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(54) **SILICONE BASED MEMBRANES FOR USE IN IMPLANTABLE GLUCOSE SENSORS**

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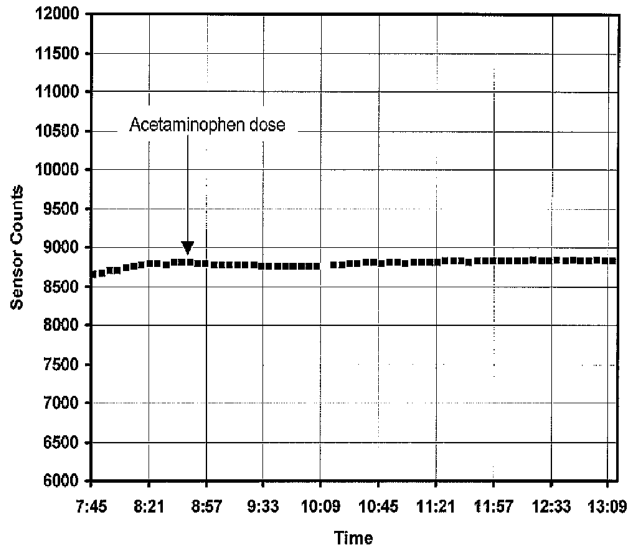
(57) **ABSTRACT**

Membrane systems incorporating silicone polymers are described for use in implantable analyte sensors. Some layers of the membrane system may comprise a blend of a silicone polymer with a hydrophilic polymer, for example, a triblock poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) polymer. Such polymeric blends provide for both high oxygen solubility and aqueous analyte solubility.

16 Claims, 8 Drawing Sheets



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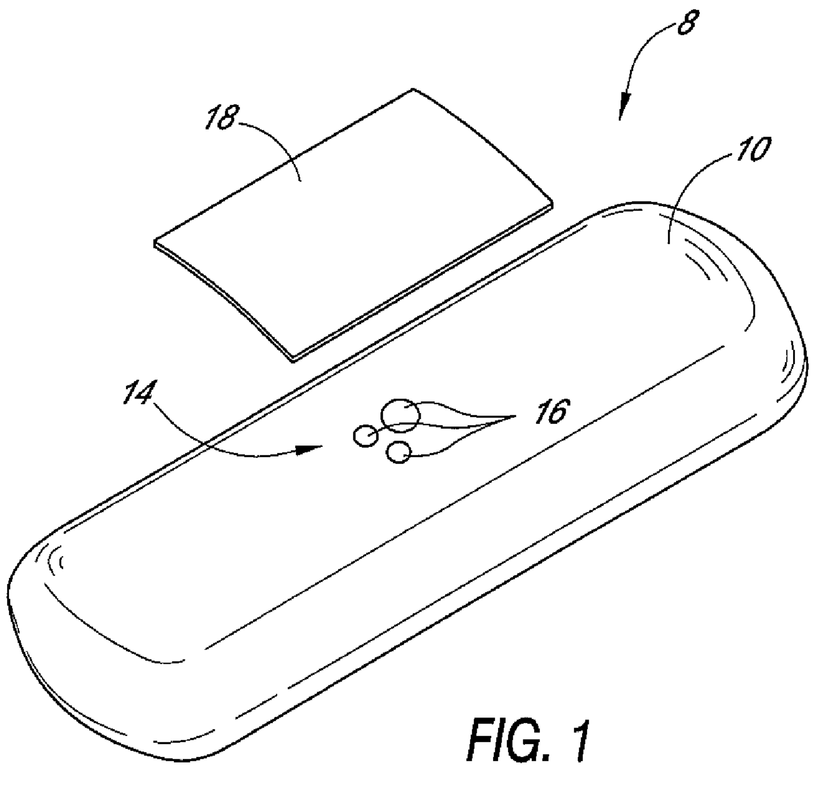
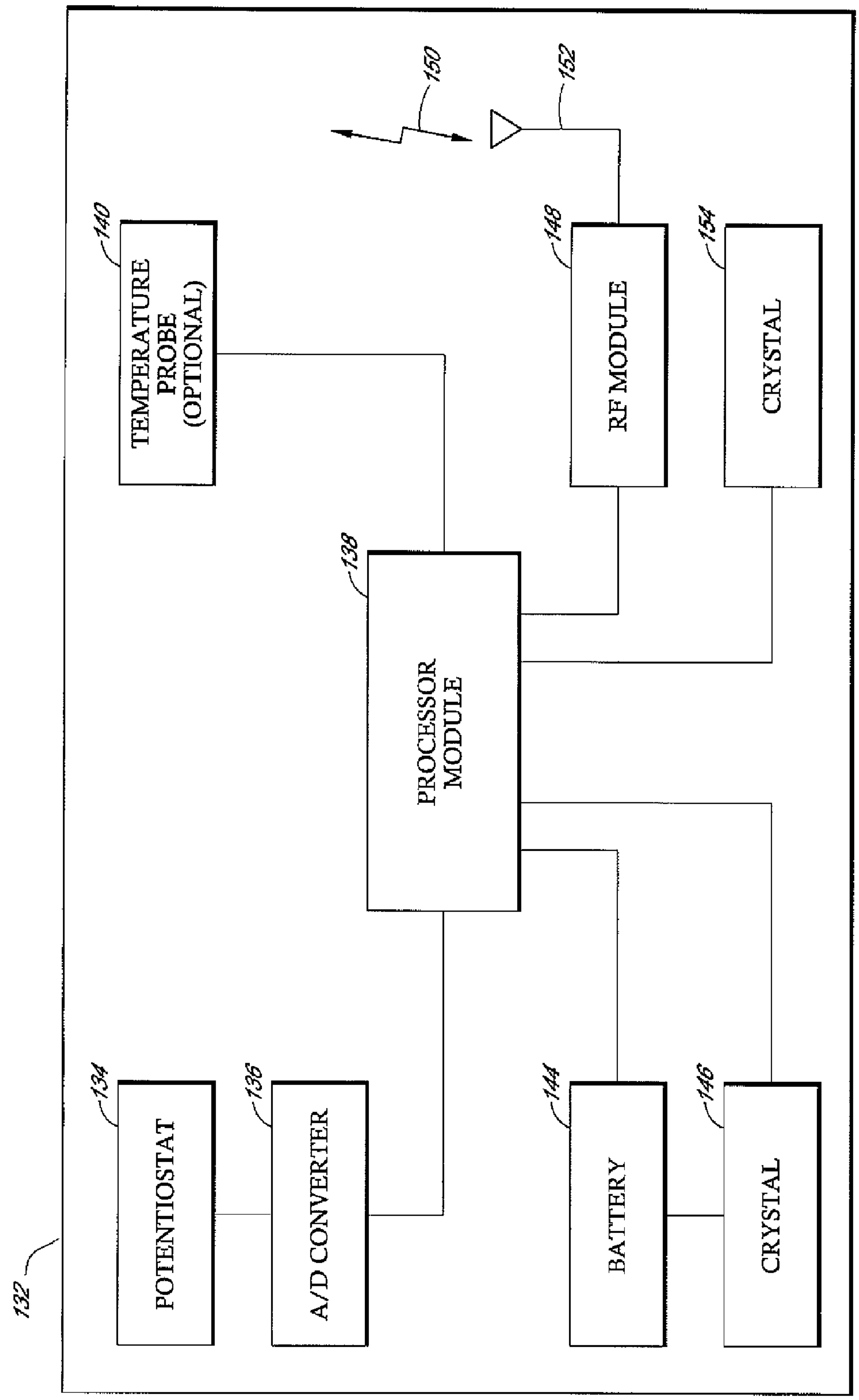


FIG. 1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152
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RF MODULE
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CRYSTAL
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A/D CONVERTER
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BATTERY
146
CRYSTAL
132

