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- (54) Title:** ANALYTE SENSORS AND METHODS OF FABRICATING THEM

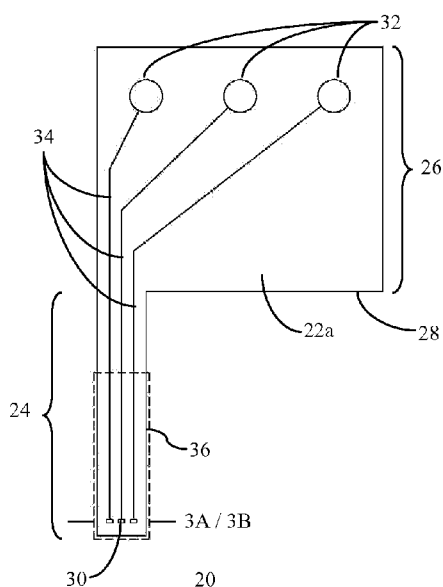


FIG. 2A

- (57) Abstract:** In vivo analyte sensors and methods of using and fabricating them are disclosed in which the sensors include a film disposed over at least one sensing section for optimizing the functioning of and/or results from the sensor, where the film includes at least one dissolvable layer.



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ANALYTE SENSORS AND METHODS OF FABRICATING THEM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Pursuant to 35 U.S.C. § 119(e), this application claims priority to U.S. Provisional Patent Application No. 61/487,973 filed on May 19, 2011, the disclosure of which is herein incorporated by reference in its entirety.

INTRODUCTION

[0001] In recent years, a variety of temporarily implantable or in vivo sensors, also referred to as biosensors, have been developed for a range of medical applications for detecting and/or quantifying specific agents, e.g., analytes, in a patient's body fluid such as blood or interstitial fluid. Such analyte sensors may be fully or partially implanted below the epidermis in a blood vessel or in the subcutaneous tissue of a patient for direct contact with blood or other extra-cellular fluid, such as interstitial fluid, wherein such sensors can be used to obtain periodic and/or continuous analyte readings over a period of time. One common application of such analyte sensors systems is in the monitoring of glucose levels in diabetic patients. Such readings can be especially useful in monitoring and/or adjusting a treatment regimen which may include the regular and/or emergent administration of insulin to the patient. Examples of such sensors and associated analyte monitoring systems can be found in U.S. Patent Nos. 6,134,461, 6,175,752, 6,284,478, 6,560,471, 6,579,690, 6,746,582, 6,932,892, 7,299,082, 7,381,184, 7,618,369 and 7,697,967, and U.S. Patent Application Publication Nos. 2008/0161666, 2009/0054748, 2009/0247857 and 2010/0081909, the disclosures of each of which are incorporated herein by reference for all purposes.

[0002] Enzyme-based sensors are devices in which an analyte-concentration-dependent biochemical reaction signal is converted into a measurable physical signal, such as an optical or an electrical signal, such as current (amperometric biosensors) or charge (coulometric biosensors). In an amperometric analyte sensor, for example, the target analyte is electrooxidized or electroreduced to an electrode to produce a current signal representative of the concentration of analyte in the body fluid. To effect the electrochemical reaction, amperometric sensors typically employ two or three electrodes, including at least one measuring or working electrode and one reference electrode. In two-electrode systems, the reference electrode also serves as a counter-electrode. In three-electrode systems, the third electrode is a counter-electrode. The measuring or working electrode is composed of a non-corroding carbon or a metal conductor and is connected to the reference electrode via a

circuit, such as a potentiostat. Typically, the two or more electrodes extend proximally to externally exposed conductive contacts for electrical connection with a sensor control unit which is typically mountable on the skin of the patient.

[0003] With implantable or *in vivo* electrochemical sensors, a sensing layer is provided in direct contact with the conductive material of the working electrode with a diffusion-limiting layer provided over the sensing layer. The sensing layer includes a chemical formulation to facilitate the electrochemical detection of the target analyte and the determination of its concentration in bodily fluid, particularly if the analyte cannot be electrolyzed at a desired rate and/or with a desired specificity on a bare electrode. The diffusion-limiting layer is often beneficial or necessary for regulating or limiting the flux of analyte to the sensing layer. By way of explanation, in a glucose sensor without a diffusion-limiting layer, the flux of glucose to the sensing layer increases linearly with the concentration of glucose. When all of the glucose arriving at the sensing layer is consumed, the measured output signal is linearly proportional to the flux of glucose and thus to the concentration of glucose. However, when the glucose consumption is limited by the kinetics of chemical or electrochemical activities in the sensing layer, the measured output signal is no longer controlled by the flux of glucose and is no longer linearly proportional to the flux or concentration of glucose. In this case, only a fraction of the glucose arriving at the sensing layer is consumed before the sensor becomes saturated, whereupon the measured signal stops increasing, or increases only slightly, with the concentration of glucose. In a glucose sensor equipped with a diffusion-limiting layer, on the other hand, the diffusion-limiting layer reduces the flux of glucose to the sensing layer such that the sensor does not become saturated and can therefore operate effectively within a much wider range of glucose concentrations. A diffusion-limiting layer is also of benefit in a biosensor that employs a wired-enzyme electrode, as the diffusion-limiting layer significantly reduces chemical and biochemical reactivity in the sensing layer and thus reduces the production of radical species that can damage the enzyme. The diffusion-limiting layer may also act as a mechanical protector that prevents the sensor components from leaching out of the sensor layer and reduces motion-associated noise.

[0004] Recent advances have been made in developing a diffusion-limiting layer for use with implantable electrochemical sensors that are mechanically strong, biocompatible and demonstrate considerable sensitivity and stability, and a large signal-to-noise ratio. U.S. Patent No. 6,932,894, for example, discloses a diffusion-limiting layer comprised of a polymer containing heterocyclic nitrogen groups, such as polyvinylpyridine or polyvinylimidazole, modifying it with a zwitterionic moiety, a non-pyridine copolymer component, and optionally another moiety that is either hydrophilic or hydrophobic in an

alcohol-buffer solution. The diffusion-limiting layer is formed *in situ* by applying an alcohol-buffer solution of a crosslinker and a modified polymer over an enzyme-containing sensing layer and allowing the solution to cure for one to two days.

[0005] While the benefits provided by a diffusion-limiting layer are well-known and appreciated, the extent of those benefits is often limited by problems associated with manufacturing the layers, particularly in their physical application to the sensor body. Typically, the layer components are formulated in a liquid solution which is then applied to the sensor structure, over the sensing layer, by dipping the sensor into the layer solution, spraying or by applying droplets of the layer solution onto the sensor structures, or by striping. These methods are ineffective in evenly distributing the layer components throughout the layer volume and they fall short in providing a highly uniform layer thickness and/or thorough sensor adhesion. Additionally, these fabrication techniques are time-consuming and/or labor-intensive, contributing to higher sensor manufacturing costs.

[0006] Even if a diffusion-limiting layer could be provided on a sensor in a highly controlled manner to provide an optimally uniform structure, the functional benefits of such a layer can be limited by physiological effects of transcutaneous or subcutaneous implantation of the biosensor itself. In particular, subcutaneous placement of the sensor produces both short-term and longer-term biochemical and cellular responses. For example, it has been found that during the initial 12 to 24 hours of sensor operation (after implantation), an analyte sensor's sensitivity may be relatively low – a phenomenon sometimes referred to as “early sensor attenuation” (ESA). Even subsequent to this initial period of ESA, spurious low readings or drop outs may be caused by the presence of blood clots also known as “thrombi” that form as a result of the transcutaneous insertion of the sensor. Such clots exist in close proximity to the subcutaneous sensor and have a tendency to “consume” the target analyte, such as glucose, at a high rate, thereby lowering the local analyte concentration. It may also be that the implanted sensor constricts adjacent blood vessels thereby restricting analyte delivery or flux to the sensor site. Still yet, as part of the immune response, a foreign body capsule may develop around the implanted sensor which may reduce the flux of analyte to the sensor, i.e., may reduce the sensitivity or accuracy of the sensor function. An *in vivo* glucose sensor, for example, with lower than normal sensitivity may report blood glucose values lower than the actual values, thus potentially underestimating hyperglycemia, and triggering false hypoglycemia alarms. In order to compensate for such effects on sensor sensitivity, the sensor may require frequent calibration over the course of the sensor's implantation period. This is often accomplished in the context of continuous glucose monitoring devices by using a reference value after the sensor has been positioned in the body, where the reference value

most often employed is obtained by use of a blood glucose test strip for which a blood sample is obtained by means of a finger stick, which is inconvenient and can cause significant discomfort to the patient.

[0007] The extent of the immune response presented by implantable sensors, as well as the amount of pain and discomfort felt by the patient, are exacerbated by the size of the sensor introducer and/or the implantable portion of the sensor, often referred to as the sensor tail. Typically, *in vivo* biosensors, such as analyte sensors, are inserted into the patient's skin using an introducer which typically has a sharp, rigid structure adapted to support the sensor during its transcutaneous insertion. Some introducers are in the form of needles having a slotted or hollow configuration in which a distal portion of the sensor is slidably carried to the desired implantation site, e.g., subcutaneous site, after which the insertion needle can be slidably withdrawn from the implanted sensor. With sensor introducers which carry the sensor within an interior or substantially interior space, there is naturally a limit on the extent to which the cross-sectional dimension of the introducer can be reduced.

