the one or more boronate or boronic acid containing compounds may include one or more of the following compounds:



[0059] In some non-limiting embodiments, the one or more compounds containing boronate or boronic acid containing moieties may be provided in the analyte indicator 106 (e.g., polymer graft) of the analyte sensor 100. In some non-limiting embodiments, one or more compounds containing boronate or boronic acid containing moieties may be incorporated into the analyte indicator 106 by polymerizing the one or more compounds containing boronate or boronic acid containing moieties as a co-monomer with indicator monomer and one or more acrylate monomers. In some non-limiting embodiments, one or more compounds containing boronate or boronic acid containing moieties may be provided as co-monomers of four monomers according to Formula III:

ABCD [Formula III], wherein A is an indicator monomer, B is a methacrylate monomer, C is a polyethylene glycol monomer, and D is a boronate or boronic acid containing moiety compound monomer, wherein A is 0.001 to 10 % by weight, B is 1 to 99 % by weight, C is 1 to 99 % by

weight, and D is 0.001 to 99% by weight of the total polymer. In some aspects, A is 0.01 to 10 % by weight, B is 1 to 99 % by weight, C is 1 to 99 % by weight, and D is 0.01 to 99% by weight of the total polymer.

[0060] In some non-limiting embodiments, the analyte indicator 106 may contain four monomers: (i) the TFM fluorescent indicator, (ii) hydroxyethylmethacrylate (HEMA), which is a methacrylate, (iii) polyethylene glycol (PEG), and (iv) a boronate or boronic acid containing moiety of Formula I. In some embodiments, the PEG may be polyethylene glycol methacrylate (PEG-methacrylate) or polyethylene glycol diacrylate (PEG-diacrylate or PEGDA), and the boronate or boronic acid containing moieties monomer of Formula I may be 4-vinylboronic acid containing moieties. In some embodiments, the four monomers may be in specific molar ratios. For example, in some non-limiting embodiments in which the analyte indicator 106 is opaque, the analyte indicator 106 may comprise 0.001 to 10 molar percent, HEMA may comprise 10 to 90 molar percent, PEGDA may comprise 10 to 90 molar percent, and the 4-vinylboronic acid containing moieties may comprise 0.001 to 90 molar percent. With this formulation, the combined (i.e., total) monomers may, in one example, be 30% by volume of the polymerization solution used for the polymerization reaction with the remainder of the polymerization solution being water (i.e., the polymerization solution may be 70% water by volume). For another example, in one non-limiting embodiment, the analyte indicator 106 may be made using a polymer solution that is 50% water by volume and 50% monomers by volume.

[0061] In some embodiments, the relative molar percent of the compound containing boronate or boronic acid containing moieties may be within a specific range. In some embodiments, the relative molar percent of the compound containing boronate or boronic acid containing moieties ranges between 0.1 and 100 molar percent. If the relative molar percent of

the compound containing boronate or boronic acid containing moieties is greater than this range, the hydrogel is not formed. If the relative molar percent of the compound containing boronate or boronic acid containing moieties is lower than this range, the unexpected longevity and functionality-boosting effects described in this disclosure may not be obtained.

In some embodiments, the PEGDA may act as a cross-linker and create a sponge-like matrix/hydrogel. In some non-limiting embodiments, the PEG-containing graft/hydrogel may become clear if a sufficient amount of additional PEG is added to the mixture (i.e., if it is fabricated with a higher concentration of PEG), and a clear polymer graft 106 may be made from such a formulation. For example, in one non-limiting embodiment, the polymer graft 106 may be made using a polymer solution that is 50-60% water by volume and 40-50% monomers by volume, where the TFM fluorescent indicator, HEMA, PEG-methacrylate, and compound containing boronate or boronic acid containing moieties may comprise 0.01 to 10 %, 1 to 99 %, 1 to 99 %, and 0.01 to 99% by weight, of the monomers in the solution. In some embodiments, the polymer graft may be synthesized using conventional free radical polymerization.