FIG. 2

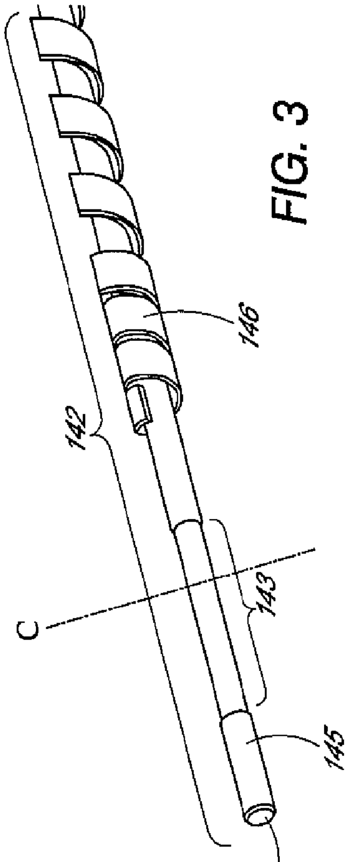


FIG. 3

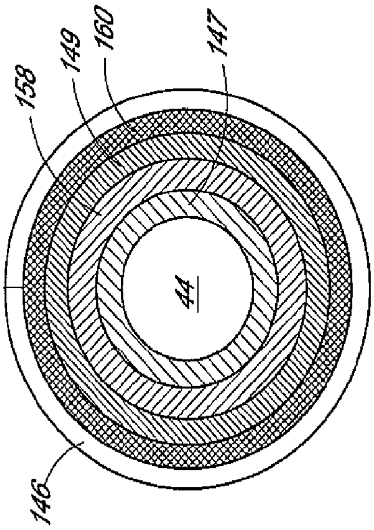


FIG. 5

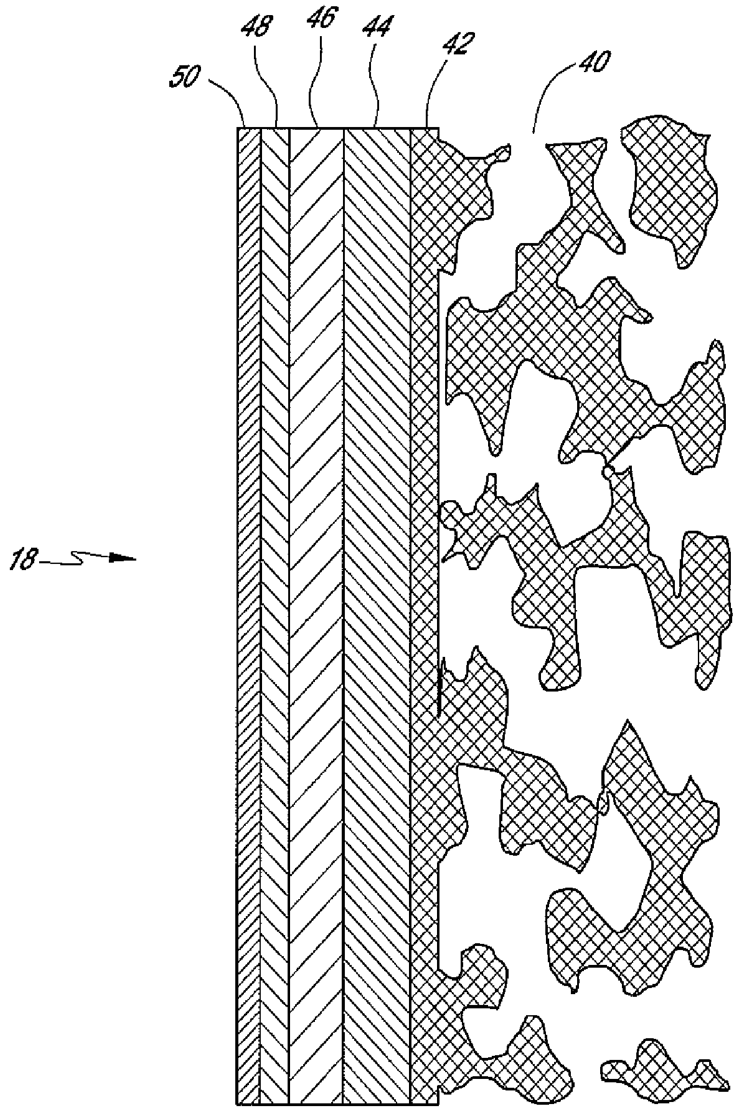


FIG. 4

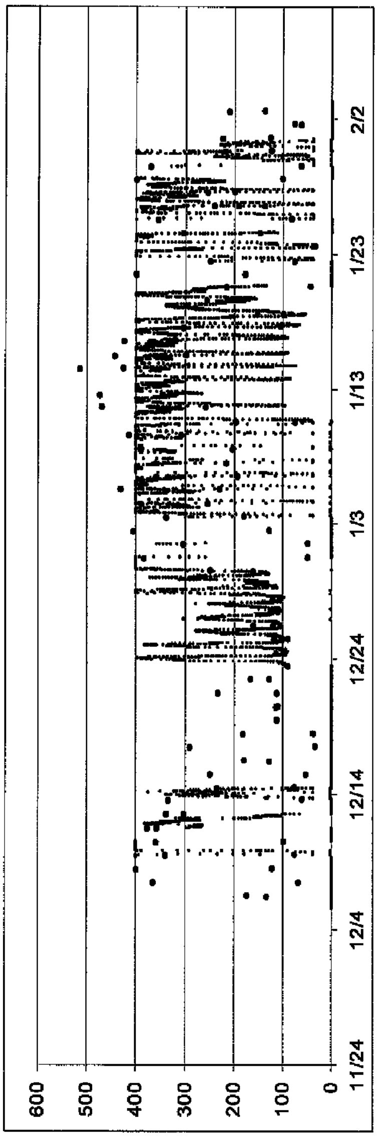


FIG. 6

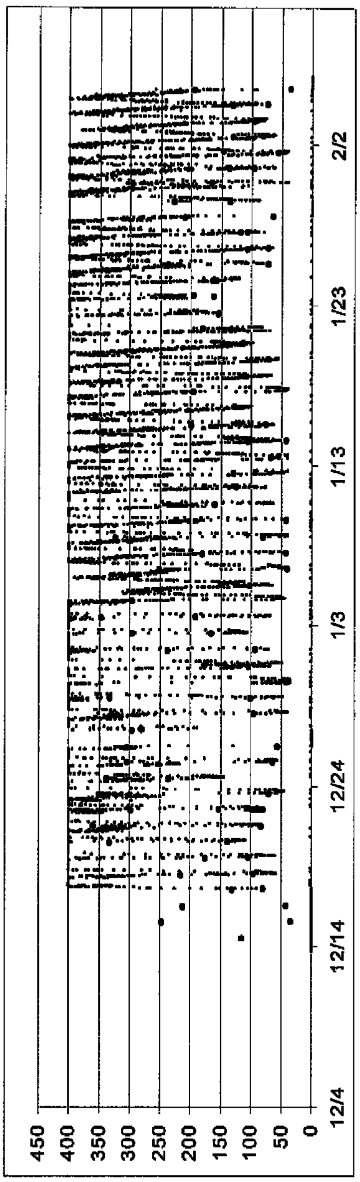
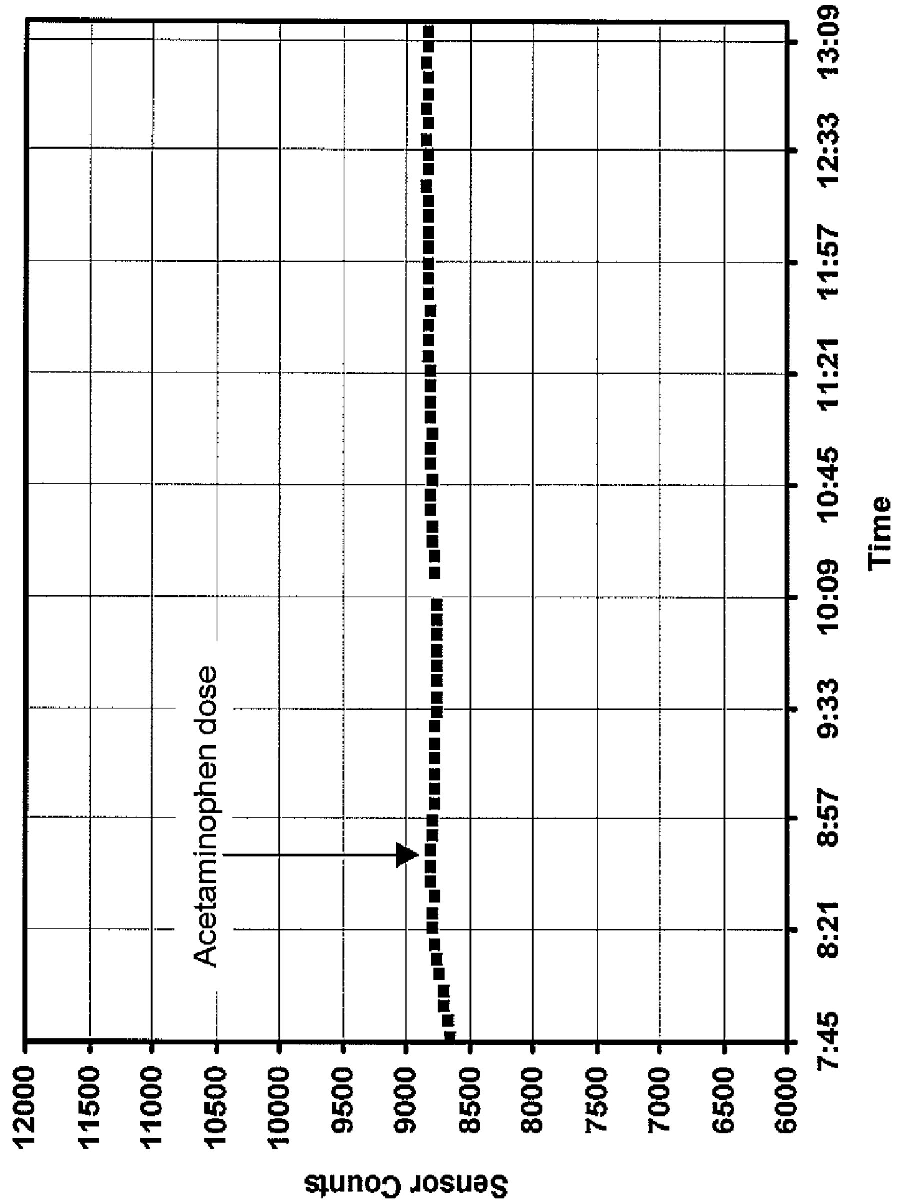


FIG. 7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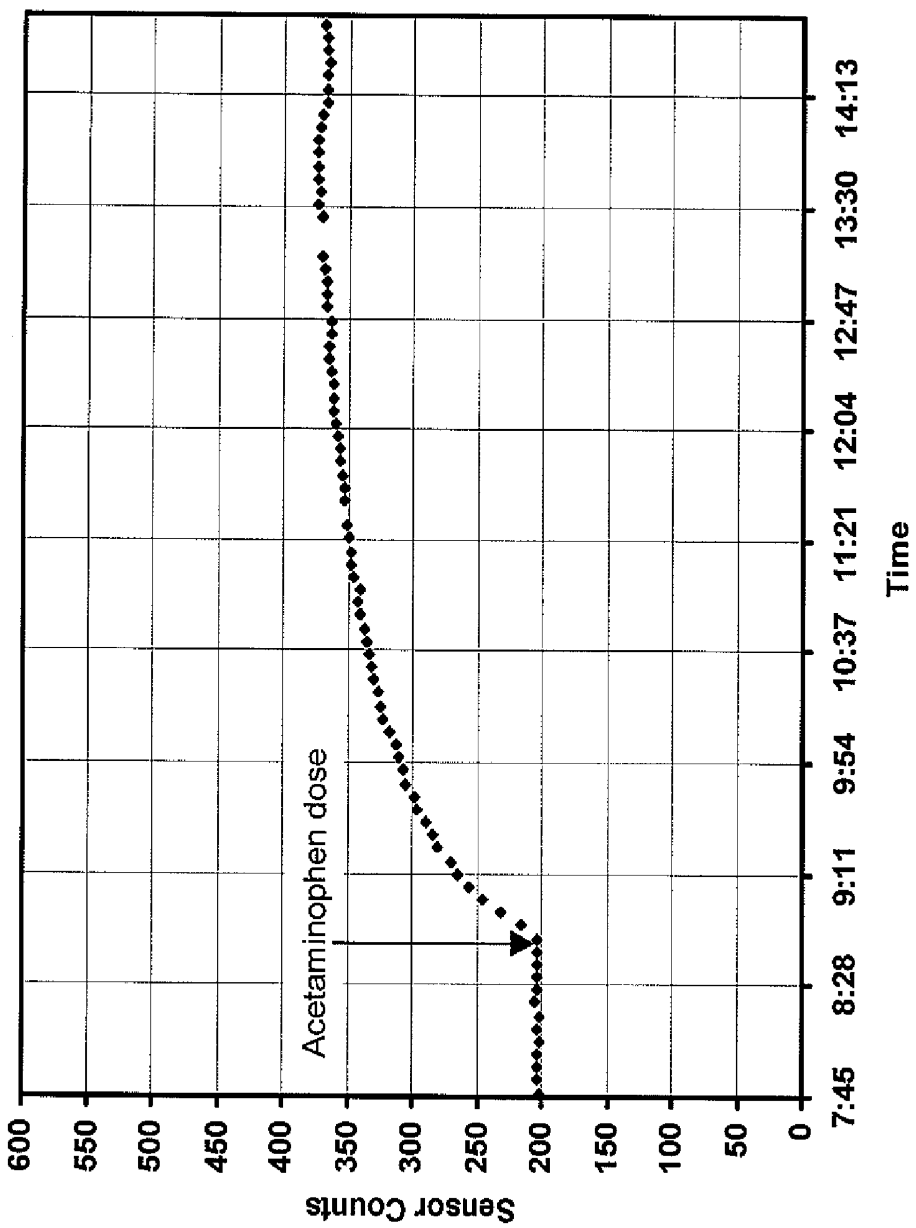
11500
11000
10500
10000
9500
9000
8500
8000
7500
7000
6500
6000
Time
7:45
8:21
8:57
9:33
10:09
10:45
11:21
11:57
12:33
13:09
Acetaminophen dose

FIG. 8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Time
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9:11
9:54
10:37
11:21
12:04
12:47
13:30
14:13
Acetaminophen dose

FIG. 9

SILICONE BASED MEMBRANES FOR USE IN IMPLANTABLE GLUCOSE SENSORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/511,982, filed Jul. 29, 2009, which is a divisional of U.S. application Ser. No. 11/404,417, filed Apr. 14, 2006, now U.S. Pat. No. 7,613,491, the disclosure of which is hereby incorporated by reference in its entirety and is made a portion of this application.

FIELD OF THE INVENTION

The invention relates to membranes for use in implantable analyte sensors (e.g., glucose sensors).

BACKGROUND OF THE INVENTION

Electrochemical sensors are useful in chemistry and medicine to determine the presence or concentration of a biological analyte. Such sensors are useful, for example, to monitor glucose in diabetic patients and lactate during critical care events.

Diabetes mellitus is a disorder in which the pancreas cannot create sufficient insulin (Type I or insulin dependent) and/or in which insulin is not effective (Type 2 or non-insulin dependent). In the diabetic state, the victim suffers from high blood sugar, which causes an array of physiological derangements (kidney failure, skin ulcers, or bleeding into the vitreous of the eye) associated with the deterioration of small blood vessels. A hypoglycemic reaction (low blood sugar) is induced by an inadvertent overdose of insulin, or after a normal dose of insulin or glucose-lowering agent accompanied by extraordinary exercise or insufficient food intake.

Conventionally, a diabetic person carries a self-monitoring blood glucose (SMBG) monitor, which typically utilizes uncomfortable finger pricking methods. Due to the lack of comfort and convenience, a diabetic normally only measures his or her glucose level two to four times per day. Unfortunately, these time intervals are spread so far apart that the diabetic likely finds out too late, sometimes incurring dangerous side effects, of a hyperglycemic or hypoglycemic condition. In fact, it is not only unlikely that a diabetic will take a timely SMBG value, but additionally the diabetic will not know if their blood glucose value is going up (higher) or down (lower) based on conventional methods.

Consequently, a variety of transdermal and implantable electrochemical sensors are being developed for continuously detecting and/or quantifying blood glucose values. Many implantable glucose sensors suffer from complications within the body and provide only short-term or less-than-accurate sensing of blood glucose. Similarly, transdermal sensors have problems in accurately sensing and reporting back glucose values continuously over extended periods of time. Some efforts have been made to obtain blood glucose data from implantable devices and retrospectively determine blood glucose trends for analysis; however these efforts do not aid the diabetic in determining real-time blood glucose information. Some efforts have also been made to obtain blood glucose data from transdermal devices for prospective data analysis, however similar problems have been observed.

SUMMARY OF THE INVENTION

One embodiment disclosed herein includes a membrane for use in an analyte sensor, the membrane including a sili-

cone elastomer and a poly(ethylene oxide) and poly(propylene oxide) co-polymer, wherein the membrane is adapted to permit diffusion of both the analyte and oxygen therethrough. In one embodiment, the silicone elastomer is a dimethyl- and methylhydrogen-siloxane copolymer. In one embodiment, the silicone elastomer comprises vinyl substituents. In one embodiment, the silicone elastomer is an elastomer produced by curing a MED-4840 mixture. In one embodiment, the copolymer comprises hydroxy substituents. In one embodiment, the co-polymer is a triblock poly(ethylene oxide)-poly (propylene oxide)-poly(ethylene oxide) polymer. In one embodiment, the co-polymer is a triblock poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide) polymer. In one embodiment, the co-polymer is a PLURONIC® polymer. In one embodiment, the co-polymer is PLURONIC® F-127. In one embodiment, the analyte is glucose. In one embodiment, at least a portion of the co-polymer is cross-linked. In one embodiment, from about 5% w/w to about 30% w/w of the membrane is the co-polymer.

Another embodiment disclosed herein includes an implantable analyte sensor having an enzyme layer comprising an enzyme for which the analyte is a substrate and a bioprotective layer positioned between the enzyme layer and tissue adjacent to the sensor when implanted, wherein the bioprotective layer comprises a silicone elastomer and a poly (ethylene oxide) and poly(propylene oxide) co-polymer. One embodiment further includes a diffusion resistance layer positioned between the enzyme layer and the bioprotective layer. In one embodiment, the diffusion resistance layer also comprises the silicone elastomer and the poly(ethylene oxide) and poly(propylene oxide) co-polymer. In one embodiment, the ratio of the silicone elastomer to the co-polymer is different in the diffusion resistance layer than in the bioprotective layer. One embodiment further includes a cell disruptive layer positioned between the bioprotective layer and tissue adjacent to the sensor when implanted. In one embodiment, the silicone elastomer is a dimethyl- and methylhydrogen-siloxane copolymer. In one embodiment, the silicone elastomer comprises vinyl substituents. In one embodiment, the silicone elastomer is an elastomer produced by curing a MED-4840 mixture. In one embodiment, the copolymer comprises hydroxy substituents. In one embodiment, the co-polymer is a triblock poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) polymer. In one embodiment, the co-polymer is a triblock poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide) polymer. In one embodiment, the co-polymer is a PLURONIC® polymer. In one embodiment, the co-polymer is PLURONIC® F-127. In one embodiment, the analyte is glucose. In one embodiment, at least a portion of the co-polymer is cross-linked. In one embodiment, from about 5% w/w to about 30% w/w of the bioprotective layer is the co-polymer. In one embodiment, the enzyme layer also comprises the silicone elastomer and the co-polymer. In one embodiment, the ratio of the silicone elastomer to the co-polymer is different in the enzyme layer than in the bioprotective layer. In one embodiment, the sensor is configured to be wholly implanted. In one embodiment, the sensor is configured to be transcutaneously implanted. In one embodiment, at least a portion of the bioprotective layer is porous and adjacent to tissue when implanted.

Another embodiment disclosed herein includes an implantable analyte sensor having an enzyme layer comprising an enzyme for which the analyte is a substrate and a diffusion resistance layer comprising a silicone elastomer and a poly(ethylene oxide) and poly(propylene oxide) co-polymer, wherein the diffusion resistance layer is positioned between the enzyme layer and tissue adjacent to the sensor when implanted. One embodiment further includes a bioprotective layer positioned between the diffusion resistance layer and tissue adjacent to the sensor when implanted. In one embodiment, the silicone elastomer is a dimethyl- and methylhydrogen-siloxane copolymer. In one embodiment, the silicone elastomer comprises vinyl substituents. In one embodiment, the silicone elastomer is an elastomer produced by curing a MED-4840 mixture. In one embodiment, the copolymer comprises hydroxy substituents. In one embodiment, the co-polymer is a PLURONIC® polymer. In one embodiment, the co-polymer is PLURONIC® F-127. In one embodiment, the analyte is glucose. In one embodiment, at least a portion of the co-polymer is cross-linked. In one embodiment, from about 5% w/w to about 30% w/w of the diffusion resistance layer is the co-polymer. In one embodiment, the ratio of the silicone elastomer to co-polymer varies within the diffusion resistance layer. In one embodiment, the sensor is configured to be wholly implanted. In one embodiment, the sensor is configured to be transcutaneously implanted.