[0008] Accordingly, it would be highly desirable to provide an *in vivo* sensor which overcomes the shortcomings of currently available *in vivo* sensors and which can be efficiently and cost-effectively manufactured. In particular, it would be advantageous to provide *in vivo* analyte sensors having a diffusion-limiting layer with one or more of the following attributes: is able to be fabricated with a high degree of reproducibility and uniformity; has material properties which minimize the biochemical, cellular and immune responses to transcutaneous introduction of the sensor; and has a physical structure which enables its implantation in a manner which does not require the use of a transcutaneous introducer. It would be additionally beneficial if such a layer had other physical, material and functional characteristics that allow for customization of the sensor to optimize its functionality and broaden its applications.

SUMMARY

[0009] Implantable or *in vivo* analyte sensors for the continuous and/or automatic detection and measurement of one or more selected analytes, and methods of fabricating and using the analyte sensors are described herein. At least a portion of the subject sensors may be implanted beneath an epidermal layer of the skin, e.g., transcutaneously implanted, for positioning within a blood vessel, subcutaneous tissue, or another suitable body location.

[0010] Embodiments of the *in vivo* analyte sensors are electrochemical analyte sensors which include an implantable portion that includes at least one sensing section that includes at least one electrode, and having a film disposed over the at least one sensing section for optimizing

the functioning of and/or results from the sensor, where the film includes at least one dissolvable layer. The subject films may include any number of additional layers where one or more of the additional layers is dissolvable or non-dissolvable. The dissolvable layer(s) may have a number of varying thicknesses and/or dissolution rates to provide a selected dissolution profile. The thicknesses and/or dissolution rates may vary along the geometry of the implantable portion of the analyte sensor. In certain embodiments, the film functions to control the ingress of physiological agents from the *in vivo* environment in which a sensor is implanted toward the sensing components of the sensor and/or to control the egress of agents, drugs or the like resident within the film to the *in vivo* environment. In some instances, this ingress/egress function is provided by the permeability and/or the dissolvability of the film *in vivo*. The material formulation of the film may be fine-tuned or customized to control which agents ingress/egress and the rate at which they ingress/egress, as well as to provide other functional and physical characteristics.

[0011] In some instances, the subject films are formulated at least in part from one or more base polymer matrices which are selected to provide the desired functional characteristics (e.g., permeability, dissolvability, dissolution rate, diffusion rate, etc.) and physical characteristics (e.g., rigidity, flexibility, strength, thickness, shape, surface characteristics, etc.). A film may include one or more layers where each individual layer may have a homogenous material formulation over its entire volume or may have a non-homogenous material formulation that varies in one or more characteristics, e.g., thickness, density, flexibility, rigidity, permeability, dissolution rate, agent or chemical content or diffusion, etc., over its volume, thickness, length or other dimension. In film embodiments having multiple layers, all layers may include identical material formulations or one or more layers may be differently formulated from the others to provide different functions. In certain embodiments, the film has at least one inner layer and at least one outer layer, where an inner layer is selectively permeable to enable passage of the target analyte to the sensor while preventing the passage of interferent molecules thereto, and an outer layer is selectively dissolvable to control the time at which the sensor becomes functionally active after the *in vivo* implantation of the sensor.

[0012] The present disclosure further provides methods of monitoring one or more target analytes within the body of a patient by use of the subject sensors. Embodiments of such methods include implanting at least a portion of an analyte sensor within the patient and selectively activating one or more analyte sensing sections by selectively dissolving the film or a layer thereof. The dissolution profile of the film may be dependent upon the thickness and/or dissolution rate of the one or more layers in the film, where the thickness and

dissolution rate may depend on the layer thickness and/or the material composition of the individual layers.

[0013] The present disclosure also provides methods of fabricating the subject *in vivo* analyte sensors where the subject films are provided in a finished solid form which is applied to the sensing portions of the analyte sensors. In certain embodiments, if the film includes more than one layer, each layer of the film is fabricated from a separate film solution which is provided on a releasable support structure, where each layer of the film is casted, drawn or extruded onto the support structure. The composition of each film solution may be selected to provide a film having a desired dissolution profile.

[0014] These and other objects, advantages, and features of the disclosure will become apparent to those persons skilled in the art upon reading the details of the disclosure as more fully described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The disclosure is best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawings are not to scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

[0016] FIG. 1 is a block diagram of an analyte monitoring system with which an *in vivo* analyte sensor of the present disclosure is usable;

[0017] FIGS. 2A and 2B are front and back views, respectively, of an embodiment of a single-sided *in vivo* analyte sensor of the present disclosure;

[0018] FIGS. 3A and 3B are cross-sectional end views of alternate electrode configurations for the single-sided *in vivo* analyte sensor of FIGS. 2A and 2B;

[0019] FIG. 4A is a front view of another embodiment of a single-sided *in vivo* analyte sensor of the present disclosure;

[0020] FIGS. 4B and 4C are cross-sectional views at different locations along the length of the tail section of the sensor of FIG. 4A;

[0021] FIG. 4D is a side view of FIG. 4A;

[0022] FIGS. 5A and 5B are front and back sides, respectively, of an embodiment of a double-sided *in vivo* analyte sensor of the present disclosure;

[0023] FIG. 5C is a cross-sectional end view of the double-sided *in vivo* analyte sensor of FIGS. 5A and 5B;

- [0024] FIGS. 6A and 6B are side views of optional tail portion configurations of the *in vivo* sensors of the present disclosure;
- [0025] FIG. 7 is a flow chart illustrating a method for manufacturing a sensor in certain embodiments of the present disclosure; and
- [0026] FIG. 8 is a flow chart illustrating a method for manufacturing a sensor including two or more sets of electrodes according to embodiments of the present disclosure.

DETAILED DESCRIPTION

- [0027] Before the subject materials, devices, systems and methods are described, it is to be understood that this disclosure is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.
- [0028] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.
- [0029] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. As used herein, the terms transcutaneous, subcutaneous and percutaneous and forms thereof may be used interchangeably.
- [0030] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided may

be different from the actual publication dates which may need to be independently confirmed.

[0031] It must be noted that as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise.

[0032] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure.

[0033] While embodiments of the subject disclosure are primarily described below with respect to implantable analyte sensors and techniques and methods for fabricating, implanting and using them, such as *in vivo* sensors for monitoring glucose, such description is in no way intended to limit the scope of the disclosure. It is understood that the subject disclosure is applicable to any medical device in which at least a portion of the device is intended to be subcutaneously implanted within body.

[0034] FIG. 1 illustrates a block diagram of an embodiment of an analyte monitoring system 10. Analyte monitoring system 10 includes, in certain embodiments, an *in vivo* analyte sensor 12, at least a portion of which is configured for implantation (e.g., subcutaneous, venous, or arterial implantation) into a patient, and a sensor electronics unit 14 which is operatively coupled to sensor 12 and typically attachable to the skin of a patient. Electronics unit 14, also referred to as a control unit, typically includes most or all of the electronic components of analyte monitoring system 10 to operate sensor 12, including, for example, providing a voltage across the electrodes of sensor 12 and collecting signals from sensor 12. Electronics unit 14 may include data processing and communication electronics, the latter of which may include a transmitter for relaying or providing data obtained using sensor 12 to another device such as a remote unit 16. The electronics unit 14 may also include a variety of optional components, such as, for example, a receiver, a power supply (e.g., a battery), an alarm system, a display, a user input mechanism, a data storage unit, a watchdog circuit, a clock, a calibration circuit, etc. Remote unit 16, if employed with electronics unit 14, may include one or more the same components and additional components such as an analyte measurement circuit for use with an *in vitro* sensor, a pager, a telephone interface, a computer interface, etc.

[0035] Analytes measurable with analyte monitoring system 10 may include, but are not limited to, glucose, lactate, acetyl choline, amylase, bilirubin, cholesterol, chorionic gonadotropin,

creatine kinase (e.g., CK-MB), creatine, DNA, fructosamine, glucose, glutamine, growth hormones, hormones, ketones, lactate, peroxide, prostate-specific antigen, prothrombin, RNA, thyroid stimulating hormone, HbA1c, and troponin. Other of the subject sensors may be configured to detect and measure drugs, such as, for example, antibiotics (e.g., gentamicin, vancomycin, and the like), digitoxin, digoxin, drugs of abuse, theophylline, and warfarin. In certain embodiments, two or more analytes and/or drugs may be monitored at the same or different times, with the same or different analyte sensor(s).

[0036] Sensors described herein may be configured for monitoring the level of the analyte over a time period which may range from minutes, hours, days, weeks, one month or longer. Of interest are analyte sensors, such as glucose sensors, that are capable of providing analyte data of a user for, and therefore have an *in vivo* operational life of, about one hour or more, e.g., about a few hours or more, e.g., about a few days or more, e.g., about three or more days, e.g., about five days or more, e.g., about seven days or more, e.g., about several weeks or months.