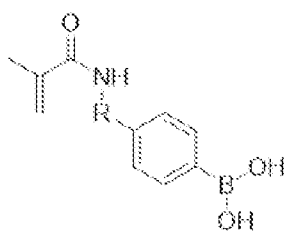
[0062] An implanted sensor including an additive-containing analyte indicator may have improved performance over a sensor that does not include an additive-containing analyte indicator. For instance, in some non-limiting embodiments, the additive may improve the longevity and functionality of the sensor 100.

[0063] 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 spirit and scope of the invention. For example, although in some embodiments, the analyte

sensor 100 may be an optical sensor, this is not required, and, in one or more alternative embodiments, the analyte sensor may be a different type of analyte sensor, such as, for example, an electrochemical sensor, a diffusion sensor, or a pressure sensor. Also, although in some embodiments, the analyte sensor 100 may be an implantable sensor, this is not required, and, in some alternative embodiments, the analyte sensor may be a transcutaneous sensor having a wired connection to an external transceiver. For example, in some alternative embodiments, the analyte sensor 100 may be located in or on a transcutaneous needle (*e.g.*, at the tip thereof). In these embodiments, instead of wirelessly communication using an antenna (*e.g.*, inductive element 114), the analyte sensor may communicate with the external transceiver using one or more wires connected between the external transceiver and a transceiver transcutaneous needle including the analyte sensor. For another example, in some alternative embodiments, the analyte sensor may be located in a catheter (*e.g.*, for intravenous blood glucose monitoring) and may communicate (wirelessly or using wires) with an external transceiver.

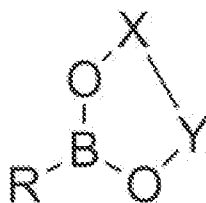
CLAIMSWhat is claimed is:

1. A sensor for measurement of an analyte in a medium within a living animal, the sensor comprising:
- a sensor housing;
- an analyte indicator covering at least a portion of the sensor housing; and
- one or more compounds containing boronate or boronic acid moieties that reduce degradation of the analyte indicator, wherein the one or more compounds containing boronic acid containing moieties are a compound of Formula I:



[Formula I], wherein R = methylene or an alkyl group, an aryl

group, a heteroaryl group, a cyclic group, a multicyclic group, a polyalkylene glycol group, a polyethylene glycol (PEG) group, a linear or substituted polyalkylene glycol or PEG group, or a combination thereof, or a compound of Formula I wherein the boronic acid is substituted with a



boronate group of Formula II:

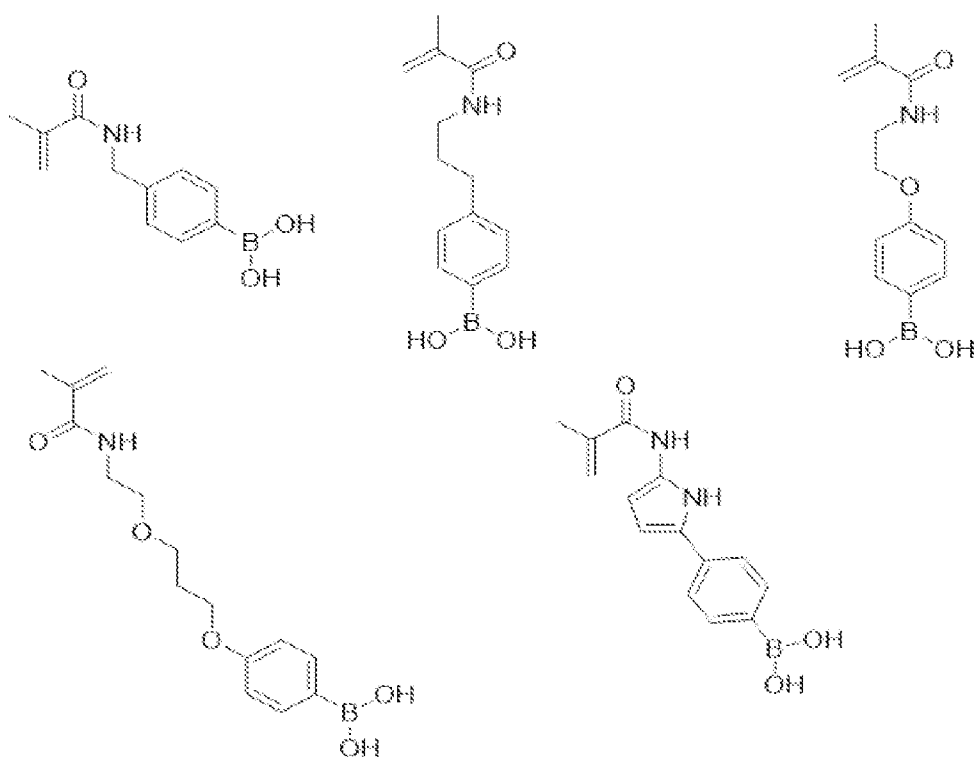
[Formula II], wherein X and Y = alkyl.