Another embodiment disclosed herein includes an implantable analyte sensor having at least one polymer membrane, wherein every polymer membrane in the sensor comprises a silicone elastomer and a poly(ethylene oxide) and poly(propylene oxide) co-polymer. In one embodiment, the silicone elastomer is a dimethyl- and methylhydrogen-siloxane copolymer. In one embodiment, the silicone elastomer comprises vinyl substituents. In one embodiment, the silicone elastomer is an elastomer produced by curing a MED-4840 mixture. In one embodiment, the copolymer comprises hydroxy substituents. In one embodiment, the co-polymer is a PLURONIC® polymer. In one embodiment, the co-polymer is PLURONIC® F-127. In one embodiment, at least a portion of the co-polymer is cross-linked. In one embodiment, from about 5% w/w to about 30% w/w of each polymer membrane is the co-polymer. In one embodiment, the sensor comprises at least two polymer membranes having a ratio of the silicone elastomer to the co-polymer that is different. In one embodiment, the sensor is configured to be wholly implanted. In one embodiment, the sensor is configured to be transcutaneously implanted.

Another embodiment disclosed herein includes a method of manufacturing a membrane for use in an analyte sensor, the method including mixing a precursor of a silicone elastomer with a poly(ethylene oxide) and poly(propylene oxide) co-polymer and heating the mixture. In one embodiment, the ratio of co-polymer to silicone elastomer that is mixed is from about 1:20 w/w to about 1:4 w/w. One embodiment further includes mixing the co-polymer with a cross-linking agent. In one embodiment, the cross-linking agent is mixed with the co-polymer prior to mixing the co-polymer with the silicone elastomer precursor. In one embodiment, the cross-linking agent is selected from the group consisting of one or more of ethylene glycol diglycidyl ether and poly(ethylene glycol) diglycidyl ether. In one embodiment, the cross-linking agent comprises dicumyl peroxide. In one embodiment, the ratio of cross-linking agent to co-polymer is from about 10 cross-linking agent molecules per co-polymer molecule to about 30 cross-linking agent molecules per co-polymer molecule. In one embodiment, the amount of cross-linking agent added relative to the silicone elastomer and co-polymer is from about 0.5% to about 15% w/w. One embodiment further includes, after the mixing step but before the heating step, drawing the mixture into a thin film. One embodiment further includes, after the drawing step but before the heating step, placing a piece of porous silicon on the thin film.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an exploded perspective view of an implantable glucose sensor in one exemplary embodiment.

FIG. **2** is a block diagram that illustrates the sensor electronics in one embodiment; however a variety of sensor electronics configurations can be implemented with the preferred embodiments.

FIG. **3** is a perspective view of a transcutaneous wire analyte sensor system.

FIG. **4** is a schematic illustration of a membrane system of the device of FIG. **1**.

FIG. **5** is a cross-sectional view through the sensor of FIG. **3** on line C-C, showing an exposed electroactive surface of a working electrode surrounded by a membrane system.

FIG. **6** is a graph depicting glucose measurements from a sensor including a silicon/hydrophilic-hydrophobic polymer blend in a diffusion resistance layer implanted in a diabetic rat model.

FIG. **7** is a graph depicting glucose measurements from a sensor including a silicon/hydrophilic-hydrophobic polymer blend in a bioprotective layer implanted in a diabetic rat model.

FIG. **8** is a graph depicting a sensor signal from a sensor including a silicon/hydrophilic-hydrophobic polymer blend membrane exposed to acetaminophen.

FIG. **9** is a graph depicting a sensor signal from a sensor not including a silicon/hydrophilic-hydrophobic polymer blend membrane exposed to acetaminophen.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The following description and examples illustrate some exemplary embodiments of the disclosed invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a certain exemplary embodiment should not be deemed to limit the scope of the present invention.

Definitions

In order to facilitate an understanding of the preferred embodiments, a number of terms are defined below.

The term "analyte" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a substance or chemical constituent in a biological fluid (for example, blood, interstitial fluid, cerebral spinal fluid, lymph fluid or urine) that can be analyzed. Analytes can include naturally occurring substances, artificial substances, metabolites, and/or reaction products. In some embodiments, the analyte for measurement by the sensing regions, devices, and methods is glucose. However, other analytes are contemplated as well, including but not limited to acarboxyprothrombin; acylcarnitine; adenine phosphoribosyl transferase; adenosine deaminase; albumin; alpha-fetoprotein; amino acid profiles (arginine (Krebs cycle), histidine/urocanic acid, homocysteine, phenylalanine/tyrosine, tryptophan); andrenostenedione; antipyrine; arabinitol enantiomers; arginase; benzoylecgonine (cocaine); biotinidase; biopterin; c-reactive protein; carnitine; carnosinase; CD4; ceruloplasmin; chenodeoxycholic acid; chloroquine; cholesterol; cholinesterase; conjugated 1-β hydroxycholic acid; cortisol; creatine kinase; creatine kinase MM isoenzyme; cyclosporin A; d-penicillamine; de-ethylchloroquine; dehydroepiandrosterone sulfate; DNA (acetylator polymorphism, alcohol dehydrogenase, alpha 1-antitrypsin, cystic fibrosis, Duchenne/Becker muscular dystrophy, glucose-6-phosphate dehydrogenase, hemoglobin A, hemoglobin S, hemoglobin C, hemoglobin D, hemoglobin E, hemoglobin F, D-Punjab, beta-thalassemia, hepatitis B virus, HCMV, HIV-1, HTLV-1, Leber hereditary optic neuropathy, MCAD, RNA, PKU, Plasmodium vivax, sexual differentiation, 21-deoxycortisol); desbutylhalofantrine; dihydropteridine reductase; diptheria/tetanus antitoxin; erythrocyte arginase; erythrocyte protoporphyrin; esterase D; fatty acids/acylglycines; free β-human chorionic gonadotropin; free erythrocyte porphyrin; free thyroxine (FT4); free tri-iodothyronine (FT3); fumarylacetoacetase; galactose/gal-1-phosphate; galactose-1-phosphate uridyltransferase; gentamicin; glucose-6-phosphate dehydrogenase; glutathione; glutathione perioxidase; glycocholic acid; glycosylated hemoglobin; halofantrine; hemoglobin variants; hexosaminidase A; human erythrocyte carbonic anhydrase I; 17-alpha-hydroxyprogesterone; hypoxanthine phosphoribosyl transferase; immunoreactive trypsin; lactate; lead; lipoproteins ((a), B/A-1, β); lysozyme; mefloquine; netilmicin; phenobarbitone; phenytoin; phytanic/pristanic acid; progesterone; prolactin; prolidase; purine nucleoside phosphorylase; quinine; reverse tri-iodothyronine (rT3); selenium; serum pancreatic lipase; sissomicin; somatomedin C; specific antibodies (adenovirus, anti-nuclear antibody, anti-zeta antibody, arbovirus, Aujeszky's disease virus, dengue virus, *Dracunculus medinensis, Echinococcus granulosus, Entamoeba histolytica, enterovirus, Giardia duodenalisa, Helicobacter pylori*, hepatitis B virus, herpes virus, HIV-1, IgE (atopic disease), influenza virus, *Leishmania donovani, leptospira*, measles/mumps/rubella, *Mycobacterium leprae, Mycoplasma pneumoniae, Myoglobin, Onchocerca volvulus*, parainfluenza virus, *Plasmodium falciparum, poliovirus, Pseudomonas aeruginosa*, respiratory syncytial virus, *rickettsia* (scrub typhus), *Schistosoma mansoni, Toxoplasma gondii, Trepenoma pallidium, Trypanosoma cruzi/rangeli*, vesicular stomatis virus, *Wuchereria bancrofti*, yellow fever virus); specific antigens (hepatitis B virus, HIV-1); succinylacetone; sulfadoxine; theophylline; thyrotropin (TSH); thyroxine (T4); thyroxine-binding globulin; trace elements; transferrin; UDP-galactose-4-epimerase; urea; uroporphyrinogen I synthase; vitamin A; white blood cells; and zinc protoporphyrin. Salts, sugar, protein, fat, vitamins, and hormones naturally occurring in blood or interstitial fluids can also constitute analytes in certain embodiments. The analyte can be naturally present in the biological fluid or endogenous, for example, a metabolic product, a hormone, an antigen, an antibody, and the like. Alternatively, the analyte can be introduced into the body or exogenous, for example, a contrast agent for imaging, a radioisotope, a chemical agent, a fluorocarbon-based synthetic blood, or a drug or pharmaceutical composition, including but not limited to insulin; ethanol; cannabis (marijuana, tetrahydrocannabinol, hashish); inhalants (nitrous oxide, amyl nitrite, butyl nitrite, chlorohydrocarbons, hydrocarbons); cocaine (crack cocaine); stimulants (amphetamines, methamphetamines, Ritalin, Cylert, Preludin, Didrex, PreState, Voranil, Sandrex, Plegine); depressants (barbituates, methaqualone, tranquilizers such as Valium, Librium, Miltown, Serax, Equanil, Tranxene); hallucinogens (phencyclidine, lysergic acid, mescaline, peyote, psilocybin); narcotics (heroin, codeine, morphine, opium, meperidine, Percocet, Percodan, Tussionex, Fentanyl, Darvon, Talwin, Lomotil); designer drugs (analogs of fentanyl, meperidine, amphetamines, methamphetamines, and phencyclidine, for example, Ecstasy); anabolic steroids; and nicotine. The metabolic products of drugs and pharmaceutical compositions are also contemplated analytes. Analytes such as neurochemicals and other chemicals generated within the body can also be analyzed, such as, for example, ascorbic acid, uric acid, dopamine, noradrenaline, 3-methoxytyramine (3MT), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5HT), and 5-hydroxyindoleacetic acid (FHIAA).

The terms "operable connection," "operably connected," and "operably linked" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and refer without limitation to one or more components linked to another component(s) in a manner that allows transmission of signals between the components. For example, one or more electrodes can be used to detect the amount of analyte in a sample and convert that information into a signal; the signal can then be transmitted to a circuit. In this case, the electrode is "operably linked" to the electronic circuitry.

The term "host" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to animals and plants, for example humans.

The terms "electrochemically reactive surface" and "electroactive surface" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and refer without limitation to the surface of an electrode where an electrochemical reaction takes place. As one example, a working electrode measures hydrogen peroxide produced by the enzyme catalyzed reaction of the analyte being detected reacts creating an electric current (for example, detection of glucose analyte utilizing glucose oxidase produces H_2O_2 as a by product, H_2O_2 reacts with the surface of the working electrode producing two protons ($2H^+$), two electrons ($2e^-$) and one molecule of oxygen (O_2) which produces the electronic current being detected). In the case of the counter electrode, a reducible species, for example, O_2 is reduced at the electrode surface in order to balance the current being generated by the working electrode.

The term "sensing region" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to the region of a monitoring device responsible for the detection of a particular analyte. The sensing region generally comprises a non-conductive body, a working electrode, a reference electrode, and/or a counter electrode (optional) passing through and secured within the body forming electrochemically reactive surfaces on the body, an electronic connective means at another location on the body, and a multi-domain membrane affixed to the body and covering the electrochemically reactive surface.

The terms "raw data stream" and "data stream" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and refer without limitation to an analog or digital signal directly related to the measured glucose concentration from the glucose sensor. In one example, the raw data stream is digital data in "counts" converted by an A/D converter from an analog signal (for example, voltage or amps) representative of a glucose concentration. The terms broadly encompass a plurality of time spaced data points from a substantially continuous glucose sensor, which comprises individual measurements taken at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes or longer.

The term "counts" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a unit of measurement of a digital signal. In one example, a raw data stream measured in counts is directly related to a voltage (for example, converted by an A/D converter), which is directly related to current from the working electrode. In another example, counter electrode voltage measured in counts is directly related to a voltage.

The term "electrical potential" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to the electrical potential difference between two points in a circuit which is the cause of the flow of a current.

The term "ischemia" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to local and temporary deficiency of blood supply due to obstruction of circulation to a part (for example, sensor). Ischemia can be caused by mechanical obstruction (for example, arterial narrowing or disruption) of the blood supply, for example.

The term "system noise" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to unwanted electronic or diffusion-related noise which can include Gaussian, motion-related, flicker, kinetic, or other white noise, for example.

The terms "signal artifacts" and "transient non-glucose related signal artifacts," as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and refer without limitation to signal noise that is caused by substantially non-glucose reaction rate-limiting phenomena, such as ischemia, pH changes, temperature changes, pressure, and stress, for example. Signal artifacts, as described herein, are typically transient and are characterized by higher amplitude than system noise.

The terms "low noise" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to noise that substantially decreases signal amplitude.

The terms "high noise" and "high spikes" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and refer without limitation to noise that substantially increases signal amplitude.

The term "silicone composition" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a composition of matter that comprises polymers having at least silicon and oxygen atoms in the backbone.

The phrase "distal to" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to the spatial relationship between various elements in comparison to a particular point of reference. For example, some embodiments of a device include a membrane system having a cell disruptive domain and a cell impermeable domain. If the sensor is deemed to be the point of reference and the cell disruptive domain is positioned farther from the sensor, then that domain is distal to the sensor.

The phrase "proximal to" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to the spatial relationship between various elements in comparison to a particular point of reference. For example, some embodiments of a device include a membrane system having a cell disruptive domain and a cell impermeable domain. If the sensor is deemed to be the point of reference and the cell impermeable domain is positioned nearer to the sensor, then that domain is proximal to the sensor.

The terms "interferants" and "interfering species" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and refer without limitation to effects and/or species that interfere with the measurement of an analyte of interest in a sensor to produce a signal that does not accurately represent the analyte measurement. In an exemplary electrochemical sensor, interfering species can include compounds with an oxidation potential that overlaps with that of the analyte to be measured.