[0037] FIGS. 2A and 2B illustrate certain embodiments of a partially implantable analyte sensor 20, such as sensor 12 of analyte monitoring system 10 (FIG. 1). In certain embodiments, sensor 20 includes a substrate 28, where a distal portion 24 of sensor 20, also referred to as the tail section, is positionable beneath the skin of the user or host for the *in vivo* determination of a concentration of an analyte in a body fluid, e.g., interstitial fluid, blood, urine, etc. Alternatively or additionally, distal portion 24 may be those positionable in a body vessel such as a vein, artery, or other portion of the body containing fluid. In certain embodiments, an *ex vivo* or proximal portion 26 is positionable outside the body, i.e., above the skin surface, and configured to be coupled to electronics unit 14 (FIG. 1).

[0038] Subject sensors in certain embodiments may have uniform dimensions along the entire length of the sensor. In certain embodiments, as depicted in FIGS. 2A-2B, sensor 20 has a distal portion 24 and a proximal portion 26 with different widths. Distal portion 24 may have a relatively narrow width to facilitate subcutaneous implantation of at least a portion of its length, and proximal portion 26 may have a relatively wider width to facilitate coupling with electronics unit 14 (FIG. 1). While the illustrated embodiment provides for a sensor having a generally flat and planar or strip configuration, in certain embodiments, either or both the distal and proximal portions may have a cylindrical or wire-like configuration.

[0039] In certain embodiments, sensor 20 is an electrochemical sensor, and includes at least two electrodes 30 where at least one of the electrodes is a working electrode formed on the implantable portion of the sensor substrate 28. While a number of examples of electrode configurations are described herein, it is understood that other configurations may also be

used. In the illustrated embodiment of FIG. 2A, sensor 20 has three sensor electrodes 30 at an end or tip of distal portion 24 which, by means of conductive traces 34, extend to electrical contacts 32 provided on proximal portion 26. Electrodes 30 may extend close to the end or tip of distal portion 24 to minimize the amount of sensor 20 that is implanted. In some instances, at least one of electrodes 30 is a working electrode and at least one other of electrodes 30 is a reference electrode, provided in any suitable pattern and configuration. For example, in certain embodiments, as shown in FIG. 3A, electrode 30a may be a reference electrode, and electrode 30b may be a working electrode with a third electrode 30c functioning as a counter electrode. In certain embodiments as shown in FIG. 3B, electrode 30a is a first working electrode, electrode 30b is a reference electrode or counter/reference electrode, and electrode 30c is a second working electrode. In certain embodiments, the signals from multiple working electrodes 30a, 30c may be averaged.

[0040] In certain embodiments, as shown in FIGS. 2A and 2B, sensor 20 is a single-sided sensor in which the electrodes 30 are provided on one side, i.e., the front side 22a, of substrate 28 with the opposite or back side 22b (as shown in FIG. 2B) of the substrate having an inactive surface. Alternatively, in other embodiments, one or more of electrodes 30 may be formed on the back side 22b of substrate 28. This may be convenient if the electrodes are formed using two different types of conductive material (e.g., carbon and silver/silver chloride). In such embodiments, only one type of conductive material needs to be applied to each side of the substrate, thereby reducing the number of steps in the manufacturing process and/or easing the registration constraints in the process. In certain embodiments, the respective counter electrode and/or reference electrodes may be formed on a second substrate (not shown) which is also implantable in the patient, or the counter and/or reference electrodes may be placed on the skin of the patient with only the working electrode or electrodes being implanted into the patient.

[0041] In certain embodiments, in order to enable the target analyte to be electrooxidized or electroreduced on the working electrode, a sensing layer 38 is provided proximate to or on working electrode 30b in FIG. 3A or, in the case where two working electrodes are used, as in the embodiment of FIG. 3B, the sensing layer 38 is provided proximate to or on at least one of the working electrodes, such as working electrode 30a. In certain embodiments, sensing layer 38 may be applied to multiple working electrodes. Sensing layer 38 may include, for example, an electron transfer agent to transfer electrons between the analyte and the working electrode (or other component), a catalyst to catalyze a reaction of the analyte and produce a response at the working electrode, or both. In certain embodiments, electron transfer agents that may be employed are electroreducible and electrooxidizable ions or

molecules having redox potentials that are a few hundred millivolts above or below the redox potential of the standard calomel electrode (SCE). When the analyte of interest is glucose, a catalyst such as a glucose oxidase, glucose dehydrogenase (e.g., pyrroloquinoline quinone (PQQ), dependent glucose dehydrogenase or oligosaccharide dehydrogenase, flavine adenine dinucleotide (FAD) dependent glucose dehydrogenase, or nicotinamide adenine dinucleotide (NAD) dependent glucose dehydrogenase) may be used. In certain embodiments, sensing layer 38 also includes one or more of an enzyme, an enzyme stabilizer, such as bovine serum albumin (BSA), and a crosslinker that crosslinks the sensing layer components. Alternatively, the sensing layer may include one or more of an enzyme, a polymeric mediator, and a crosslinker that crosslinks the sensing layer components. The components of the sensing layer may be in a fluid or gel or formed as a solid composition. In certain embodiments, the components of the sensing layer are non-leachably disposed on the sensor. Examples of sensing layers that may be employed are described in, among others, U.S. Patent Nos. 5,262,035, 5,264,104, 5,543,326, 6,605,200, 6,605,201, 6,676,819, and 7,299,082, the disclosures of each of which are incorporated herein by reference for all purposes.

[0042] Disposed over at least the implantable portion of sensor distal portion 24, in certain embodiments, is a film 36. Film 36 includes one or more layers for optimizing the functioning of and/or results from the sensor 20, where at least one of the layers is dissolvable. Film 36 may also optionally include one or more non-dissolvable layers. As discussed in greater detail below, the dissolvable layer(s) may have a number of varying thicknesses and/or dissolution rates to provide a selected dissolution profile which may vary along the geometry of the distal portion 24 of sensor 20.

[0043] In certain embodiments, film 36 functions to control the ingress of physiological agents from the *in vivo* environment in which a sensor is implanted (such as a patient's interstitial fluid or blood stream) toward the sensing components of the sensor and/or to control the egress of agents, drugs or the like resident within the film to the *in vivo* environment. In some instances, this ingress/egress function is provided by the permeability and/or the dissolvability *in vivo* of the material of film 36. The formulation of film 36 may be fine-tuned or customized to control which agents ingress/egress and the rate at which they ingress/egress, as well as to provide other functional and physical characteristics.

[0044] In certain embodiments, film 36 is formulated at least in part from one or more base polymer matrices which are selected to provide the desired functional characteristics (e.g., permeability, dissolvability, dissolution rate, diffusion rate, etc.) and physical characteristics (e.g., rigidity, flexibility, strength, thickness, shape, surface characteristics, etc.) of film 36. Film 36 may include one or more layers where each individual layer may have a homogenous

material formulation over its entire volume or may have a non-homogeneous material formulation that varies in one or more characteristics, e.g., thickness, density, flexibility, rigidity, permeability, dissolution rate, agent or chemical content or diffusion, etc., over its volume, thickness, length or other dimension. In certain embodiments where film 36 has multiple layers, all the layers may include identical material formulations or one or more layers may be differently formulated from the others to provide different functions. In certain embodiments, film 36 has at least one inner layer and at least one outer layer, where an inner layer is selectively permeable to enable passage of the target analyte, such as glucose, to the sensing components (i.e. working electrode 30b (FIG. 3A) with sensing layer disposed thereon) while preventing the passage of interferent molecules thereto, and an outer layer is selectively dissolvable to control the time at which sensor 20 becomes functionally active after *in vivo* implantation.

[0045] In certain embodiments, film 36 may be configured, particularly in terms of permeability, to function as a diffusion-limiting layer to regulate or limit the flux of an analyte to sensing layer 38 (FIGS. 3A and 3B) and working electrodes while restricting the diffusion of the sensing layer components (e.g., an electron transfer agent and/or a catalyst) out of sensing layer 38. In a glucose sensor without a diffusion-limiting layer, the flux of glucose to the sensing layer increases linearly with the concentration of glucose. When all of the glucose arriving at the sensing layer 38 is consumed, the measured output signal is linearly proportional to the flux of glucose and thus to the concentration of glucose. However, when the glucose consumption is limited by the kinetics of chemical or electrochemical activities in the sensing layer 38, the measured output signal is no longer controlled by the flux of glucose and is no longer linearly proportional to the flux or concentration of glucose. In this case, only a fraction of the glucose arriving at the sensing layer is consumed before the sensor becomes saturated, whereupon the measured signal stops increasing, or increases only slightly, with the concentration of glucose. In a glucose sensor equipped with a diffusion-limiting layer, in certain embodiments, the diffusion-limiting layer reduces the flux of glucose to the sensing layer 38 such that the sensor does not become saturated and can therefore operate effectively within a much wider range of glucose concentrations.

[0046] For *in vivo* sensors, in certain embodiments, the diffusion-limiting layer may be made using a film that absorbs 5 wt. % or less of fluid over 24 hours at 37°C (body temperature). Suitable polymers for use as a diffusion-limiting layer are those which preferably have pores with well-defined, uniform pore sizes and high aspect ratios, and have diameters in the range from 3 nm to 20,000 nm diameter pores, such as from 5 nm to 500 nm pores. In certain

embodiments, the aspect ratio of the pores is two or greater, such as five or greater. Examples of polymeric layers are those made from polycarbonate, polyolefin and polyester, combinations thereof, and the like. Additional information about and disclosure of diffusion-limiting layers for use in analyte sensors can be found in U.S. Patent Nos. 6,175,752 and 6,932,894, the disclosures of each of which are incorporated herein by reference for all purposes.