2. The sensor of claim 1, wherein the sensor is implantable within a living animal.

3. The sensor of claim 1 or 2, wherein the one or more compounds containing boronate or boronic acid moieties are co-monomers with the analyte indicator.
4. The sensor of any one of claims 1-3, wherein the one or more compounds containing boronate or boronic acid moieties are co-monomers with the analyte indicator in a hydrogel.
5. The sensor of any one of claims 1-4, wherein the one or more compounds containing boronate or boronic acid moieties are entrapped in a hydrogel covering at least a portion of the sensor housing.
6. The sensor of any one of claims 1-5, wherein the one or more compounds containing boronate or boronic acid moieties reduce chemical degradation and/or oxidation of the analyte indicator.
7. The sensor of claim 6, wherein the one or more compounds containing boronate or boronic acid moieties reduce a degradation rate of the analyte indicator.
8. The sensor of claim 6 or 7, wherein the one or more compounds containing boronate or boronic acid moieties bind to degradative species.

9. The sensor of any one of claims 6-8, wherein the one or more compounds containing boronic acid containing moieties sequester degradative species so as to reduce, and/or prevent degradation of the analyte indicator by the degradative species.

10. The sensor of any one of claims 1-9, wherein the compound containing boronate or boronic acid moieties is selected from



11. The sensor of any one of claims 1-10, wherein the analyte indicator covering at least a portion of the sensor housing comprises a polymer comprising co-monomers of four monomers according to Formula II: $A_xB_yC_zD_w$ [Formula II],

wherein A is an analyte indicator monomer, B is a methacrylate monomer, C is a polyethylene glycol monomer, and D is a compound or monomer containing boronate or boronic

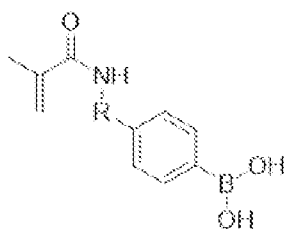
acid moieties, wherein A is 0.01 to 10 % by weight, B is 1 to 99 % by weight, C is 1 to 99 % by weight, and D is 0.01 to 99% by weight of the total polymer.

12. The sensor of claim 11, wherein the one or more compounds containing boronate or boronic acid moieties are provided at a molar ratio of 0.1 to 100 to the analyte indicator monomer.

13. The sensor of any one of claims 1-12, wherein the sensor comprises at least one drug eluting polymer matrix that covers a portion of the sensor housing.

14. A method of fabricating a sensor for measurement of an analyte in a medium within a living animal, the method comprising:

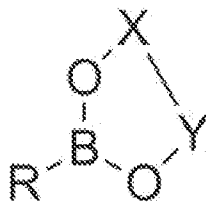
applying an analyte indicator to a sensor housing of the sensor such that the applied analyte indicator covers at least a portion of the sensor housing, wherein the analyte indicator comprises one or more compounds containing boronate or boronic acid moieties that reduce degradation of the analyte indicator, wherein the one or more compounds containing boronic acid containing moieties are a compound of Formula I:



[Formula I], wherein R = methylene or an alkyl group, an aryl

group, a heteroaryl group, a cyclic group, a multicyclic group, a polyalkylene glycol group, a polyethylene glycol (PEG) group, a linear or substituted polyalkylene glycol or PEG group, or a

combination thereof, or a compound of Formula I wherein the boronic acid is substituted with a



boronate group of Formula II:

[Formula II], wherein X and Y = alkyl.