As employed herein, the following abbreviations apply: Eq and Eqs (equivalents); mEq (milliequivalents); M (molar); mM (millimolar) μM (micromolar); N (Normal); mol (moles); mmol (millimoles); μmol (micromoles); nmol (nanomoles); g (grams); mg (milligrams); μg (micrograms); Kg (kilograms); L (liters); mL (milliliters); dL (deciliters); μL (microliters); cm (centimeters); mm (millimeters); μm (micrometers); nm (nanometers); h and hr (hours); min. (minutes); s and sec. (seconds); ° C. (degrees Centigrade).

Overview

Membrane systems of the preferred embodiments are suitable for use with implantable devices in contact with a biological fluid. For example, the membrane systems can be utilized with implantable devices such as devices for monitoring and determining analyte levels in a biological fluid, for example, glucose levels for individuals having diabetes. In some embodiments, the analyte-measuring device is a continuous device. Alternatively, the device can analyze a plurality of intermittent biological samples. The analyte-measuring device can use any method of analyte-measurement, including enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, radiometric, or the like.

Although some of the description that follows is directed at glucose-measuring devices, including the described membrane systems and methods for their use, these membrane systems are not limited to use in devices that measure or monitor glucose. These membrane systems are suitable for use in a variety of devices, including, for example, those that detect and quantify other analytes present in biological fluids (including, but not limited to, cholesterol, amino acids, alcohol, galactose, and lactate), cell transplantation devices (see, for example, U.S. Pat. Nos. 6,015,572, 5,964,745, and 6,083,523), drug delivery devices (see, for example, U.S. Pat. Nos. 5,458,631, 5,820,589, and 5,972,369), and the like. Preferably, implantable devices that include the membrane systems of the preferred embodiments are implanted in soft tissue, for example, abdominal, subcutaneous, and peritoneal tissues, the brain, the intramedullary space, and other suitable organs or body tissues.

In addition to the glucose-measuring device described below, the membrane systems of the preferred embodiments can be employed with a variety of known glucose measuring-devices. In some embodiments, the electrode system can be used with any of a variety of known in vivo analyte sensors or monitors, such as U.S. Pat. No. 6,001,067 to Shults et al.; U.S. Pat. No. 6,702,857 to Brauker et al.; U.S. Pat. No. 6,212,416 to Ward et al.; U.S. Pat. No. 6,119,028 to Schulman et al.; U.S. Pat. No. 6,400,974 to Lesho; U.S. Pat. No. 6,595,919 to Berner et al.; U.S. Pat. No. 6,141,573 to Kurnik et al.; U.S. Pat. No. 6,122,536 to Sun et al.; European Patent Application EP 1153571 to Varall et al.; U.S. Pat. No. 6,512,939 to Colvin et al.; U.S. Pat. No. 5,605,152 to Slate et al.; U.S. Pat. No. 4,431,004 to Bessman et al.; U.S. Pat. No. 4,703,756 to Gough et al.; U.S. Pat. No. 6,514,718 to Heller et al.; U.S. patent to U.S. Pat. No. 5,985,129 to Gough et al.; WO Patent Application Publication No. 04/021877 to Caduff; U.S. Pat. No. 5,494,562 to Maley et al.; U.S. Pat. No. 6,120,676 to Heller et al.; and U.S. Pat. No. 6,542,765 to Guy et al., each of which are incorporated in there entirety herein by reference. In general, it is understood that the disclosed embodiments are applicable to a variety of continuous glucose measuring device configurations.

FIG. **1** is an exploded perspective view of one exemplary embodiment comprising an implantable glucose sensor **10** that utilizes amperometric electrochemical sensor technology to measure glucose. In this exemplary embodiment, a body **12** with a sensing region **14** includes an electrode system **16** and sensor electronics, which are described in more detail with reference to FIG. **2**.

In this embodiment, the electrode system **16** is operably connected to the sensor electronics (FIG. **2**) and includes electroactive surfaces, which are covered by a membrane system **18**. The membrane system **18** is disposed over the electroactive surfaces of the electrode system **16** and provides one or more of the following functions: 1) supporting tissue ingrowth (cell disruptive domain); 2) protection of the exposed electrode surface from the biological environment (cell impermeable domain); 3) diffusion resistance (limitation) of the analyte (resistance domain); 4) a catalyst for enabling an enzymatic reaction (enzyme domain); 5) limitation or blocking of interfering species (interference domain); and/or 6) hydrophilicity at the electrochemically reactive surfaces of the sensor interface (electrolyte domain), for example, as described in co-pending U.S. patent application Ser. No. 10/838,912, filed May 3, 2004, published in Publication No. 20050245799, and entitled "IMPLANTABLE ANALYTE SENSOR," the contents of which are hereby incorporated herein by reference in their entirety. The membrane system can be attached to the sensor body **12** by mechanical or chemical methods, for example, such as is described in the co-pending application Ser. No. 10/838,912 mentioned above.

The membrane system **18** of the preferred embodiments, which are described in more detail below with reference to FIGS. **5** and **6**, is formed at least partially from silicone materials. While not being bound by any particular theory, it is believed that silicone materials provide enhanced bio-stability when compared to other polymeric materials such as polyurethane. In addition, when a porous silicone cell disruptive layer (described in detail below) is used, silicone included in any underlying layer can promote bonding of the layer to the porous silicone cell disruptive layer. Finally, silicone has high oxygen permeability, thus promoting oxygen transport to the enzyme layer (described in detail below).

In some embodiments, the electrode system **16**, which is located on or within the sensing region **14**, is comprised of at least a working and a reference electrode with an insulating material disposed therebetween. In some alternative embodiments, additional electrodes can be included within the electrode system, for example, a three-electrode system (working, reference, and counter electrodes) and/or including an additional working electrode (which can be used to generate oxygen, measure an additional analyte, or can be configured as a baseline subtracting electrode, for example).

In the exemplary embodiment of FIG. **1**, the electrode system includes three electrodes (working, counter, and reference electrodes), wherein the counter electrode is provided to balance the current generated by the species being measured at the working electrode. In the case of a glucose oxidase based glucose sensor, the species being measured at the working electrode is H_2O_2. Glucose oxidase, GOX, catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate according to the following reaction:

$$\text{GOX+Glucose+}O_2 \rightarrow \text{Gluconate+}H_2O_2\text{+reduced GOX}$$

The change in H_2O_2 can be monitored to determine glucose concentration because for each glucose molecule metabolized, there is a proportional change in the product H_2O_2. Oxidation of H_2O_2 by the working electrode is balanced by reduction of ambient oxygen, enzyme generated H_2O_2, or other reducible species at the counter electrode. The H_2O_2 produced from the glucose oxidase reaction further reacts at the surface of working electrode and produces two protons (2H+), two electrons (2e−), and one oxygen molecule (O_2). In such embodiments, because the counter electrode utilizes oxygen as an electron acceptor, the most likely reducible species for this system are oxygen or enzyme generated peroxide. There are two main pathways by which oxygen can be consumed at the counter electrode. These pathways include a four-electron pathway to produce hydroxide and a two-electron pathway to produce hydrogen peroxide. In addition to the counter electrode, oxygen is further consumed by the reduced glucose oxidase within the enzyme domain. Therefore, due to the oxygen consumption by both the enzyme and the counter electrode, there is a net consumption of oxygen within the electrode system. Theoretically, in the domain of the working electrode there is significantly less net loss of oxygen than in the region of the counter electrode. In addition, there is a close correlation between the ability of the counter electrode to maintain current balance and sensor function.

In general, in electrochemical sensors wherein an enzymatic reaction depends on oxygen as a co-reactant, depressed function or inaccuracy can be experienced in low oxygen environments, for example in vivo. Subcutaneously implanted devices are especially susceptible to transient ischemia that can compromise device function; for example, because of the enzymatic reaction required for an implantable amperometric glucose sensor, oxygen must be in excess over glucose in order for the sensor to effectively function as a glucose sensor. If glucose becomes in excess, the sensor turns into an oxygen sensitive device. In vivo, glucose concentration can vary from about one hundred times or more that of the oxygen concentration. Consequently, oxygen becomes a limiting reactant in the electrochemical reaction and when insufficient oxygen is provided to the sensor, the sensor is unable to accurately measure glucose concentration. Those skilled in the art interpret oxygen limitations resulting in depressed function or inaccuracy as a problem of availability of oxygen to the enzyme and/or counter electrode. Oxygen limitations can also be seen during periods of transient ischemia that occur, for example, under certain postures or when the region around the implanted sensor is compressed so that blood is forced out of the capillaries. Such ischemic periods observed in implanted sensors can last for many minutes or even an hour or longer.

FIG. **2** is a block diagram that illustrates the sensor electronics in one embodiment. In this embodiment, a potentiostat **134** is shown, which is operably connected to an electrode system (such as described above) and provides a voltage to the electrodes, which biases the sensor to enable measurement of an current signal indicative of the analyte concentration in the host (also referred to as the analog portion). In some embodiments, the potentiostat includes a resistor (not shown) that translates the current into voltage. In some alternative embodiments, a current to frequency converter is provided that is configured to continuously integrate the measured current, for example, using a charge counting device.

An A/D converter **136** digitizes the analog signal into a digital signal, also referred to as "counts" for processing. Accordingly, the resulting raw data stream in counts, also referred to as raw sensor data, is directly related to the current measured by the potentiostat **134**.

A processor module **138** includes the central control unit that controls the processing of the sensor electronics **132**. In some embodiments, the processor module includes a microprocessor, however a computer system other than a microprocessor can be used to process data as described herein, for example an ASIC can be used for some or all of the sensor's central processing. The processor typically provides semi-permanent storage of data, for example, storing data such as sensor identifier (ID) and programming to process data streams (for example, programming for data smoothing and/or replacement of signal artifacts such as is described in U.S. Publication No. US-2005-0043598-A1). The processor additionally can be used for the system's cache memory, for example for temporarily storing recent sensor data. In some embodiments, the processor module comprises memory storage components such as ROM, RAM, dynamic-RAM, static-RAM, non-static RAM, EEPROM, rewritable ROMs, flash memory, or the like.

In some embodiments, the processor module comprises a digital filter, for example, an infinite impulse response (IIR) or finite impulse response (FIR) filter, configured to smooth the raw data stream from the A/D converter. Generally, digital filters are programmed to filter data sampled at a predetermined time interval (also referred to as a sample rate). In some embodiments, wherein the potentiostat is configured to measure the analyte at discrete time intervals, these time intervals determine the sample rate of the digital filter. In some alternative embodiments, wherein the potentiostat is configured to continuously measure the analyte, for example, using a current-to-frequency converter as described above, the processor module can be programmed to request a digital value from the A/D converter at a predetermined time interval, also referred to as the acquisition time. In these alternative embodiments, the values obtained by the processor are advantageously averaged over the acquisition time due the continuity of the current measurement. Accordingly, the acquisition time determines the sample rate of the digital filter. In preferred embodiments, the processor module is configured with a programmable acquisition time, namely, the predetermined time interval for requesting the digital value from the A/D converter is programmable by a user within the digital circuitry of the processor module. An acquisition time of from about 2 seconds to about 512 seconds is preferred; however any acquisition time can be programmed into the processor module. A programmable acquisition time is advantageous in optimizing noise filtration, time lag, and processing/battery power.

Preferably, the processor module is configured to build the data packet for transmission to an outside source, for example, an RF transmission to a receiver as described in more detail below. Generally, the data packet comprises a plurality of bits that can include a preamble, a unique identifier identifying the electronics unit, the receiver, or both, (e.g., sensor ID code), data (e.g., raw data, filtered data, and/or an integrated value) and/or error detection or correction. Preferably, the data (transmission) packet has a length of from about 8 bits to about 128 bits, preferably about 48 bits; however, larger or smaller packets can be desirable in certain embodiments. The processor module can be configured to transmit any combination of raw and/or filtered data. In one exemplary embodiment, the transmission packet contains a fixed preamble, a unique ID of the electronics unit, a single five-minute average (e.g., integrated) sensor data value, and a cyclic redundancy code (CRC).

In some embodiments, the processor module further comprises a transmitter portion that determines the transmission interval of the sensor data to a receiver, or the like. In some embodiments, the transmitter portion, which determines the interval of transmission, is configured to be programmable. In one such embodiment, a coefficient can be chosen (e.g., a number of from about 1 to about 100, or more), wherein the coefficient is multiplied by the acquisition time (or sampling rate), such as described above, to define the transmission interval of the data packet. Thus, in some embodiments, the transmission interval is programmable from about 2 seconds to about 850 minutes, more preferably from about 30 second to about 5 minutes; however, any transmission interval can be programmable or programmed into the processor module. However, a variety of alternative systems and methods for providing a programmable transmission interval can also be employed. By providing a programmable transmission interval, data transmission can be customized to meet a variety of design criteria (e.g., reduced battery consumption, timeliness of reporting sensor values, etc.)

Conventional glucose sensors measure current in the nanoAmp range. In some embodiments, the preferred embodiments are configured to measure the current flow in the picoAmp range, and in some embodiments, femtoAmps. Namely, for every unit (mg/dL) of glucose measured, at least one picoAmp of current is measured. Preferably, the analog portion of the A/D converter **136** is configured to continuously measure the current flowing at the working electrode and to convert the current measurement to digital values representative of the current. In one embodiment, the current flow is measured by a charge counting device (e.g., a capacitor). Preferably, a charge counting device provides a value (e.g., digital value) representative of the current flow integrated over time (e.g., integrated value). In some embodiments, the value is integrated over a few seconds, a few minutes, or longer. In one exemplary embodiment, the value is integrated over 5 minutes; however, other integration periods can be chosen. Thus, a signal is provided, whereby a high sensitivity maximizes the signal received by a minimal amount of measured hydrogen peroxide (e.g., minimal glucose requirements without sacrificing accuracy even in low glucose ranges), reducing the sensitivity to oxygen limitations in vivo (e.g., in oxygen-dependent glucose sensors).

In some embodiments, the electronics unit is programmed with a specific ID, which is programmed (automatically or by the user) into a receiver to establish a secure wireless communication link between the electronics unit and the receiver. Preferably, the transmission packet is Manchester encoded; however, a variety of known encoding techniques can also be employed.

A battery **154** is operably connected to the sensor electronics **132** and provides the power for the sensor. In one embodiment, the battery is a lithium manganese dioxide battery; however, any appropriately sized and powered battery can be used (for example, AAA, nickel-cadmium, zinc-carbon, alkaline, lithium, nickel-metal hydride, lithium-ion, zinc-air, zinc-mercury oxide, silver-zinc, and/or hermetically-sealed). In some embodiments, the battery is rechargeable, and/or a plurality of batteries can be used to power the system. The sensor can be transcutaneously powered via an inductive coupling, for example. In some embodiments, a quartz crystal **96** is operably connected to the processor **138** and maintains system time for the computer system as a whole, for example for the programmable acquisition time within the processor module.