[0047] In certain embodiments, a diffusion-limiting layer, in addition to regulating the flux of the target analyte toward the sensing components and limiting the diffusion of the sensing component out of the sensing layer, may also be configured to prevent the infusion or permeation of interferents, i.e., molecules or other species that are electroreducible or electrooxidizable at the working electrode, either directly or via an electron transfer agent, to produce a false signal. Alternatively, a diffusion-limiting layer may be provided as one layer of a composite film. In either case, a diffusion-limiting layer or film may be much less permeable to one or more interferents than to the target analyte. The diffusion-limiting layer may include ionic components, such as Nafion®, incorporated into a polymeric matrix to reduce the permeability of the diffusion-limiting layer to ionic interferents having the same charge as the ionic components.

[0048] In certain embodiments, a film's ability to dissolve or disintegrate over time depends of the solubility of the film's base polymer(s). One or more fillers may be added to the water-soluble polymer(s) in a dispersed phase to modify the dissolution rate of the film. Other components such as starches and polysaccharides can be added to promote or delay the film's disintegration. The concentration of these materials may be varied over a dimension of the film to customize the dissolution profile. For example, a portion of the film's length may be configured to dissolve at a faster rate than another portion of its length. Certain benefits and advantages of this feature of the subject films are evident in the embodiments of FIGS. 4A-4D and 5A-5C.

[0049] FIGS. 4A-4D illustrate a single-sided sensor 40 of the present disclosure having tail (or distal) section 42 and proximal section 44 constructs similar to those of sensor 20 of FIGS. 2A and 2B. Referring to FIGS. 4A-4D, in certain embodiments, sensor 40 has two sets of electrodes provided on tail (or distal) section 42; a first or proximal electrode set 52 and a second or distal electrode set 56. In some instances, both sets of electrodes are provided on the same surface of substrate 46. FIGS. 4B and 4C illustrate cross-sectional views of first and second electrode sets 52, 56, respectively. First electrode set 52 includes, for example, a working electrode 52a covered by sensing layer 54, and counter and reference electrodes 52b, 52c, respectively. Second electrode set 56 includes, for example, counter, reference and

working electrodes 56a, 56b and 56c, respectively, with a sensing layer 58 provided over working electrode 56c. The formulations of the respective sensing layers 54, 58 may be the same to detect the same target analyte, or may differ from each other for detecting different analytes. It should be noted that the electrode configurations in the illustrated embodiments are merely examples, and any suitable combination of electrodes may be employed with sensor 40. In certain configurations, both electrode sets share the same set of contact pads 48 and conductive traces 50, where electrodes 52a and 56a are electrically coupled to a first conductive trace and contact pad; electrodes 52b and 56b are electrically coupled to a second conductive trace and contact pad; and electrodes 52c and 56c are electrically coupled to a third conductive trace and contact pad. The respective electrochemical component sets, thus, provide two functional sensors or sensing sections. Any desired number of additional sensing sections may be provided on a single sensor substrate by adding sets of electrodes and their associated sensing layers.

[0050] In certain embodiments, the two (or more) sensing sections and their respective electrode sets 52, 56, become functionally active, i.e., provide the necessary electrochemical reaction in the presence of a target analyte, starting at two (or more) separate times, where their functional time periods may be non-overlapping, substantially non-overlapping, or partially overlapping. For example, first electrode set 52 may be employed first in time for a first useful sensing life and second electrode set 56 may be employed second in time for a second useful sensing life. In some cases, the time differential is accomplished by film 60, which includes at least one layer which encases or coats at least the implantable portion of sensor tail section 42, and which is at least partially comprised of one or more water-soluble, hydrophilic polymers. In certain embodiments, using film 60 to selectively expose one or more sensing sections of a sensor having a plurality of sensing sections provides the benefit of reducing the number of sensor removals and replacements a patient performs. It is noted that film 60 may include one or more additional layers which are not dissolvable or partially dissolvable, e.g., dissolvable in sections, and are permeable to provide the necessary diffusion-limiting and/or interferent-restricting functions discussed above.

[0051] With homogenous films, in certain embodiments, the time variance in the available functionality of the respective sensor portions may be accomplished by selectively varying the thickness of film 60 along the length of tail section 42 in order to vary the time at which electrode sets 52, 56, or at least a permeable membrane layer (not shown) and/or sensing layers 54, 58, are exposed to the physiological environment in which sensor 40 has been implanted. For example, as shown in FIGS. 4B-4D, film 60 has a first thickness 62a (FIGS. 4B and 4D) disposed on a first or proximal portion or length of tail section 42, including

electrode set 52, including electrodes 52a, 52b, and 52c, and has a second thickness 62b (FIGS. 4C and 4D) disposed on a second or distal portion or length of tail section 42, including electrode set 56, including electrodes 56a, 56b, and 56c, where second thickness 62b is greater than first thickness 62a.

[0052] In certain embodiments, film 60 may have multiple dissolvable layers or coats, where, for example, a first layer 60a is disposed on the entire implantable length of tail section 42, including both sets of electrodes 52, 56, and a second layer 60b is disposed on a distal portion of tail section 42, including distal electrode set 56 but not proximal electrode set 52, as illustrated in FIG. 4D. In certain embodiments, the two dissolvable layers 60a, 60b have the same disintegration/dissolution properties. As such, the first or proximal electrode set 52 will be exposed to the *in vivo* environment (such as interstitial fluid or blood stream) first, and the second or distal electrodes 56 will be exposed at a later point in time. The thickness of layer 60b may be selected so that second electrode set 56 becomes exposed as the useful life of the first electrode set 52 expires. Alternatively, the thickness of layer 60b may be such that it dissolves prior to expiration of the useful life of electrodes 52 so that there are substantially no time gaps in monitoring of the target analyte. The thicknesses of each of the layers 60a and 60b may be selected to provide the desired dissolution and sensor activation profiles.

[0053] In certain embodiments, a first sensing portion may be provided without a film disposed thereon, with only the second, third, etc. sensing portions coated with one or more layers of a film. In some instances, this configuration may be efficient and simple for embodiments where the film is used only for its time-delay function. It is also noted that while the illustrated sensor embodiment of FIGS. 4A-4D is configured such that the proximal electrode set 52 is the first sensing section exposed to the *in vivo* environment, by virtue of the relative thickness of film 60 adjacent that section, in alternative embodiments, film 60 may have a proximal portion that is thicker than the distal portion such that electrode sets 52, 56 are exposed to the elements in reverse order (e.g., electrode set 56 is exposed first, and electrode set 52 is exposed second).

[0054] In certain embodiments, a manner of controlling and time-varying the exposure of the various sensor portions of sensor 40 is to provide a non-homogenous film in which the dissolution profile of film 60, i.e., the rate at which the film dissolves upon exposure to the *in vivo* environment, varies along the length of tail section 42. This may be accomplished by providing two or more dissolvable layers 60a and 60b having different dissolution rates, where the respective layer thicknesses may or may not vary. In certain embodiments, a single layer may be provided which has a continuous thickness but varying dissolution profile along the length of tail section 42.

[0055] In embodiments of FIGS. 2A, 2B, 3A, 3B and 4A-4D, the respective sensors 20 and 40 are single-sided sensors in which the electrochemical components are provided on one side of the respective sensor substrates. Certain embodiments of the present disclosure include double-sided sensors in which both sides of the sensor are functionally active, i.e., sensing components, e.g., electrodes, traces, contacts, etc., are provided on both sides of the sensor substrate. FIGS. 5A-5C illustrate an example of a double-sided sensor for use in certain embodiments. Referring to FIGS. 5A-5C, sensor 70 is formed by substrate 78 having a similar physical construct and shape similar to those discussed and described above, with a distal tail section 74, configured for *in vivo* implantation, and an *ex vivo* proximal portion 76. As shown in FIG. 5A, a first sensor side 72a includes a first set of contact pads 92, conductive traces 90, and a first electrode set 80, including working electrode 80a, counter electrode 80b and reference electrode 80c (FIG. 5C). As shown in FIG. 5B, a second sensor side 72b includes a second set of electrochemical components including electrode set 84, conductive traces 94 and contact pads 96, where electrode 84a is a counter electrode, electrode 84b is a reference electrode and electrode 84c is a working electrode (FIG. 5C). A sensing layer 82, 86 covers each of the working electrodes 80a, 84c, respectively. A dissolvable film 88 surrounds the surfaces of tail section 74, covering both electrode sets 80 and 84. The thickness and/or dissolution profile of dissolvable film 88 may be varied to control the time at which each electrode set 80, 84 is exposed to the *in vivo* environment and may begin communicating signals representative of the target analyte. For example, with a homogenous film, the portion of film 88 disposed on the second electrode set 84 may have a thickness 98b which is greater than the thickness 98a of the portion of film 88 disposed on the first electrode set 80, as shown in FIG. 5C. As such, first electrode set 80 becomes exposed to the *in vivo* environment prior to second electrode set 84. In certain embodiments, the differential in the respective thickness of 98a and 98b may dictate the time delay at which the second electrode set 84 commences active operation. In certain embodiments, the dissolution profile of film 88 may be varied such that the portion of film 88 covering the first side 72a of sensor 70 dissolves at a faster rate than the portion of film 88 covering the second side 72b of sensor 70, where the dissolvable film thickness on the respective substrate sides may be the same or different.