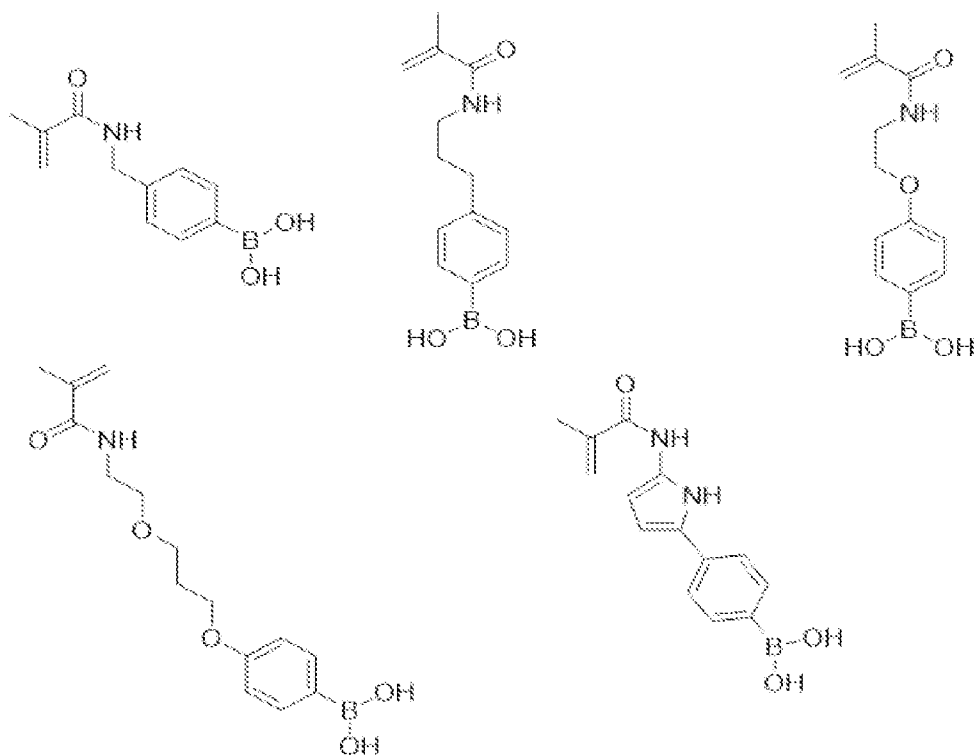
15. The method of claim 14, wherein the one or more compounds containing boronate or boronic acid moieties are co-monomers with the analyte indicator.
16. The method of claim 14 or 15, wherein the one or more compounds containing boronate or boronic acid moieties are co-monomers with the analyte indicator in a hydrogel.
17. The method of any one of claims 14-16, wherein the one or more compounds containing boronate or boronic acid moieties are entrapped in a hydrogel covering at least a portion of the sensor housing.
18. The method of any one of claims 14-17, wherein the one or more compounds containing boronate or boronic acid moieties reduce chemical degradation and/or oxidation of the analyte indicator.
19. The method of any one of claims 14-18, wherein the one or more compounds containing boronate or boronic acid moieties reduce a degradation rate of the analyte indicator.

20. The method of any one of claims 14-19, wherein the one or more compounds containing boronate or boronic acid moieties interact or react with a degradative species without compromising signal integrity or performance of the sensor device, wherein the degradative species is hydrogen peroxide, a reactive oxygen species, a reactive nitrogen species, enzymes, free radical or metal ions.

21. The method of claim 19, wherein the one or more compounds containing boronate or boronic acid moieties bind to the degradative species.