Optional temperature probe **140** is shown, wherein the temperature probe is located on the electronics assembly or the glucose sensor itself. The temperature probe can be used to measure ambient temperature in the vicinity of the glucose sensor. This temperature measurement can be used to add temperature compensation to the calculated glucose value.

An RF module **158** is operably connected to the processor **138** and transmits the sensor data from the sensor to a receiver within a wireless transmission **160** via antenna **152**. In some embodiments, a second quartz crystal **154** provides the time base for the RF carrier frequency used for data transmissions from the RF transceiver. In some alternative embodiments, however, other mechanisms, such as optical, infrared radiation (IR), ultrasonic, or the like, can be used to transmit and/or receive data.

In the RF telemetry module of the preferred embodiments, the hardware and software are designed for low power requirements to increase the longevity of the device (for example, to enable a life of from about 3 to about 24 months, or more) with maximum RF transmittance from the in vivo environment to the ex vivo environment for wholly implantable sensors (for example, a distance of from about one to ten meters or more). Preferably, a high frequency carrier signal of from about 402 MHz to about 433 MHz is employed in order to maintain lower power requirements. In some embodiments, the RF module employs a one-way RF communication link to provide a simplified ultra low power data transmission and receiving scheme. The RF transmission can be OOK or FSK modulated, preferably with a radiated transmission power (EIRP) fixed at a single power level of typically less than about 100 microwatts, preferably less than about 75 microwatts, more preferably less than about 50 microwatts, and most preferably less than about 25 microwatts.

Additionally, in wholly implantable devices, the carrier frequency may be adapted for physiological attenuation levels, which is accomplished by tuning the RF module in a simulated in vivo environment to ensure RF functionality after implantation; accordingly, the preferred glucose sensor can sustain sensor function for 3 months, 6 months, 12 months, or 24 months or more.

The above description of sensor electronics associated with the electronics unit is applicable to a variety of continuous analyte sensors, such as non-invasive, minimally invasive, and/or invasive (e.g., transcutaneous and wholly implantable) sensors. For example, the sensor electronics and data processing as well as the receiver electronics and data processing described below can be incorporated into the wholly implantable glucose sensor disclosed in U.S. Publication No. US-2005-0245799-A1 and U.S. patent application Ser. No. 10/885,476 filed Jul. 6, 2004 and entitled, "SYSTEMS AND METHODS FOR MANUFACTURE OF AN ANALYTE-MEASURING DEVICE INCLUDING A MEMBRANE SYSTEM."

In one alternative embodiment, rather than the sensor being wholly implanted, a transcutaneous wire sensor is utilized. For example, one such suitable wire sensor **142** is depicted in FIG. **3**. This sensor comprises a platinum wire working electrode **144** with insulating coating **145** (e.g., parylene). A silver or silver/silver chloride reference electrode wire **146** is helically wound around the insulating coating **145**. A portion of the insulating coating **145** is removed to create an exposed electroactive window **143** around which a membrane as described herein can be disposed. Further details regarding such wire sensors may be found in U.S. application Ser. No. 11/157,746, filed Jun. 21, 2005 and entitled "TRANSCUTANEOUS ANALYTE SENSOR," which is incorporated herein by reference in its entirety.

Membrane Systems of the Preferred Embodiments

As described below with reference to FIG. **4**, the membrane system **18** can include two or more layers that cover an implantable device, for example, an implantable glucose sensor. Similarly, as described below with reference to FIG. **5**, two or more layers of the membrane system may be disposed on a transcutaneous wire sensor. In the example of an implantable enzyme-based electrochemical glucose sensor, the membrane prevents direct contact of the biological fluid sample with the electrodes, while controlling the permeability of selected substances (for example, oxygen and glucose) present in the biological fluid through the membrane for reaction in an enzyme rich domain with subsequent electrochemical reaction of formed products at the electrodes.

The membrane systems of preferred embodiments are constructed of one or more membrane layers. Each distinct layer can comprise the same or different materials. Furthermore, each layer can be homogenous or alternatively may comprise different domains or gradients where the composition varies.

FIG. **4** is an illustration of a membrane system in one preferred embodiment. The membrane system **18** can be used with a glucose sensor such, as is described above with reference to FIG. **1**. In this embodiment, the membrane system **18** includes a cell disruptive layer **40** most distal of all domains from the electrochemically reactive surfaces, a bioprotective layer **42** less distal from the electrochemically reactive surfaces than the cell disruptive layer, a diffusion resistance layer **44** less distal from the electrochemically reactive surfaces than the bioprotective layer, an enzyme layer **46** less distal from the electrochemically reactive surfaces than the diffusion resistance layer, an interference layer **48** less distal from the electrochemically reactive surfaces than the enzyme layer, and an electrode layer **50** adjacent to the electrochemically reactive surfaces. However, it is understood that the membrane system can be modified for use in other devices, by including only two or more of the layers, or additional layers not recited above.

FIG. **5** is an illustration of a membrane system in one preferred embodiment of a transcutaneous wire sensor. FIG. **5** is a cross-sectional view through the sensor of FIG. **3** on line C-C. In this embodiment, the membrane system includes an electrode layer **147**, an interference layer **148**, and enzyme layer **149**, and a diffusion resistance layer **150** wrapped around the platinum wire working electrode **144**. In some embodiments, this membrane system also includes a cell impermeable layer as described below. In some embodiments, the transcutaneous wire sensor is configured for short-term implantation (e.g., 1-30 days). Accordingly, in these embodiments, the cell disruptive layer may not be required because a foreign body capsule does not form in the short duration of implantation.

In some embodiments, the membrane systems for use in implantable sensors is formed as a physically continuous membrane, namely, a membrane having substantially uniform physical structural characteristics from one side of the membrane to the other. However, the membrane can have chemically heterogeneous domains, for example, domains resulting from the use of block copolymers (for example, polymers in which different blocks of identical monomer units alternate with each other), but can be defined as homogeneous overall in that each of the above-described layers functions by the preferential diffusion of some substance through the homogeneous membrane.

Some layers of the membrane systems **18** of the preferred embodiments include materials with high oxygen solubility. In some embodiments, the membrane systems **18** with high oxygen solubility simultaneously permit efficient transport of aqueous solutions of the analyte.

In one embodiment, one or more layer(s) is/are formed from a composition that, in addition to providing high oxygen solubility, allows for the transport of glucose or other such water-soluble molecules (for example, drugs). In one embodiment, these layers comprise a blend of a silicone polymer with a hydrophilic polymer. By "hydrophilic polymer," it is meant that the polymer has a substantially hydrophilic domain in which aqueous substances can easily dissolve. In one embodiment, the hydrophilic polymer has a molecular weight of at least about 1000 g/mol, 5,000 g/mol, 8,000 g/mol, 10,000 g/mol, or 15,000 g/mol. In one embodiment, the hydrophilic polymer comprises both a hydrophilic domain and a partially hydrophobic domain (e.g., a copolymer). The hydrophobic domain(s) facilitate the blending of the hydrophilic polymer with the hydrophobic silicone polymer. In one embodiment, the hydrophobic domain is itself a polymer (i.e., a polymeric hydrophobic domain). For example, in one embodiment, the hydrophobic domain is not a simple molecular head group but is rather polymeric. In various embodiments, the molecular weight of any covalently continuous hydrophobic domain within the hydrophilic polymer is at least about 500 g/mol, 700 g/mol, 1000 g/mol, 2000 g/mol, 5000 g/mol, or 8,000 g/mol. In various embodiments, the molecular weight of any covalently continuous hydrophilic domain within the hydrophilic polymer is at least about 500 g/mol, 700 g/mol, 1000 g/mol, 2000 g/mol, 5000 g/mol, or 8,000 g/mol.

In various embodiments, the ratio of the silicone polymer to hydrophilic polymer in a particular layer is selected to provide an amount of oxygen and water-soluble molecule solubility such that oxygen and water-soluble molecule transport through the layer is optimized according to the desired function of that particular layer. Furthermore, in some embodiments, the ratio of silicone polymer to hydrophilic polymer as well as the polymeric compositions are selected such that a layer constructed from the material has interference characteristics that inhibit transport of one or more interfering species through the layer. Some known interfering species for a glucose sensor include, but are not limited to, acetaminophen, ascorbic acid, bilirubin, cholesterol, creatinine, dopamine, ephedrine, ibuprofen, L-dopa, methyl dopa, salicylate, tetracycline, tolazamide, tolbutamide, triglycerides, and uric acid. Accordingly, in some embodiments, a silicone polymer/hydrophilic polymer layer as disclosed herein is less permeable to one or more of these interfering species than to the analyte, e.g., glucose.

In some embodiments, silicone polymer/hydrophilic polymer blends are used in multiple layers of a membrane. In some of these embodiments, the ratio of silicone polymer to hydrophilic polymer in the layers incorporating the blends varies according to the desired functionality of each layer. The relative amounts of silicone polymer and hydrophilic polymer described below are based on the respective amounts found in the cured polymeric blend. Upon introduction into an aqueous environment, some of the polymeric components may leach out, thereby changing the relative amounts of silicone polymer and hydrophilic polymer. For example, significant amounts of the portions of the hydrophilic polymer that are not cross-linked may leach out.

In some embodiments, the amount of any cross-linking between the silicone polymer and the hydrophilic polymer is substantially limited. In various embodiments, at least about 75%, 85%, 95%, or 99% of the silicone polymer is not covalently linked to the hydrophilic polymer. In some embodiments, the silicone polymer and the hydrophilic polymer do not cross link at all unless a cross-linking agent is used (e.g., such as described below). Similarly, in some embodiments, the amount of any entanglement (e.g., blending on a molecular level) between the silicone polymer and the hydrophilic polymer is substantially limited. In one embodiment, the silicone polymer and hydrophilic polymers form microdomains. For example, in one embodiment, the silicone polymer forms micellar structures surrounded by a network of hydrophilic polymer.

The silicone polymer for use in the silicone/hydrophilic polymer blend may be any suitable silicone polymer. In some embodiments, the silicone polymer is a liquid silicone rubber that may be vulcanized using a metal- (e.g., platinum), peroxide-, heat-, ultraviolet-, or other radiation-catalyzed process. In some embodiments, the silicone polymer is a dimethyl- and methylhydrogen-siloxane copolymer. In some embodiments, the copolymer has vinyl substituents. In some embodiments, commercially available silicone polymers may be used. For example, commercially available silicone polymer precursor compositions may be used to prepare the blends, such as described below. In one embodiment, MED-4840 available from NUSIL® Technology LLC is used as a precursor to the silicone polymer used in the blend. MED-4840 consists of a 2-part silicone elastomer precursor including vinyl-functionalized dimethyl- and methylhydrogen-siloxane copolymers, amorphous silica, a platinum catalyst, a crosslinker, and an inhibitor. The two components may be mixed together and heated to initiate vulcanization, thereby forming an elastomeric solid material. Other suitable silicone polymer precursor systems include, but are not limited to, MED-2174 peroxide-cured liquid silicone rubber available from NUSIL® Technology LLC, SILASTIC® MDX4-4210 platinum-cured biomedical grade elastomer available from DOW CORNING®, and Implant Grade Liquid Silicone Polymer (durometers 10-50) available from Applied Silicone Corporation.

The hydrophilic polymer for use in the blend may be any suitable hydrophilic polymer, including but not limited to components such as polyvinylpyrrolidone (PVP), polyhydroxyethyl methacrylate, polyvinylalcohol, polyacrylic acid, polyethers such as polyethylene glycol or polypropylene oxide, and copolymers thereof, including, for example, di-block, tri-block, alternating, random, comb, star, dendritic, and graft copolymers (block copolymers are discussed in U.S. Pat. Nos. 4,803,243 and 4,686,044, which are incorporated herein by reference). In one embodiment, the hydrophilic polymer is a copolymer of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO). Suitable such polymers include, but are not limited to, PEO-PPO diblock copolymers, PPO-PEO-PPO triblock copolymers, PEO-PPO-PEO triblock copolymers, alternating block copolymers of PEO-PPO, random copolymers of ethylene oxide and propylene oxide, and blends thereof. In some embodiments, the copolymers may be optionally substituted with hydroxy substituents. Commercially available examples of PEO and PPO copolymers include the PLURONIC® brand of polymers available from BASF®. Some PLURONIC® polymers are triblock copolymers of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) having the general molecular structure:

$$HO—(CH_2CH_2O)_x—(CH_2CH_2CH_2O)_y—(CH_2CH_2O)_x—OH$$

where the repeat units x and y vary among various PLURONIC® products. The poly(ethylene oxide) blocks act as a hydrophilic domain allowing the dissolution of aqueous agents in the polymer. The poly(propylene oxide) block acts as a hydrophobic domain facilitating the blending of the PLURONIC® polymer with a silicone polymer. In one embodiment, PLURONIC® F-127 is used having x of approximately 100 and y of approximately 65. The molecular weight of PLURONIC® F-127 is approximately 12,600 g/mol as reported by the manufacture. Other PLURONIC® polymers include PPO-PEO-PPO triblock copolymers (e.g., PLURONIC® R products). Other suitable commercial polymers include, but are not limited to, SYNPERONICS® products available from UNIQEMA®.

The polyether structure of PLURONIC® polymers is relatively inert. Accordingly, without being bound by any particular theory, it is believed that the PLURONIC® polymers do not substantially react with the components in MED-4840 or other silicone polymer precursors.

Those of skill in the art will appreciate that other copolymers having hydrophilic and hydrophobic domains may be used. For example, in one alternative embodiment, a triblock copolymer having the structure hydrophobic-hydrophilic-hydrophobic may be used. In another alternative embodiment, a diblock copolymer having the structure hydrophilic-hydrophobic is used.