[0056] It should be noted that while only a single sensing section is provide on each side of substrate 78, with the two opposing sensing sections positioned at approximately the same position along the length of tail section 74, more than one sensing section may be provide on each substrate side with a matched or unmatched number of sensing sections provided on the opposing sides. Further, while each of the illustrated sensing sections includes its own

electrode set and associated sensing layer, multiple sensing sections may be provided having a common electrode set. For example, a sensor may be provided with a single set of electrodes on the same sensor side but with more than one sensing section where the multiple sensing sections are spaced apart along the length of the electrode traces on the tail section of the sensor. Activation of the various sensing sections may be accomplished by a dissolvable film having varying thicknesses and/or dissolution rates to selectively expose the various sensing layers over the useful life of the sensor. For example, three or more spaced apart sensing layers may be provided over a single set of electrodes. The dissolvable film may be configured such that the first (e.g., most distal) sensing layer is exposed first, followed by exposure of the second, proximally adjacent sensing layer after or near the end of the useful life of the first sensing layer, with the third, most proximal sensing layer exposed after or near the end of the useful life of the second sensing layer.

[0057] As used herein, the term “sensing section” is intended to be non-limiting, including the at least the components necessary to enable an electrochemical reaction with the target analyte, and as such includes at least one electrode or set of electrodes and an optional sensing layer and an optional diffusion-limiting layer. Further, each sensing section may be configured to detect and monitor a different analyte, or two or more may be configured to monitor the same analyte. For example, a sensor may be provided with four sensing sections, two on each side of the sensor substrate where the pair of sensing sections on one side of the substrate is configured to detect glucose and the pair on the opposite side is configured to detect ketones. The dissolvable film at a distal portion of the sensor tail section covering one glucose sensing section and one ketone sensing section may have a thickness and/or dissolution rate that varies from that of a proximal portion of the dissolvable film which extends over the second glucose and ketone sensing sections.

[0058] In addition to permeability and/or dissolution characteristics, with any of the subject sensor embodiments, one or more layers of the film may function to carry and deliver agents to the *in vivo* environment which are beneficial to that the physiology of the insertion site and/or further optimize the performance of the sensor. For example, the film or a layer thereof may include an anti-clotting agent at an outer surface thereof which may reduce or substantially eliminate the clotting of blood or other body fluid around the sensor while it is implanted. Blood clots may foul the sensor or reduce the amount of analyte which diffuses into the sensor. Examples of useful anti-clotting agents include heparin and tissue plasminogen activator (TPA), as well as other known anti-clotting agents. The film or a layer thereof may also include an antibiotic to minimize the risk of infection and resulting inflammation at the insertion site. The film or a layer thereof may also include a

biocompatible layer or otherwise be configured across a thickness dimension to prevent the penetration of large molecules into the sensing section. This may be accomplished by using a layer having a pore size that is smaller than biomolecules to be excluded. Such biomolecules may foul the electrodes and/or the sensing layer thereby reducing the effectiveness of the sensor. The biocompatible layer may also prevent protein adhesion to the sensor and other undesirable interactions between the sensor and the surrounding environment. In certain embodiments, hydrogels contain 20 wt. % or more fluid when in equilibrium with the surrounding analyte-containing fluid. Examples of suitable hydrogels are described in U.S. Patent No. 5,593,852, the disclosure of which is incorporated herein by reference, and include, but are not limited to, crosslinked polyethylene oxides, such as polyethylene oxide tetraacrylate, and the like.

[0059] In addition to the fluid dynamic, chemical and physiological functions provided by the subject film, the film may have customized physical and mechanical properties to facilitate overall sensor function and durability as well as transcutaneous implantation of the sensor. For example, the film may be configured to be flexible to provide comfort to the patient for an extended period of time where the sensor is implanted. In some cases, plasticizers and/or humectants can be added to the base polymer(s) to increase the film's overall flexibility, while preventing brittleness or breakage. In other embodiments, where a more rigid sensor is desirable, less of these materials may be used in the composition of the film. For example, all or a portion of the length along the outer surface of the film along the tail section of the sensor may be configured to be rigid to facilitate penetration of the tail section of the sensor into the skin during implantation of the sensor. The portion of the film covering the distal end of the tail section of the sensor may have a skin-penetrating configuration, such as a sharp or pointed tip. FIGS. 6A and 6B illustrate examples of tip configurations for such purpose. In FIG. 6A, tail section 90 is provided with a film 92 coated thereon with a distal portion formed in a symmetrical pointed tip 94a. In FIG. 6B, the film 92 includes a distal portion formed into an asymmetrical pointed tip 94b.

[0060] The present disclosure is also directed to methods and techniques for fabricating the subject sensors and the subject films. The sensors, including the substrate, electrodes, conductive traces, contact pads, dielectric layer(s), if any, sensing layer(s), and diffusion-limiting layers may be fabricated separately from the subject film. The film may be provided separately and applied to the sensor in a subsequent fabrication step. As such, a sensor may be fabricated according to known sensor fabrication processes and techniques, including web-based manufacturing techniques, many of the steps of which are disclosed in U.S. Patent No. 6,103,003 and U.S. Patent Application No. 12/842,013, the disclosures of each of which

are incorporated herein by reference for all purposes. In some embodiments, the sensing layer is provided as a component layer of a composite film and, as such, is applied to the sensor as part of the film. In some embodiments, the sensing layer and the diffusion-limiting layer are provided as component layers of a composite film and, as such, are applied to the sensor as part of the film.

[0061] FIG. 7 is a flow chart illustrating a method for manufacturing a sensor in certain embodiments of the present disclosure. Referring to FIG. 7, a sensor body is manufactured from a substrate and electrodes (with any necessary sensing layers disposed thereon), contact pads, and conductive traces are formed on the substrate (710). In certain embodiments, the substrate is formed from a flexible non-conducting material and the electrodes, contact pads, and conductive traces are formed from a conductive material, such as a conductive carbon, silver/silver chloride, or gold, and the like. Examples of materials and methods for manufacturing the sensor substrate, electrodes, contact pads, and conductive traces can be found in, among others, U.S. Patent Nos. 6,175,752, 6,134,461, and 6,103,003 and U.S. Patent Application No. 12/714,439, the disclosures of each of which are incorporated herein by reference for all purposes. Returning to FIG. 7, a desired time after insertion to sensor electrode exposure to the *in vivo* elements, such the interstitial fluid or blood stream of the user, is determined (720). Once the desired time until exposure is determined (720), parameters, such as dimensions, thickness, and materials, of a dissolvable film corresponding to the desired time until exposure are determined (730). A dissolvable film with parameters as determined in 730 is applied to at least a portion of the sensor, including the section of the sensor including the electrodes (740).

[0062] FIG. 8 is a flow chart illustrating a method for manufacturing a sensor including two or more sets of electrodes. Referring to FIG. 8, a sensor body including a substrate and at least two sets of electrodes (wherein each set of electrodes includes at least one working electrode), is manufactured (810). Desired times after insertion of the sensor to exposure of each set of electrodes to the *in vivo* elements is determined (820). Once the desired times until exposure are determined, corresponding dissolvable film parameters are determined (830). Once the parameters are determined, corresponding dissolvable films are applied to at least the portions of the sensor including the corresponding sets of electrodes (840). In certain embodiments, as described above, a single dissolvable film is utilized over all the sets of electrodes and the parameters determined to correspond to the desired time until exposure are varying thickness of the film. In other embodiments, the parameters for the dissolvable film correspond to multiple dissolvable films, such that the electrode sets are each covered by

a different dissolvable film, where each dissolvable film has a dissolution rate corresponding to the desired time until exposure of the respective electrode set.

[0063] To initiate the fabrication process, a continuous film or web of substrate material is provide. The sensor substrate may be formed using a variety of non-conducting materials, including, for example, polymeric or plastic materials and ceramic materials. The sensor webbing may be pre-cut or have perforations therein to define the individual sensor precursors. At least the portion of the substrate webbing from which the sensor distal portions are to be formed may be flexible (although rigid materials may also be used for implantable sensors) to minimize discomfort to the patient and allow for a wider range of activities. Suitable materials for a flexible substrate include, for example, plastic or polymeric materials and other non-conducting, flexible, deformable materials. Examples of useful plastic or polymeric materials include thermoplastics such as polycarbonates, polyesters (e.g., Mylar™ and polyethylene terephthalate (PET)), polyvinyl chloride (PVC), polyurethanes, polyethers, polyamides, polyimides, or copolymers of these thermoplastics, such as PETG (glycol-modified polyethylene terephthalate).