22. The method of claim 20 or 21, wherein the one or more compounds containing boronate or boronic acid moieties sequester the degradative species so as to reduce, and/or prevent degradation of the analyte indicator by the degradative species.

23. The method of any one of claims 14-22, wherein the compound boronate or boronic acid moieties is selected from



24. The method of any one of claims 14-23, wherein the analyte indicator covering at least a portion of the sensor housing comprises a polymer comprising co-monomers of four monomers according to Formula III: ABCD [Formula III],

wherein A is an analyte indicator monomer, B is a methacrylate monomer, C is a polyethylene glycol monomer, and D is a compound or monomer containing boronate or boronic acid moieties, wherein A is 0.01 to 10 % by weight, B is 1 to 99 % by weight, C is 1 to 99 % by weight, and D is 0.01 to 99% by weight of the total polymer.

25. The method of claim 24, wherein the one or more compounds containing boronate or boronic acid moieties are provided at a molar ratio of 0.1 to 100 to the analyte indicator monomer.

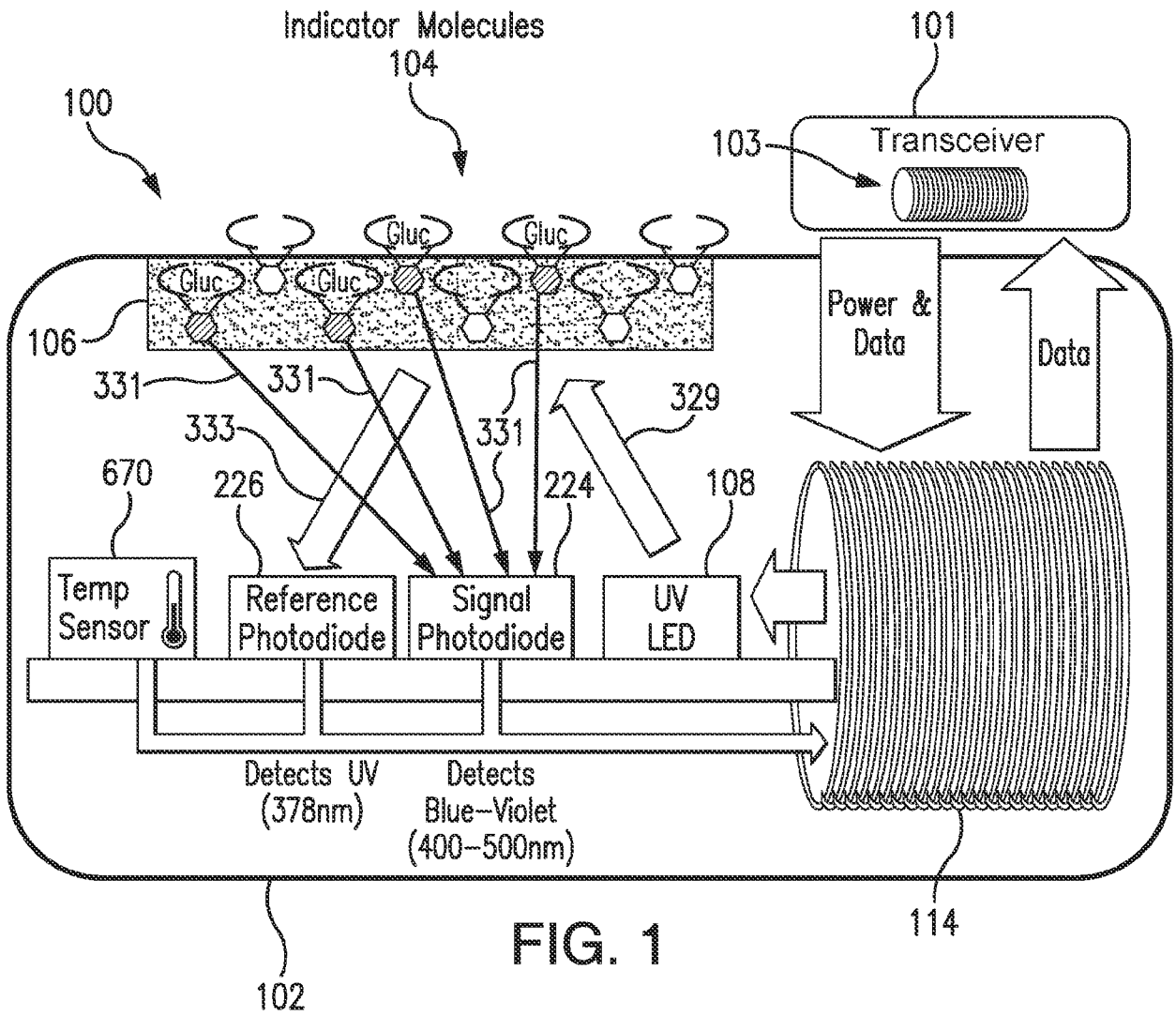
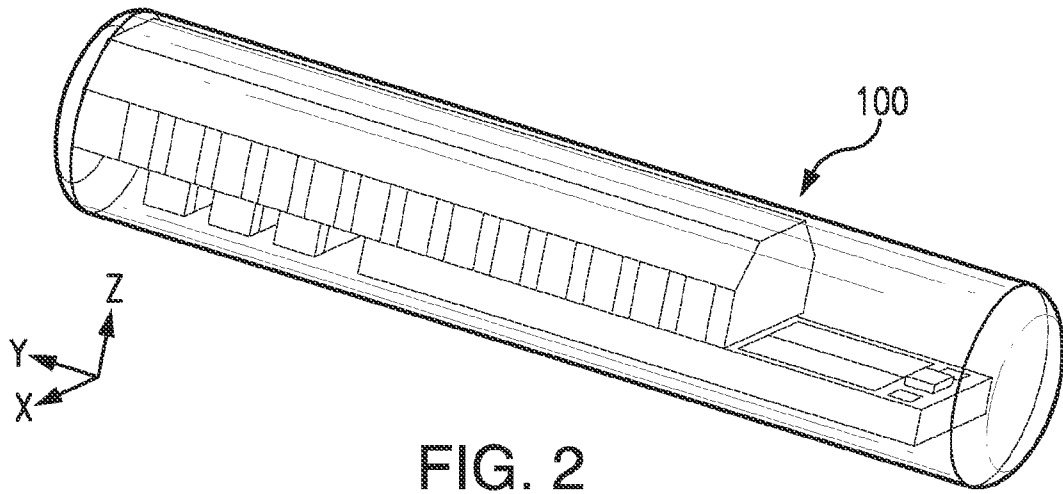
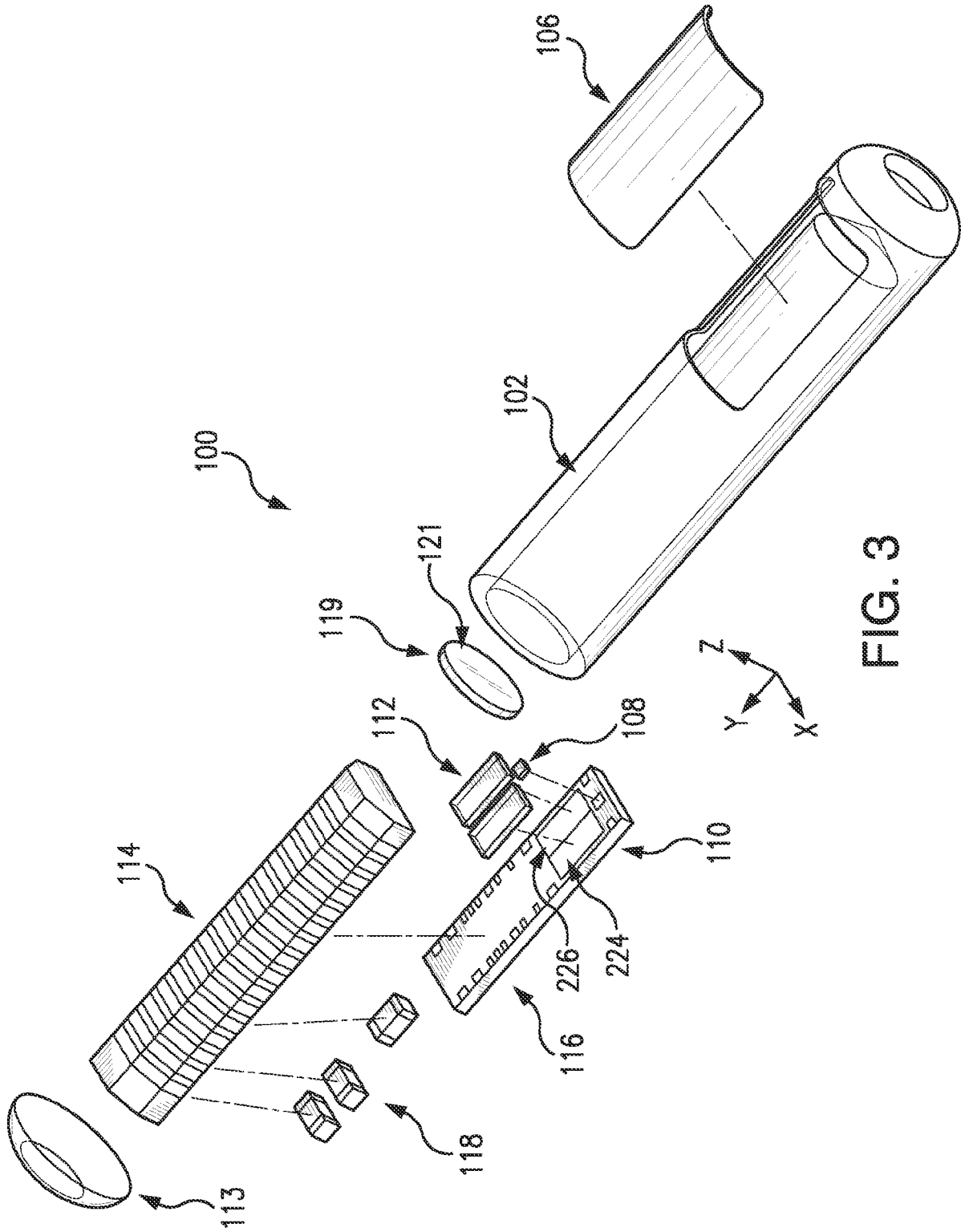