Synthesis of Silicone/Hydrophilic Polymer Blend Layers

Layers that include a silicone polymer-hydrophilic polymer blend may be made using any of the methods of forming polymer blends known in the art. In one embodiment, a silicone polymer precursor (e.g., MED-4840) is mixed with a solution of a hydrophilic polymer (e.g., PLURONIC® F-127 dissolved in a suitable solvent such as acetone, ethyl alcohol, or 2-butanone). The mixture may then be drawn into a film or applied in a multi-layer membrane structure using any method known in the art (e.g., spraying, painting, dip coating, vapor depositing, molding, 3-D printing, lithographic techniques (e.g., photolithograph), micro- and nano-pipetting printing techniques, etc.). The mixture may then be cured under high temperature (e.g., 50-150° C.). Other suitable curing methods include ultraviolet or gamma radiation, for example. During curing, the silicone polymer precursor will vulcanize and the solvent will evaporate. In one embodiment, after the mixture is drawn into a film, another preformed layer of the membrane system is placed on the film. Curing of the film then provides bonding between the film and the other preformed layer. In one embodiment, the preformed layer is the cell disruptive layer. In one embodiment, the cell disruptive layer comprises a preformed porous silicone membrane. In other embodiments, the cell disruptive layer is also formed from a silicone polymer/hydrophilic polymer blend. In some embodiments, multiple films are applied on top of the preformed layer. Each film may posses a finite interface with adjacent films or may together form a physically continuous structure having a gradient in chemical composition.

Some amount of cross-linking agent may also be included in the mixture to induce cross-linking between hydrophilic polymer molecules. For example, when using a PLURONIC® polymer, a cross-linking system that reacts with pendant or terminal hydroxy groups or methylene, ethylene, or propylene hydrogen atoms may be used to induce cross linking. Non-limiting examples of suitable cross-linking agents include ethylene glycol diglycidyl ether (EGDE), poly (ethylene glycol) diglycidyl ether (PEGDE), or dicumyl peroxide (DCP). While not being bound by any particular theory, at low concentrations, these cross-linking agents are believed to react primarily with the PLURONIC® polymer with some amount possibly inducing cross-linking in the silicone polymer or between the PLURONIC® polymer and the silicone polymer. In one embodiment, enough cross-linking agent is added such that the ratio of cross-linking agent molecules to hydrophilic polymer molecules added when synthesizing the blend is about 10 to about 30 (e.g., about 15 to about 20). In one embodiment, from about 0.5% to about 15% w/w of cross-linking agent is added relative to the total dry weights of cross-linking agent, silicone polymer, and hydrophilic polymer added when blending the ingredients (in one example, about 1% to about 10%). In one embodiment, from about 5% to about 30% of the dry ingredient weight is the PLURONIC® polymer. During the curing process, substantially all of the cross-linking agent is believed to react, leaving substantially no detectable unreacted cross-linking agent in the final film.

In some embodiments, other agents may be added to the mixture to facilitate formation of the blend. For example, a small amount of butylhydroxy toluene (BHT) (e.g., about 0.01% w/w) or other suitable antioxidant may be mixed with a PLURONIC® to stabilize it.

In some alternative embodiments, precursors of both the silicone polymer and hydrophilic polymer may be mixed prior to curing such that polymerization of both the silicone polymer and the hydrophilic polymer occur during curing. In another embodiment, already polymerized silicone polymer is mixed with a hydrophilic polymer such that no significant polymerization occurs during curing.

Cell Disruptive Domain

The cell disruptive layer **40** is positioned most distal to the implantable device and is designed to support tissue ingrowth, to disrupt contractile forces typically found in a foreign body capsule, to encourage vascularity within the membrane, and/or to disrupt the formation of a barrier cell layer. In one embodiment, the cell disruptive layer **40** has an open-celled configuration with interconnected cavities and solid portions, wherein the distribution of the solid portion and cavities of the cell disruptive layer includes a substantially co-continuous solid domain and includes more than one cavity in three dimensions substantially throughout the entirety of the first domain. Cells can enter into the cavities; however they cannot travel through or wholly exist within the solid portions. The cavities allow most substances to pass through, including, for example, cells, and molecules. U.S. Pat. No. 6,702,857, filed Jul. 27, 2001, and entitled "MEMBRANE FOR USE WITH IMPLANTABLE DEVICES" and U.S. patent application Ser. No. 10/647,065, filed Aug. 22, 2003, published in U.S. Publication No. 2005/0112169 A1 and entitled, "POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES" describe membranes having a cell disruptive domain and are both incorporated herein by reference in their entirety.

The cell disruptive layer **40** is preferably formed from high oxygen soluble materials such as polymers formed from silicone, fluorocarbons, perfluorocarbons, or the like. In these embodiments, transport of water-soluble agents such as an aqueous analyte occurs primarily through the pores and cavities of the layer. In some embodiments, the cell disruptive domain is formed from polyethylene-co-tetrafluoroethylene, polyolefin, polyester, polycarbonate, biostable polytetrafluoroethylene, homopolymers, copolymers, terpolymers of polytetrafluoroethylene, polyurethanes, polypropylene (PP), polyvinylchloride (PVC), polyvinylidene fluoride (PVDF), polybutylene terephthalate (PBT), polymethylmethacrylate (PMMA), polyether ether ketone (PEEK), polyurethanes, cellulosic polymers, polysulfones or block copolymers thereof including, for example, di-block, tri-block, alternating, random and graft copolymers. In other embodiments, the cell disruptive layer is formed from a silicone composition with a non-silicon containing hydrophile such as such as polyethylene glycol, propylene glycol, pyrrolidone, esters, amides, or carbonates covalently incorporated or grafted therein such that water-soluble agents can also be transported through polymeric matrix of the cell disruptive layer **40**. Such compositions are described for example in U.S. application Ser. No. 10/695,636, filed Oct. 28, 2003, published in Publication No. 2005/0090607 and entitled "SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE," which is incorporated herein by reference in its entirety. In still other embodiments, the cell disruptive layer is formed from a monomer, polymer, copolymer, or blend including one or more of: lactic acid, glycolic acid, anhydrides, phospazenes, vinyl alcohol, ethylene vinyl alcohol, acetates, ϵ-caprolactone, β-hydroxybutyrate, γ-ethyl glutamate, DTH iminocarbonate, Bisphenol A iminocarbonate, sebacic acid, hexadecanoic acid, saccharides, chitosan, hydyoxyethyl methacrylate (HEMA), ceramics, hyaluronic acid (HA), collagen, gelatin, starches, hydroxy apatite, calcium phosphates, bioglasses, amino acid sequences, proteins, glycoproteins, protein fragments, agarose, fibrin, n-butylene, isobutylene, dioxanone, nylons, vinyl chlorides, amides, ethylenes, n-butyl methacrylate (BMA), metal matrix composites (MMCs), metal oxides (e.g. aluminum), DETOSU-1,6 HD-t-CDM ortho ester, styrene, and plasma treated surfaces of any of the above.

In some embodiments, the cell disruptive layer **40** is formed from silicone polymer/hydrophilic polymer blends such as described above. Due to the open-cell configuration of the cell disruptive layer **40**, the ratio of silicone polymer to hydrophilic polymer may be chosen to increase the structural integrity of the layer so that the open-cell configuration is maintained. Alternatively, the structural integrity of the cell disruptive layer can be increased by choosing a silicone polymer having properties suitable for increasing structural integrity (e.g., a silicone polymer having an increased durometer). In one embodiment, the concentration of hydrophilic polymer (e.g., PLURONIC® F-127) relative to silicone polymer (e.g., MED-4840) is from about 1% to about 30%, preferably from about 5% to about 20% in the cell disruptive layer **40**.

In preferred embodiments, the thickness of the cell disruptive domain is from about 10 or less, 20, 30, 40, 50, 60, 70, 80, or 90 microns to about 1500, 2000, 2500, or 3000 or more microns. In more preferred embodiments, the thickness of the cell disruptive domain is from about 100, 150, 200 or 250 microns to about 1000, 1100, 1200, 1300, or 1400 microns. In even more preferred embodiments, the thickness of the cell disruptive domain is from about 300, 350, 400, 450, 500, or 550 microns to about 500, 550, 600, 650, 700, 750, 800, 850, or 900 microns.

The cell disruptive domain is optional and can be omitted when using an implantable device that does not prefer tissue ingrowth, for example, a short-lived device (for example, less than one day to about a week or up to about one month) or one that delivers tissue response modifiers.

Bioprotective Layer

The bioprotective layer **42** is positioned less distal to the implantable device than the cell disruptive layer, and can be resistant to cellular attachment, impermeable to cells, and/or is composed of a biostable material. When the bioprotective layer is resistant to cellular attachment (for example, attachment by inflammatory cells, such as macrophages, which are therefore kept a sufficient distance from other domains, for example, the enzyme domain), hypochlorite and other oxidizing species are short-lived chemical species in vivo, and biodegradation does not occur. Additionally, the materials preferred for forming the bioprotective layer **42** may be resistant to the effects of these oxidative species and have thus been termed biodurable. See, for example, U.S. Pat. No. 6,702,857, filed Jul. 27, 2001, and entitled "MEMBRANE FOR USE WITH IMPLANTABLE DEVICES" and U.S. patent application Ser. No. 10/647,065, filed Aug. 22, 2003, published in Publication No. 20050112169 and entitled, "POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES," both of which are incorporated herein by reference in their entirety.

In one embodiment, bioprotective layer **42** is formed from high oxygen soluble materials such as polymers formed from silicone, fluorocarbons, perfluorocarbons, or the like. In one embodiment, the cell impermeable domain is formed from a silicone composition with a hydrophile such as such as polyethylene glycol, propylene glycol, pyrrolidone, esters, amides, carbonates, or polypropylene glycol covalently incorporated or grafted therein. In still other embodiments, the bioprotective layer is formed from a monomer, polymer, copolymer, or blend including one or more of: lactic acid, glycolic acid, anhydrides, phospazenes, vinyl alcohol, ethylene vinyl alcohol, acetates, ϵ-caprolactone, β-hydroxybutyrate, γ-ethyl glutamate, DTH iminocarbonate, Bisphenol A iminocarbonate, sebacic acid, hexadecanoic acid, saccharides, chitosan, hydyoxyethyl methacrylate (HEMA), ceramics, hyaluronic acid (HA), collagen, gelatin, starches, hydroxy apatite, calcium phosphates, bioglasses, amino acid sequences, proteins, glycoproteins, protein fragments, agarose, fibrin, n-butylene, isobutylene, dioxanone, nylons, vinyl chlorides, amides, ethylenes, n-butyl methacrylate (BMA), metal matrix composites (MMCs), metal oxides (e.g. aluminum), DETOSU-1,6 HD-t-CDM ortho ester, styrene, and plasma treated surfaces of any of the above.

In one preferred embodiment, the bioprotective layer **42** is formed from silicone polymer/hydrophilic polymer blends such as described above. It is advantageous that the cell impermeable layer **42** have both high oxygen and aqueous analyte solubility so that sufficient reactants reach the enzyme layer. Accordingly, in one embodiment, the concentration of hydrophilic polymer (e.g., PLURONIC® F-127) relative to silicone polymer (e.g., MED-4840) is relatively high, e.g., from about 10% to about 30% in the bioprotective layer **42**. In one embodiment, the concentration of hydrophilic polymer is from about 15% to about 25% (e.g., about 20%).

In preferred embodiments, the thickness of the bioprotective layer is from about 10 or 15 microns or less to about 125, 150, 175, 200 or 250 microns or more. In more preferred embodiments, the thickness of the bioprotective layer is from about 20, 25, 30, or 35 microns to about 60, 65, 70, 75, 80, 85, 90, 95, or 100 microns. In even more preferred embodiments, the bioprotective layer is from about 20 or 25 microns to about 50, 55, or 60 microns thick.

The cell disruptive layer **40** and bioprotective layer **42** of the membrane system can be formed together as one unitary structure. Alternatively, the cell disruptive and bioprotective layers **40**, **42** of the membrane system can be formed as two layers mechanically or chemically bonded together. In one embodiment, the cell disruptive layer **40** and bioprotective layer **42** consist of a unitary structure having graduated properties. For example, the porosity of the unitary structure may vary from high porosity at the tissue side of the layer to very low or no porosity at the sensor side. In addition, the chemical properties of such a graduated structure may also vary. For example, the concentration of the hydrophilic polymer may vary throughout the structure, increasing in concentration toward the sensor side of the layer. The lower concentration on the tissue side allows for increased structural integrity to support an open-celled structure while the higher concentration on the sensor side promotes increased transport of aqueous analytes through the polymer blend.

Diffusion Resistance Layer

The diffusion resistance layer **44** or **150** is situated more proximal to the implantable device relative to the cell disruptive layer. The diffusion resistance layer controls the flux of oxygen and other analytes (for example, glucose) to the underlying enzyme domain. As described in more detail elsewhere herein, there exists a molar excess of glucose relative to the amount of oxygen in blood; that is, for every free oxygen molecule in extracellular fluid, there are typically more than 100 glucose molecules present (see Updike et al., Diabetes Care 5:207-21(1982)). However, an immobilized enzyme-based sensor employing oxygen as cofactor is supplied with oxygen in non-rate-limiting excess in order to respond linearly to changes in glucose concentration, while not responding to changes in oxygen tension. More specifically, when a glucose-monitoring reaction is oxygen-limited, linearity is not achieved above minimal concentrations of glucose. Without a semipermeable membrane situated over the enzyme domain to control the flux of glucose and oxygen, a linear response to glucose levels can be obtained only up to about 40 mg/dL. However, in a clinical setting, a linear response to glucose levels is desirable up to at least about 500 mg/dL.

The diffusion resistance layer **44** or **150** includes a semipermeable membrane that controls the flux of oxygen and glucose to the underlying enzyme layer **46** or **147**, preferably rendering oxygen in non-rate-limiting excess. As a result, the upper limit of linearity of glucose measurement is extended to a much higher value than that which is achieved without the diffusion resistance layer. In one embodiment, the diffusion resistance layer **44** or **150** exhibits an oxygen-to-glucose permeability ratio of approximately 200:1. As a result, one-dimensional reactant diffusion is adequate to provide excess oxygen at all reasonable glucose and oxygen concentrations found in the subcutaneous matrix (See Rhodes et al., Anal. Chem., 66:1520-1529 (1994)). In some embodiments, a lower ratio of oxygen-to-glucose can be sufficient to provide excess oxygen by using a high oxygen soluble domain (for example, a silicone material) to enhance the supply/transport of oxygen to the enzyme membrane and/or electroactive surfaces. By enhancing the oxygen supply through the use of a silicone composition, for example, glucose concentration can be less of a limiting factor. In other words, if more oxygen is supplied to the enzyme and/or electroactive surfaces, then more glucose can also be supplied to the enzyme without creating an oxygen rate-limiting excess.