[0064] After the substrate material is heat treated as necessary, the electrodes, conductive traces and conductive contacts are then formed on one or both sides of the substrate web (depending on whether a sensor having one or two functional sides is being fabricated) by one or more of a variety of techniques, e.g., chemical vapor deposition (CVD), physical vapor deposition, sputtering, reactive sputtering, printing, coating, ablating (e.g., laser ablation), painting, dip coating, etching and the like. Where the electrodes are provided in a co-planar manner, i.e., where two or more electrodes are positioned on the same side of the substrate and in the same plane (e.g., side-by side) of the substrate, as in the illustrated embodiments herein, sufficient spacing is provided between the electrodes/traces/pads to prevent undesired conduction between them. Alternatively, a dielectric or insulating material is disposed between the electrodes/traces/pads. In a stacked or layered electrode configuration, the “primary” conductive layers are provided first, extending distally along the tail section of the sensor precursors to any suitable length. Next, the sensing layer (where not a component of the film) and secondary conductive layers, if employed, are formed on the primary conductive layers on the respective sides of the substrates or substrate web. In certain embodiments, one or more of the electrodes of the same sensing section may be disposed on opposing sides of the substrate. In such double-sided sensor embodiments, the corresponding electrode contacts may be on the same or different sides of the substrate. For example, an electrode may be on a first side and its respective contact may be on a second side, e.g., a trace connecting the electrode and the contact may traverse through the substrate. In any of the single- or double-

sided sensor embodiments, the respective conducting and insulating material layers may be provided over a webbing of sequentially aligned sensor precursors prior to singulation of the sensors or over a plurality of sensors where the sensors have been singulated from each other (and the substrate webbing) prior to provision of the one or more material layers.

[0065] Selection of the conductive materials for the respective electrodes is based in part on the desired rate of reaction of the sensing layer's mediator at an electrode. In some instances, the rate of reaction for the redox mediator at the counter/reference electrode is controlled by, for example, choosing a material for the counter/reference electrode that would require an overpotential or a potential higher than the applied potential to increase the reaction rate at the counter/ reference electrode. For example, some redox mediators may react faster at a carbon electrode than at a silver/silver chloride (Ag/AgCl) or gold electrode. The conductive traces may be formed using a conductive material such as carbon (e.g., graphite), a conductive polymer, a metal or alloy (e.g., gold or gold alloy), or a metallic compound (e.g., ruthenium dioxide or titanium dioxide), and the like. The electrical contacts may be made with the same material as that used for the conductive traces or, alternatively, may be made from a carbon or other non-metallic material, such as a conducting polymer. Other suitable conductive materials for the electrodes, conductive traces and contact pads include but are not limited to aluminum, carbon (such as graphite), cobalt, copper, gallium, gold, indium, iridium, iron, lead, magnesium, mercury (as an amalgam), nickel, niobium, osmium, palladium, platinum, rhenium, rhodium, selenium, silicon (e.g., doped polycrystalline silicon), silver, tantalum, tin, titanium, tungsten, uranium, vanadium, zinc, zirconium, mixtures thereof, and alloys, oxides, or metallic compounds of these elements.

[0066] Finally, one or more film layers (e.g., dissolvable film layers as described herein) are provided, preferably on each functional side of the sensor webbing or singulated sensors, i.e., each of the sensor webbing or singulated sensors on which electrochemical components have been formed. In certain embodiments, the one or more film layers are provided in the form of a pre-fabricated film which includes one or more water-soluble polymers, as discussed above, which are customized to provide the desired dissolution profile once the sensor has been implanted *in vivo*. In addition to the fillers, starches, polysaccharides, plasticizers, humectants, etc. added to the base polymer(s), as mentioned above, thickeners, buffers, stabilizers and other additives may be added to the film solution to provide the desired characteristics of the film. In certain embodiments the sensing components of the sensing layers which, in the illustrated embodiments are provided as a distinct layer from the subject films, may be incorporated into the film solution by being soluble in the solution, or

suspended or dispersed therein. As such, the sensing layer, upon application to the sensor substrate, typically resides as the innermost layer disposed on the sensor.

[0067] The resulting film solution is then further processed into a film format or construct by one or more casting, drawing or extrusion techniques. For example, the solution may be roll-coated onto a release-treated support structure, such as paper or plastic, or the like. In certain embodiments, the film is then dried to remove the solvent component, producing the final film. In certain cases, the processes are repeated for each film layer to provide a composite film structure having multiple layers. The dry composite film may then be further processed to provide the desired shape and/or size by any suitable techniques, such as die-cutting, etc., prior to applying the film to the sensor webbing or precursors.

[0068] Alternatively or in addition to the manufacturing techniques discussed above, the subject sensors may be fabricated by one or more extrusion methods. For example, the sensor substrate material may be made of a polymer material which may be formed in the desired shape by an extrusion process, in which case, the conductive and insulating materials, as well as the sensing components (if not incorporated into the film to be applied), are formed or provided on the substrate material after extrusion of the substrate material. In still other embodiments, the subject sensors may be fabricated by an extrusion process in which some or all of the conductive and non-conductive materials, e.g., substrate material, insulating materials, etc. are co-extruded in one or more extrusion processes. The layers of the film may then be applied to the extruded sensors, either one at a time, or collectively by means of a web-based process. Still yet, the film layer(s) may be provided in solution form and applied to the sensors as part of a comprehensive extrusion process. Examples of sensors fabricated by extrusion methods are disclosed in U.S. Patent Application Publication No. 2008/0200897 and U.S. Patent Application Nos. 12/495,618, 12/495,696, 12/495,709, 12/495,712 and 12/495,730, the disclosures of each of which are incorporated herein by reference for all purposes.

[0069] The preceding merely illustrates the principles of the disclosure. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the disclosure and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the disclosure and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the disclosure as well as specific examples thereof, are intended to encompass both structural and

functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present disclosure, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present disclosure is embodied by the appended claims.

CLAIMS

What is claimed is:

1. An *in vivo* analyte sensor comprising:
an implantable portion comprising at least one sensing section comprising at least one electrode; and
a film disposed over the at least one sensing section, the film comprising at least one dissolvable layer.
2. The analyte sensor of claim 1, wherein the at least one sensing section comprises a sensing layer disposed on at least a portion of the electrode.
3. The analyte sensor of claim 2, wherein the at least one sensing section further comprises a diffusion-limiting layer disposed on at least a portion of the sensing layer.
4. The analyte sensor of claim 2, wherein the film further comprises a diffusion-limiting layer.
5. The analyte sensor of claim 4, wherein the diffusion-limiting layer is an innermost layer of the film.
6. The analyte sensor of any of the preceding claims, wherein the film further comprises a sensing layer.
7. The analyte sensor of claim 6, wherein the sensing layer is an innermost layer of the film.
8. The analyte sensor of claim 6, wherein the film further comprises a diffusion-limiting layer disposed on at least a portion of the sensing layer.
9. The analyte sensor of any of the preceding claims, wherein the film further comprises at least one non-dissolvable layer wherein the dissolvable layer is disposed on at least a portion of the non-dissolvable layer.
10. The analyte sensor of claim 9, wherein the at least one non-dissolvable layer comprises one or more of a sensing layer and a diffusion-limiting layer.
11. The analyte sensor of any of the preceding claims, wherein the film comprises one or more of an anti-clotting agent and an antibiotic.

12. The analyte sensor of any of the preceding claims, wherein the at least one dissolvable layer has a varying thickness dimension.

13. The analyte sensor of any of the preceding claims, wherein the at least one dissolvable layer has a constant thickness dimension.

14. The analyte sensor of any of the preceding claims, wherein the at least one dissolvable layer comprises a homogenous composition.

15. The analyte sensor of any of the preceding claims, wherein the at least one dissolvable layer comprises a non-homogenous composition.

16. The analyte sensor of claim 15, wherein the at least one dissolvable layer has different dissolution rates along a length of the implantable portion.

17. The analyte sensor of any of the preceding claims, wherein the film at a distal portion of the implantable portion of the sensor has a skin-penetrating configuration.

18. The analyte sensor of any of the preceding claims, wherein the film comprises at least two dissolvable layers.

19. The analyte sensor of claim 18, wherein the at least two dissolvable layers have the same thickness dimension.

20. The analyte sensor of claim 18, wherein the at least two dissolvable layers have different thickness dimensions.

21. The analyte sensor of claim 18, wherein the at least two dissolvable layers have the same composition.

22. The analyte sensor of claim 18, wherein the two dissolvable layers have different compositions.

23. The analyte sensor of any of the preceding claims, wherein the implantable portion comprises at least two sensing sections.

24. The analyte sensor of claim 23 wherein the thickness of the at least one dissolvable layer over a first sensing section is different than the thickness of the at least one dissolvable layer over a second sensing section.

25. The analyte sensor of claim 23 wherein at least one sensing section is on a first side of the implantable portion and at least one sensing section is on a second side of the implantable portion.

26. The analyte sensor of claim 23 wherein the at least two sensing sections are on the same side of the implantable portion.

27. A method of fabricating an *in vivo* analyte sensor, the method comprising:
providing a sensor substrate comprising an implantable portion comprising at least one sensing section provided thereon, the sensing section comprising at least one electrode disposed on the sensor substrate;
removing a film from a support structure, the film comprising at least one layer; and
disposing the film over the at least one sensing section, wherein the film comprises at least one dissolvable layer.

28. The method of claim 27, further comprising applying a film solution onto the support structure.

29. The method of claim 28, wherein the applying a film solution comprises casting, drawing or extruding the film solution onto the support structure.

30. The method of claim 28, further comprising repeating the applying the film solution for each layer in the film.

31. The method of claim 30, further comprising forming the film in a desired shape prior to removing the film from the support structure.

32. The method of claim 28, wherein the film solution comprises one or more water-soluble polymers.

33. The method of claim 32, wherein the film solution has a composition selected to provide a film having a desired dissolution profile.