FIG. 1





INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/75489

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - INV. A61B 5/1473, A61B 5/145, G01N 27/26 (2022.01)
 ADD. G01N 27/327 (2022.01)
 CPC - INV. A61B 5/1473, A61B 5/145, G01N 27/26
 ADD. G01N 27/327

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0054251 A1 (Senseonics, Incorporated) 20 February 2020 (20.02.2020); para[0009] para[0017]	1-3, 14-16
A	WO 2007/124132 A2 (University Of Utah Research Foundation) 01 November 2007 (01.11.2007); p59	1-3, 14-16
A	US 2012/0097540 A1 (James et al.) 26 April 2012 (26.04.2012); Fig. 3 para[0005]	1-3, 14-16
A	US 9,931,068 B2 (Senseonics, Incorporated) 03 April 2018 (03.04.2018); entire document	1-3, 14-16
A	US 2019/0159708 A1 (Senseonics, Incorporated) 30 May 2019 (30.05.2019); entire document	1-3, 14-16

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

* Special categories of cited documents:
 "A" document defining the general state of the art which is not considered to be of particular relevance
 "D" document cited by the applicant in the international application
 "E" earlier application or patent but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed
 "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "&" document member of the same patent family

Date of the actual completion of the international search 03 November 2022	Date of mailing of the international search report NOV 21 2022
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriguez Telephone No. PCT Helpdesk: 571-272-4300
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/75489

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 4-13, 17-25
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.