In one embodiment, the diffusion resistance layer **44** or **150** is preferably formed from high oxygen soluble materials such as polymers formed from silicone, fluorocarbons, perfluorocarbons, or the like. In one embodiment, the resistance domain is formed from a silicone composition with a hydrophile such as such as polyethylene glycol, propylene glycol, pyrrolidone, esters, amides, carbonates, or polypropylene glycol covalently incorporated or grafted therein. In some alternative embodiments, the diffusion resistance layer is formed from polyurethane, for example, a polyurethane urea/polyurethane-block-polyethylene glycol blend. In still other embodiments, the diffusion resistance layer is formed from a monomer, polymer, copolymer, or blend including one or more of: lactic acid, glycolic acid, anhydrides, phospazenes, vinyl alcohol, ethylene vinyl alcohol, acetates, ε-caprolactone, β-hydroxybutyrate, γ-ethyl glutamate, DTH iminocarbonate, Bisphenol A iminocarbonate, sebacic acid, hexadecanoic acid, saccharides, chitosan, hydyoxyethyl methacrylate (HEMA), ceramics, hyaluronic acid (HA), collagen, gelatin, starches, hydroxy apatite, calcium phosphates, bioglasses, amino acid sequences, proteins, glycoproteins, protein fragments, agarose, fibrin, n-butylene, isobutylene, dioxanone, nylons, vinyl chlorides, amides, ethylenes, n-butyl methacrylate (BMA), metal matrix composites (MMCs), metal oxides (e.g. aluminum), DETOSU-1,6 HD-t-CDM ortho ester, styrene, and plasma treated surfaces of any of the above.

In some preferred embodiments, the diffusion resistance layer **44** or **150** is formed from silicone polymer/hydrophilic polymer blends such as described above. In some alternative embodiments, the diffusion resistance layer **44** or **150** is formed from silicone polymer/hydrophilic polymer blends. In order to restrict the transport of an aqueous analyte such as glucose, lower concentrations of hydrophilic polymer can be employed. Accordingly, in one embodiment, the concentration of hydrophilic polymer (e.g., PLURONIC® F-127) relative to silicone polymer (e.g., MED-4840) is from about 1% to about 15% in the diffusion resistance layer **44** (e.g., from about 6% to about 10%).

In some alternative embodiments, the diffusion resistance layer includes a polyurethane membrane with both hydrophilic and hydrophobic regions to control the diffusion of glucose and oxygen to an analyte sensor, the membrane being fabricated easily and reproducibly from commercially available materials. A suitable hydrophobic polymer component is a polyurethane, or polyetherurethaneurea. Polyurethane is a polymer produced by the condensation reaction of a diisocyanate and a difunctional hydroxyl-containing material. A polyurethaneurea is a polymer produced by the condensation reaction of a diisocyanate and a difunctional amine-containing material. Preferred diisocyanates include aliphatic diisocyanates containing from about 4 to about 8 methylene units. Diisocyanates containing cycloaliphatic moieties can also be useful in the preparation of the polymer and copolymer components of the membranes of preferred embodiments. The material that forms the basis of the hydrophobic matrix of the diffusion resistance layer can be any of those known in the art as appropriate for use as membranes in sensor devices and as having sufficient permeability to allow relevant compounds to pass through it, for example, to allow an oxygen molecule to pass through the membrane from the sample under examination in order to reach the active enzyme or electrochemical electrodes. Examples of materials which can be used to make non-polyurethane type membranes include vinyl polymers, polyethers, polyesters, polyamides, inorganic polymers such as polysiloxanes and polycarbosiloxanes, natural polymers such as cellulosic and protein based materials, and mixtures or combinations thereof.

In one embodiment, the hydrophilic polymer component is polyethylene oxide. For example, one useful hydrophilic copolymer component is a polyurethane polymer that includes about 20% hydrophilic polyethylene oxide. The polyethylene oxide portions of the copolymer are thermodynamically driven to separate from the hydrophobic portions of the copolymer and the hydrophobic polymer component. The 20% polyethylene oxide-based soft segment portion of the copolymer used to form the final blend affects the water pick-up and subsequent glucose permeability of the membrane.

In some embodiments, the diffusion resistance layer **44** or **150** can be formed as a unitary structure with the bioprotective layer **42**; that is, the inherent properties of the diffusion resistance layer **44** or **150** can provide the functionality described with reference to the bioprotective layer **42** such that the bioprotective layer **42** is incorporated as a part of diffusion resistance layer **44** or **150**. In these embodiments, the combined diffusion resistance layer/bioprotective layer can be bonded to or formed as a skin on the cell disruptive layer **40**. As discussed above, the diffusion resistance layer/bioprotective layer may also be part of a unitary structure with the cell disruptive layer **40** such that the outer layer of the membrane system is graduated to the interface with the enzyme layer. In another embodiment, the diffusion resistance layer/bioprotective layer may also be part of a unitary structure with the cell disruptive layer **40** including a chemical gradient with transition properties between the outer layer and the enzyme layer. In another embodiment, the diffusion resistance layer **44** or **150** is formed as a distinct layer and chemically or mechanically bonded to the cell disruptive layer **40** (if applicable) or the bioprotective layer **42** (when the resistance domain is distinct from the cell impermeable domain).

In still another embodiment, the diffusion resistance layer may be a distinct layer from the cell disruptive layer or the bioprotective layer but may nonetheless include a chemical gradient such that its diffusion resistance property transitions from one side of the layer to the other. Similarly, the cell disruptive layer and bioprotective layers may also include a chemical gradient. Where multiple such layers have chemical gradients, the chemical compositions at the interface between two layers may be identical or different.

In preferred embodiments, the thickness of the resistance domain is from about 0.05 microns or less to about 200 microns or more. In more preferred embodiments, the thickness of the resistance domain is from about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 10, 15, 20, 25, 30, or 35 microns to about, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 19.5, 20, 30, 40, 50, 60, 70, 75, 80, 85, 90, 95, or 100 microns. In more preferred embodiments, the thickness of the resistance domain is from about 2, 2.5 or 3 microns to about 3.5, 4, 4.5, or 5 microns in the case of a transcutaneously implanted sensor or from about 20 or 25 microns to about 40 or 50 microns in the case of a wholly implanted sensor.

Enzyme Layer

An immobilized enzyme layer **46** or **149** is situated less distal from the electrochemically reactive surfaces than the diffusion resistance layer **44** or **150**. In one embodiment, the immobilized enzyme layer **46** or **149** comprises glucose oxidase. In other embodiments, the immobilized enzyme layer **46** or **149** can be impregnated with other oxidases, for example, galactose oxidase, cholesterol oxidase, amino acid oxidase, alcohol oxidase, lactate oxidase, or uricase. For example, for an enzyme-based electrochemical glucose sensor to perform well, the sensor's response should neither be limited by enzyme activity nor cofactor concentration.

The enzyme layer **44** or **149** is preferably formed from high oxygen soluble materials such as polymers formed from silicone, fluorocarbons, perfluorocarbons, or the like. In one embodiment, the enzyme domain is formed from a silicone composition with a hydrophile such as such as polyethylene glycol, propylene glycol, pyrrolidone, esters, amides, carbonates, or polypropylene glycol covalently incorporated or grafted therein. In one embodiment, the enzyme layer **44** or **149** is formed from polyurethane.

In one embodiment, high oxygen solubility within the enzyme layer can be achieved by using a polymer matrix to host the enzyme within the enzyme layer that has a high solubility of oxygen. In one exemplary embodiment of fluorocarbon-based polymers, the solubility of oxygen within a perfluorocarbon-based polymer is 50-volume %. As a reference, the solubility of oxygen in water is approximately 2-volume %.

In one preferred embodiment, the enzyme layer is formed from silicone polymer/hydrophilic polymer blends such as described above. In one embodiment, the concentration of hydrophilic polymer (e.g., PLURONIC® F-127) relative to silicone polymer (e.g., MED-4840) is relatively high, e.g., from about 10% to about 30% in the bioprotective layer **42**. In one embodiment, the concentration of hydrophilic polymer is from about 15% to about 25% (e.g., about 20%).

Utilization of a high oxygen solubility material for the enzyme layer is advantageous because the oxygen dissolves more readily within the layer and thereby acts as a high oxygen soluble domain optimizing oxygen availability to oxygen-utilizing sources (for example, the enzyme and/or counter electrode). When the diffusion resistance layer **44** or **149** and enzyme layer **46** or **150** both comprise a high oxygen soluble material, the chemical bond between the enzyme layer **46** or **150** and diffusion resistance layer **44** or **149** can be optimized, and the manufacturing made easy.

In some alternative embodiments, the enzyme domain is constructed of aqueous dispersions of colloidal polyurethane polymers including the enzyme.

In preferred embodiments, the thickness of the enzyme domain is from about 0.05 micron or less to about 20, 30 40, 50, 60, 70, 80, 90, or 100 microns or more. In more preferred embodiments, the thickness of the enzyme domain is between about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, 4, or 5 microns and 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 19.5, 20, 25, or 30 microns. In even more preferred embodiments, the thickness of the enzyme domain is from about 2, 2.5, or 3 microns to about 3.5, 4, 4.5, or 5 microns in the case of a transcutaneously implanted sensor or from about 6, 7, or 8 microns to about 9, 10, 11, or 12 microns in the case of a wholly implanted sensor.

Interference Layer

The interference layer **48** or **148** is situated less distal to the implantable device than the immobilized enzyme layer. Interferants are molecules or other species that are electro-reduced or electro-oxidized at the electrochemically reactive surfaces, either directly or via an electron transfer agent, to produce a false signal (for example, urate, ascorbate, or acetaminophen). In one embodiment, the interference layer **48** or **148** prevents the penetration of one or more interferants into the electrolyte phase around the electrochemically reactive surfaces. Preferably, this type of interference layer is much less permeable to one or more of the interferants than to the analyte.

In one embodiment, the interference domain **48** or **148** can include ionic components incorporated into a polymeric matrix to reduce the permeability of the interference layer to ionic interferants having the same charge as the ionic components. In another embodiment, the interference layer **48** or **148** includes a catalyst (for example, peroxidase) for catalyzing a reaction that removes interferants. U.S. Pat. Nos. 6,413,396 and 6,565,509 disclose methods and materials for eliminating interfering species, both of which are incorporated herein by reference in their entirety; however in the preferred embodiments any suitable method or material can be employed.

In another embodiment, the interference layer **48** or **148** includes a thin membrane that is designed to limit diffusion of species, for example, those greater than 34 kD in molecular weight, for example. The interference layer permits analytes and other substances (for example, hydrogen peroxide) that are to be measured by the electrodes to pass through, while preventing passage of other substances, such as potentially interfering substances. In one embodiment, the interference layer **48** or **148** is constructed of polyurethane. In an alternative embodiment, the interference layer **48** or **148** comprises a high oxygen soluble polymer.

In one embodiment, the interference layer **48** or **148** is formed from silicone polymer/hydrophilic polymer blends such as described above. As described herein, such polymer blends can have the characteristics of limiting transport of one or more interferants therethrough. Because of this property, the use of the polymer blends in a membrane layer other than the interference layer may also confer interferant resistance properties in those layers, potentially eliminating the need for a separate interference layer. In some embodiments, these layers allow diffusion of glucose therethrough but limit diffusion of one or more interferant therethrough.

In some embodiments, the interference layer **48** or **148** is formed from one or more cellulosic derivatives. In general, cellulosic derivatives include polymers such as cellulose acetate, cellulose acetate butyrate, 2-hydroxyethyl cellulose, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate trimellitate, and the like.

In one preferred embodiment, the interference layer **48** or **148** is formed from cellulose acetate butyrate. Cellulose acetate butyrate with a molecular weight of about 10,000 daltons to about 75,000 daltons, preferably from about 15,000, 20,000, or 25,000 daltons to about 50,000, 55,000, 60,000, 65,000, or 70,000 daltons, and more preferably about 20,000 daltons is employed. In certain embodiments, however, higher or lower molecular weights can be preferred. Additionally, a casting solution or dispersion of cellulose acetate butyrate at a weight percent of about 15% to about 25%, preferably from about 15%, 16%, 17%, 18%, 19% to about 20%, 21%, 22%, 23%, 24% or 25%, and more preferably about 18% is preferred. Preferably, the casting solution includes a solvent or solvent system, for example an acetone: ethanol solvent system. Higher or lower concentrations can be preferred in certain embodiments. A plurality of layers of cellulose acetate butyrate can be advantageously combined to form the interference domain in some embodiments, for example, three layers can be employed. It can be desirable to employ a mixture of cellulose acetate butyrate components with different molecular weights in a single solution, or to deposit multiple layers of cellulose acetate butyrate from different solutions comprising cellulose acetate butyrate of different molecular weights, different concentrations, and/or different chemistries (e.g., functional groups). It can also be desirable to include additional substances in the casting solutions or dispersions, e.g., functionalizing agents, crosslinking agents, other polymeric substances, substances capable of modifying the hydrophilicity/hydrophobicity of the resulting layer, and the like.

In one alternative embodiment, the interference layer **48** or **148** is formed from cellulose acetate. Cellulose acetate with a molecular weight of about 30,000 daltons or less to about 100,000 daltons or more, preferably from about 35,000, 40,000, or 45,000 daltons to about 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, or 95,000 daltons, and more preferably about 50,000 daltons is preferred. Additionally, a casting solution or dispersion of cellulose acetate at a weight percent of about 3% to about 10%, preferably from about 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, or 6.5% to about 7.5%, 8.0%, 8.5%, 9.0%, or 9.5%, and more preferably about 8% is preferred. In certain embodiments, however, higher or lower molecular weights and/or cellulose acetate weight percentages can be preferred. It can be desirable to employ a mixture of cellulose acetates with molecular weights in a single solution, or to deposit multiple layers of cellulose acetate from different solutions comprising cellulose acetates of different molecular weights, different concentrations, or different chemistries (e.g., functional groups). It can also be desirable to include additional substances in the casting solutions or dispersions such as described in more detail above.

Layer(s) prepared from combinations of cellulose acetate and cellulose acetate butyrate, or combinations of layer(s) of cellulose acetate and layer(s) of cellulose acetate butyrate can also be employed to form the interference layer **48** or **148**.