34. A method of monitoring a target analyte within the body of a patient, the method comprising:

implanting at least a portion of an analyte sensor within the patient, the portion of the analyte sensor implanted comprising at least two sensing sections, each sensing section configured to sense the target analyte;

activating a first sensing section at a first predetermined time; and

activating a second sensing section at a second predetermined time.

35. The method of claim 34, wherein the activating the first sensing section comprises dissolving a film disposed over the first sensing section and wherein the activating the second sensing section comprises dissolving a film disposed over the second sensing section.

36. The method of claim 35, wherein the film disposed over the first sensing section and the film disposed over the second sensing section form a single film.

37. The method of claim 36, wherein the thickness of the film disposed over the first sensing section is less than the thickness of the film disposed over second sensing section.

38. The method of claim 36 wherein the thickness of the film is substantially constant and the rate of dissolution of the film disposed over the first sensing section is greater than the rate of dissolution of the film disposed over the second sensing section.

39. The method of claim 35, wherein the second sensing section is activated when the first sensing section is substantially exhausted.

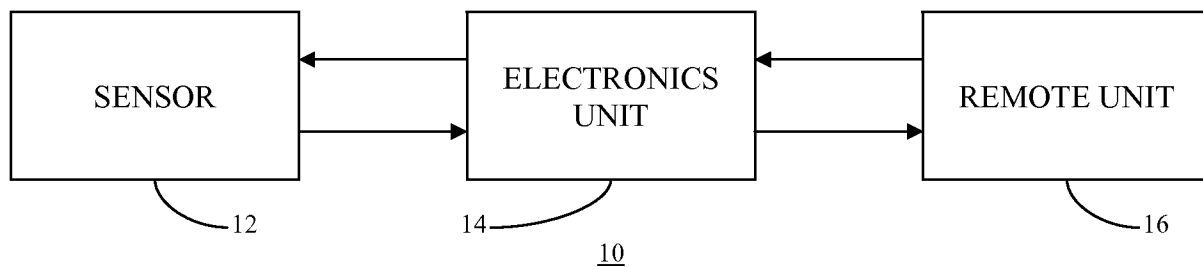


FIG. 1

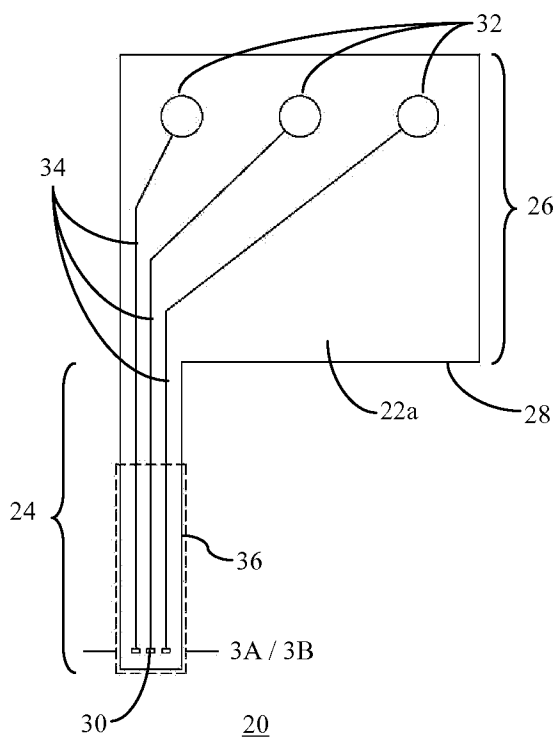


FIG. 2A

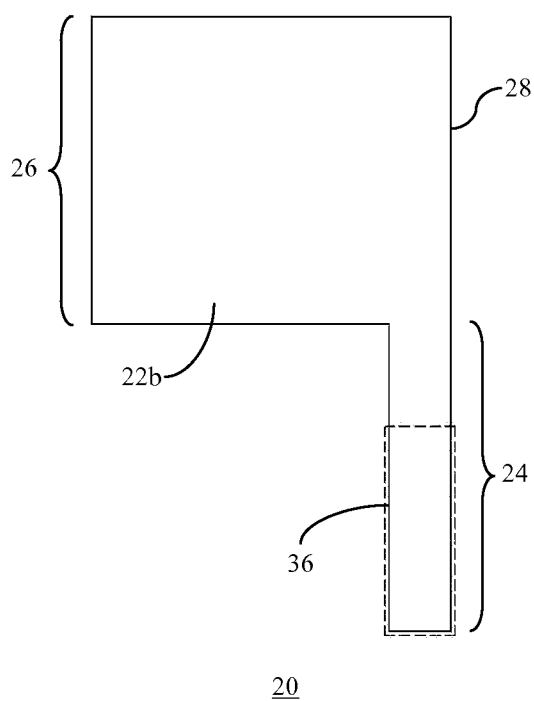


FIG. 2B

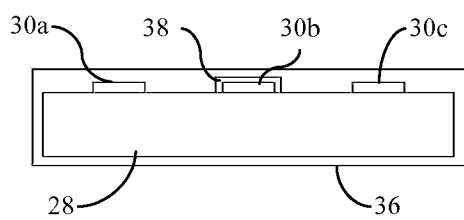


FIG. 3A

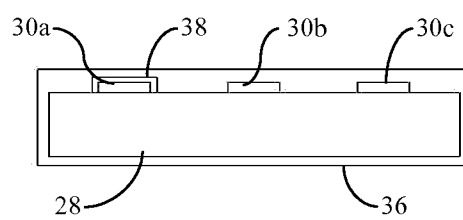


FIG. 3B

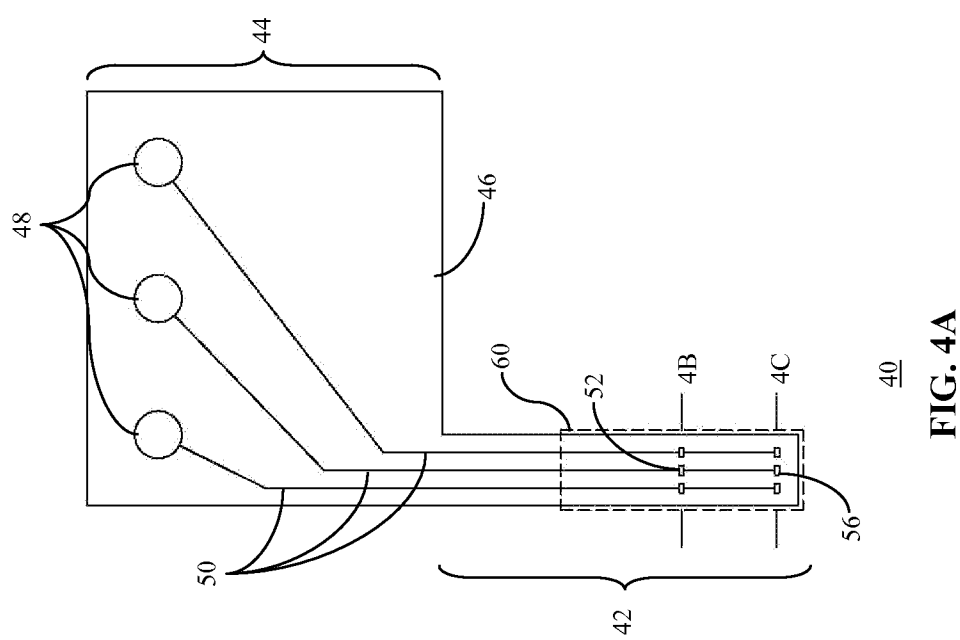


FIG. 4A

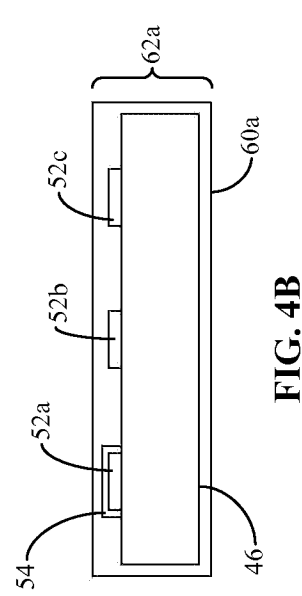


FIG. 4B

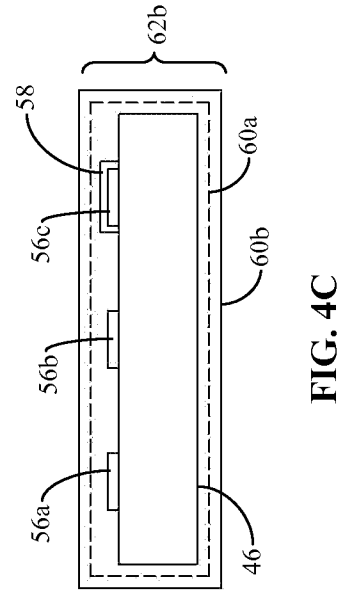


FIG. 4C

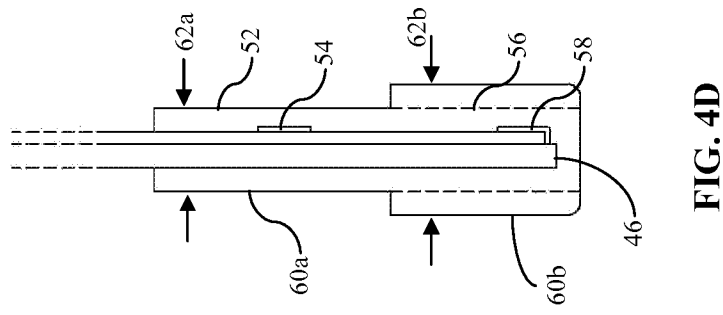


FIG. 4D

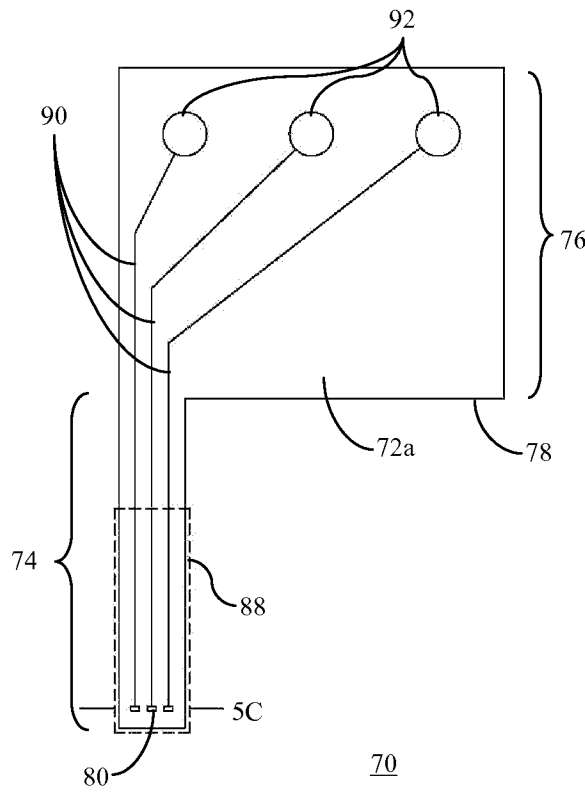


FIG. 5A

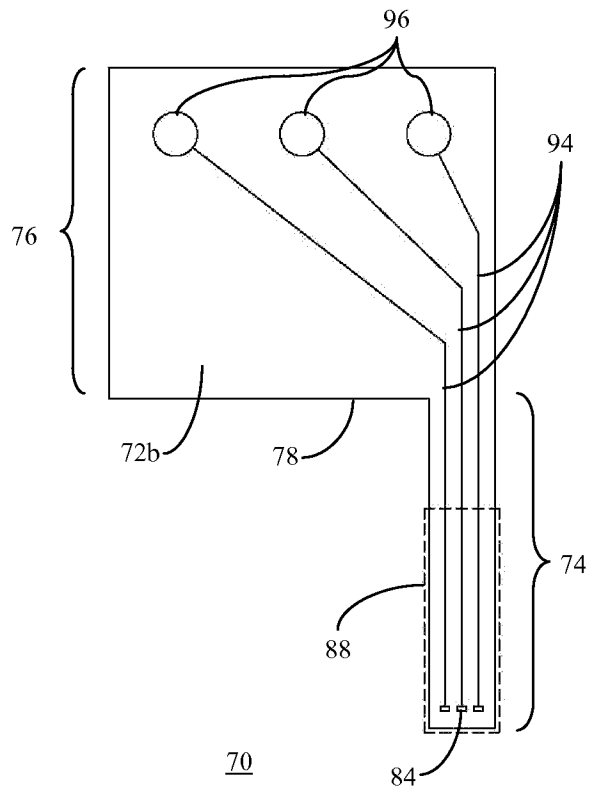


FIG. 5B

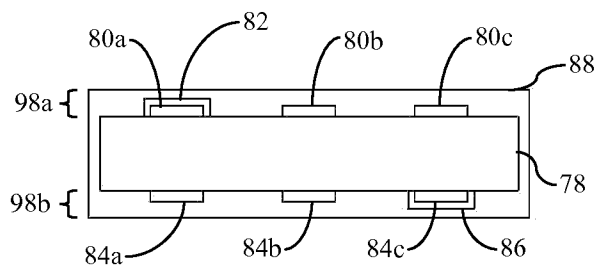


FIG. 5C

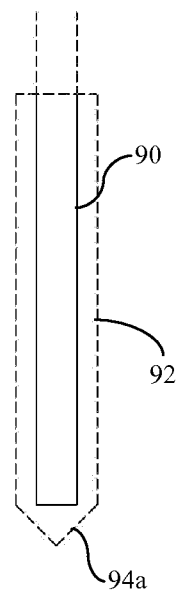


FIG. 6A

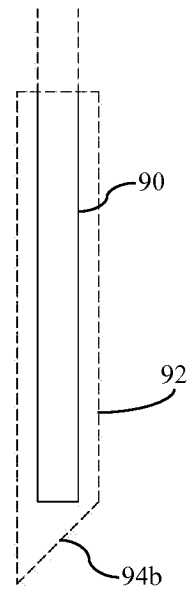


FIG. 6B

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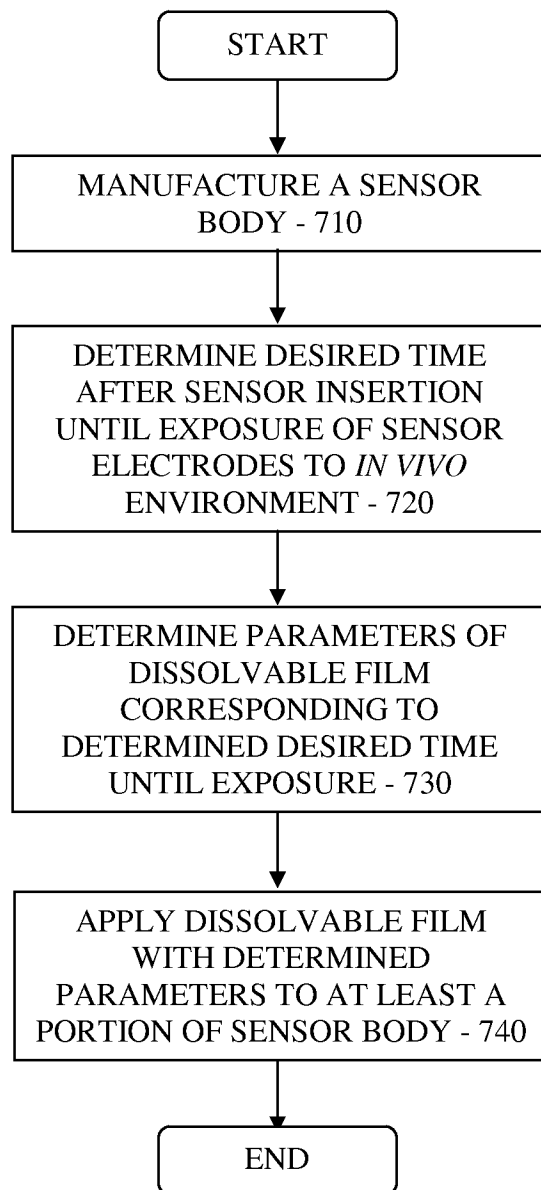


FIG. 7

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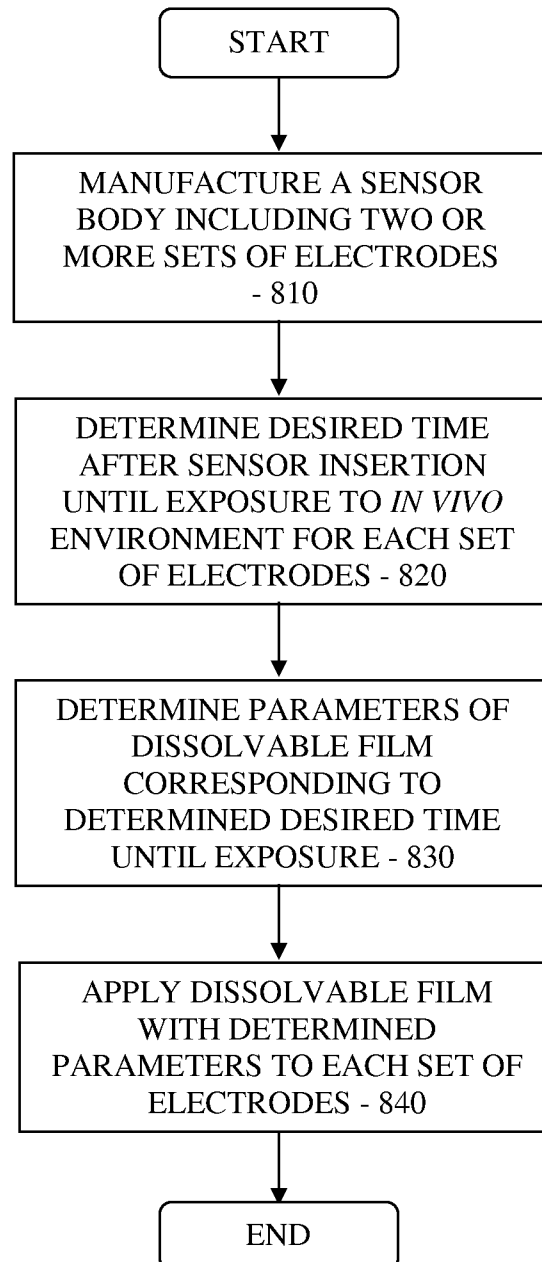


FIG. 8