In some alternative embodiments, additional polymers, such as Nafion®, can be used in combination with cellulosic derivatives to provide equivalent and/or enhanced function of the interference layer **48** or **148**. As one example, a 5 wt % Nafion® casting solution or dispersion can be used in combination with a 8 wt % cellulose acetate casting solution or dispersion, e.g., by dip coating at least one layer of cellulose acetate and subsequently dip coating at least one layer Nafion® onto a needle-type sensor such as described with reference to the preferred embodiments. Any number of coatings or layers formed in any order may be suitable for forming the interference domain of the preferred embodiments.

In some alternative embodiments, more than one cellulosic derivative can be used to form the interference layer **48** or **148** of the preferred embodiments. In general, the formation of the interference domain on a surface utilizes a solvent or solvent system in order to solvate the cellulosic derivative (or other polymer) prior to film formation thereon. In preferred embodiments, acetone and ethanol are used as solvents for cellulose acetate; however one skilled in the art appreciates the numerous solvents that are suitable for use with cellulosic derivatives (and other polymers). Additionally, one skilled in the art appreciates that the preferred relative amounts of solvent can be dependent upon the cellulosic derivative (or other polymer) used, its molecular weight, its method of deposition, its desired thickness, and the like. However, a percent solute of from about 1% to about 25% is preferably used to form the interference domain solution so as to yield an interference layer **48** or **148** having the desired properties. The cellulosic derivative (or other polymer) used, its molecular weight, method of deposition, and desired thickness can be adjusted, depending upon one or more other of the parameters, and can be varied accordingly as is appreciated by one skilled in the art.

In some alternative embodiments, other polymer types that can be utilized as a base material for the interference layer **48** or **148** include polyurethanes, polymers having pendant ionic groups, and polymers having controlled pore size, for example. In one such alternative embodiment, the interference domain includes a thin, hydrophobic membrane that is non-swellable and restricts diffusion of low molecular weight species. The interference layer **48** or **148** is permeable to relatively low molecular weight substances, such as hydrogen peroxide, but restricts the passage of higher molecular weight substances, including glucose and ascorbic acid. Other systems and methods for reducing or eliminating interference species that can be applied to the membrane system of the preferred embodiments are described in co-pending U.S. patent application Ser. No. 10/896,312 filed Jul. 21, 2004 and entitled "ELECTRODE SYSTEMS FOR ELECTROCHEMICAL SENSORS," Ser. No. 10/991,353, filed Nov. 16, 2004 and entitled, "AFFINITY DOMAIN FOR AN ANALYTE SENSOR," Ser. No. 11/007,635, filed Dec. 7, 2004 and entitled "SYSTEMS AND METHODS FOR IMPROVING ELECTROCHEMICAL ANALYTE SENSORS" and Ser. No. 11/004,561, filed Dec. 3, 2004 and entitled, "CALIBRATION TECHNIQUES FOR A CONTINUOUS ANALYTE SENSOR."

In preferred embodiments, the thickness of the interference domain is from about 0.05 microns or less to about 20 microns or more. In more preferred embodiments, the thickness of the interference domain is between about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5 microns and about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 19.5 microns. In more preferred embodiments, the thickness of the interference domain is from about 0.6, 0.7, 0.8, 0.9, or 1 micron to about 2, 3, or 4 microns.

Electrode Layer

An electrode layer **50** or **147** is situated more proximal to the electrochemically reactive surfaces than the interference layer **48** or **148**. To ensure the electrochemical reaction, the electrode layer **50** or **147** includes a semipermeable coating that maintains hydrophilicity at the electrochemically reactive surfaces of the sensor interface. The electrode layer **50** or **147** enhances the stability of the interference layer **48** or **148** by protecting and supporting the material that makes up the interference layer. The electrode layer **50** or **147** also assists in stabilizing the operation of the device by overcoming electrode start-up problems and drifting problems caused by inadequate electrolyte. The buffered electrolyte solution contained in the electrode layer also protects against pH-mediated damage that can result from the formation of a large pH gradient between the substantially hydrophobic interference domain and the electrodes due to the electrochemical activity of the electrodes. In some embodiments, the electrode layer may not be used, for example, when an interference layer is not provided.

In one embodiment, the electrode layer **50** or **147** includes a flexible, water-swellable, substantially solid gel-like film (e.g., a hydrogel) having a "dry film" thickness of from about 0.05 microns to about 100 microns, more preferably from about 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5, 4, 4.5, 5, or 5.5 to about 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 18, 19, 19.5, 20, 30, 40, 50, 60, 70, 80, 90, or 100 microns. In even more preferred embodiments, the thickness of the electrolyte domain is from about 2, 2.5 or 3 microns to about 3.5, 4, 4.5, or 5 microns in the case of a transcutaneously implanted sensor or from about 6, 7, or 8 microns to about 9, 10, 11, or 12 microns in the case of a wholly implanted sensor. "Dry film" thickness refers to the thickness of a cured film cast from a coating formulation onto the surface of the membrane by standard coating techniques.

In some embodiments, the electrode layer **50** or **147** is formed of a curable mixture of a urethane polymer and a hydrophilic polymer. Particularly preferred coatings are formed of a polyurethane polymer having anionic carboxylate functional groups and non-ionic hydrophilic polyether segments, which is crosslinked in the presence of polyvinylpyrrolidone and cured at a moderate temperature of about 50° C. In some preferred embodiments, the electrode layer **50** or **147** is formed from high oxygen soluble materials such as polymers formed from silicone, fluorocarbons, perfluorocarbons, or the like. In one preferred embodiment, the electrode layer **50** or **147** is formed from silicone polymer/hydrophilic polymer blends such as described above.

Underlying the electrode layer is an electrolyte phase is a free-fluid phase including a solution containing at least one compound, typically a soluble chloride salt, which conducts electric current. In one embodiment wherein the membrane system is used with a glucose sensor such as is described herein, the electrolyte phase flows over the electrodes and is in contact with the electrolyte layer. The devices of the preferred embodiments contemplate the use of any suitable electrolyte solution, including standard, commercially available solutions. Generally, the electrolyte phase can have the same osmotic pressure or a lower osmotic pressure than the sample being analyzed. In preferred embodiments, the electrolyte phase comprises normal saline.

In various embodiments, any of the layers discussed above can be omitted, altered, substituted for, and/or incorporated together. For example, a distinct bioprotective layer may not exist. In such embodiments, other domains accomplish the function of the bioprotective layer. As another example, the interference layer can be eliminated in certain embodiments wherein two-electrode differential measurements are employed to eliminate interference, for example, one electrode being sensitive to glucose and electrooxidizable interferants and the other only to interferants, such as is described in U.S. Pat. No. 6,514,718, which is incorporated herein by reference in its entirety. In such embodiments, the interference layer can be omitted.

In one embodiment, the membrane system **18** comprises only two layers. One layer is the enzyme layer as described above. The second layer is positioned more distal than the enzyme layer and serves one or more of the functions described above for the cell disruptive layer, bioprotective layer, and diffusion resistance layer. In one embodiment, this second layer is graduated either structurally and/or chemically as describe above such that different domains of the second layer serve different functions such as cell disruption, bio-protection, or diffusion resistance. In one embodiment, both layers of this membrane system are formed from silicone polymer/hydrophilic polymer blends such as described above.

In one embodiment, every layer in the membrane system **18** is formed from silicone polymer/hydrophilic polymer blends such as described above. Such uniformity in ingredients allows for ease of manufacturing while at the same time allowing for tailoring of properties by varying the ratio of silicone polymer to hydrophilic polymer.

EXAMPLES

Example 1

MED-4840/PLURONIC® F-127 Bioprotective Layer

30 g of PLURONIC® F-127 (PF-127) was dissolved under stiffing in 100 g of anhydrous acetone at 40° C. 13 g of acetone was added to 37.3 g of the PF-127 solution followed by adding 4.8 g of dicumyl peroxide (DCP). 40 g of MED-4840

was mixed in a speed mixer at a speed of 3300 rpm for 60 seconds. The MED-4840 mixture was then placed in a motorized mechanical mixer equipped with a spiral dough hook. The mixture was stirred at low speed for 30 s. The stiffing speed was then increased to medium-low and the PF-127/DCP solution was added at a rate of 3.5-4.0 g every 30 seconds. After all of the PF-127/DCP solution was added, the mixture was stirred at medium speed for 3 minutes. The mixture was then placed in a Speed Mixer and mixed at 3300 rpm for 60 seconds. This process was repeated until the desired viscosity was reached.

5-10 mL of the mixture was placed in an evenly-distributed line between the arms of the drawdown blade on a drawdown machine. The drawdown machine was used to create a 9 inch long and 0.0045 inch thick film at a speed of about 0.7 inches/minute. A preformed piece of porous silicone (to act as a cell disruptive layer) was placed skin side down on the drawn film and tapped lightly to promote the polymeric mixture to penetrate into the pores of the porous silicone. The film was then cured for 1.5 hours at 100° C.

Example 2

MED-4840/PLURONIC® F-127 Diffusion Resistance Layer on Implanted Sensor

A MED-4840/PLURONIC® F-127 membrane was manufactured using 8.4% PLURONIC® and 1.8% of a DCP cross-linking agent. This membrane was placed over a two-layer membrane having an enzyme layer and an electrode layer. The combined membrane layers were placed on a wholly implantable glucose sensor. The sensor was sterilized and implanted into a diabetic rat model. FIG. **6** is a graph depicting the resulting glucose sensor measurements over the course of approximately two months. The small points in FIG. **6** depict glucose concentrations measured by the sensor and the large points depict glucose concentrations measured by separate blood glucose assays. The graph indicates a close correlation between the sensor glucose measurements and the blood glucose measurements.

Example 3

MED-4840/PLURONIC® F-127 Bioprotective Layer on Implanted Sensor

A MED-4840/PLURONIC® F-127 membrane was manufactured using 20% PLURONIC® and a 20:1 ratio of DCP cross-linking agent per PLURONIC®. Prior to curing, the material was drawn down and a cell-disruptive porous silicone membrane was placed on the uncured layer. After curing, the combined bioprotective/porous silicone membrane was placed over a four-layer membrane having a diffusion resistance layer, enzyme layer, interference layer, and electrode layer. The combined membrane layers were placed on a wholly implantable glucose sensor. The sensor was sterilized and implanted into a diabetic rat model. FIG. **7** is a graph depicting the resulting glucose sensor measurements over the course of approximately two months. The small points in FIG. **7** depict glucose concentrations measured by the sensor and the large points depict glucose concentrations measured by separate blood glucose assays. The graph indicates a close correlation between the sensor glucose measurements and the blood glucose measurements.

Example 4

MED-4840/PLURONIC® F-127 Diffusion Resistance Layer Interference Properties

A MED-4840/PLURONIC® F-127 membrane was manufactured using 8.4% PLURONIC® and 3.7% DCP. This membrane was placed over two-layer membrane having an electrode layer and an enzyme layer. The combined membrane layers were installed on a wholly implantable glucose sensor. The sensor was placed into a 2L bath filled with PBS (phosphate buffered saline). The continuously stirred bath was brought to 37° C. and the sensor allowed to equilibrate for a minimum of 1 hour until the sensors reached a flat line continuous baseline signal. Acetaminophen was then added to the bath to a dilution of 3.8 mg/dl. The sensor was then allowed to equilibrate over 1 hour while measurements were continuously recorded from the sensor. FIG. **8** is a graph show the sensor signal over the course of the hour. The graph indicates that the signal changed by less than 1%. Thus, the sensor was substantially insensitive to the presence of acetaminophen, indicating that the membrane substantially reduces transport of acetaminophen therethrough.

As a comparative example, a wholly implantable glucose sensor with a membrane not including a silicone/hydrophilic-hydrophobic polymer blend was tested. The membrane in this sensor included a three-layer membrane having an electrode layer, an enzyme layer, and a polyurethane diffusion resistance layer. A porous silicone cell disruptive layer was added on top. The sensor was placed into a 2L bath filled with PBS (saline). The continuously stirred bath was brought to 37° C. and the sensor allowed to equilibrate for a minimum of 1 hour until the sensors reached a flat line continuous baseline signal. Acetaminophen was then added to the bath to a dilution of 3.8 mg/dl. The sensor was then allowed to equilibrate over 1 hour while measurements were continuously recorded from the sensor. FIG. **9** is a graph show the sensor signal over the course of the hour. The graph indicates that the signal changed by more than 15% after introduction of the acetaminophen. Thus, without the silicone/hydrophilic-hydrophobic polymer blend sensor was sensitive to the acetaminophen interferant.

Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in U.S. Pat. Nos. 4,994,167; 4,757,022; 6,001,067; 6,741,877; 6,702,857; 6,558,321; 6,931,327; and U.S. Pat. No. 6,862,465.

Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in U.S. Publication No. US-2005-0176136-A1; U.S. Publication No. US-2005-0251083-A1; U.S. Publication No. US-2005-0143635-A1; U.S. Publication No. US-2005-0181012-A1; U.S. Publication No. US-2005-0177036-A1; U.S. Publication No. US-2005-0124873-A1; U.S. Publication No. US-2005-0051440-A1; U.S. Publication No. US-2005-0115832-A1; U.S. Publication No. US-2005-0245799-A1; U.S. Publication No. US-2005-0245795-A1; U.S. Publication No. US-2005-0242479-A1; U.S. Publication No. US-2005-0182451-A1; U.S. Publication No. US-2005-0056552-A1; U.S. Publication No. US-2005-0192557-A1; U.S. Publication No. US-2005-0154271-A1; U.S. Publication No. US-2004-0199059-A1; U.S. Publication No. US-2005-0054909-A1; U.S. Publication No. US-2005-0112169-A1; U.S. Publication No. US-2005-0051427-A1; U.S. Publication No. US-2003-0032874; U.S. Publication No. US-2005-0103625-A1; U.S. Publication No. US-2005-0203360-A1; U.S. Publication No. US-2005-0090607-A1; U.S. Publication No. US-2005-0187720-A1;

U.S. Publication No. US-2005-0161346-A1; U.S. Publication No. US-2006-0015020-A1; U.S. Publication No. US-2005-0043598-A1; U.S. Publication No. US-2003-0217966-A1; U.S. Publication No. US-2005-0033132-A1; U.S. Publication No. US-2005-0031689-A1; U.S. Publication No. US-2004-0045879-A1; U.S. Publication No. US-2004-0186362-A1; U.S. Publication No. US-2005-0027463-A1; U.S. Publication No. US-2005-0027181-A1; U.S. Publication No. US-2005-0027180-A1; U.S. Publication No. US-2006-0020187-A1; U.S. Publication No. US-2006-0036142-A1; U.S. Publication No. US-2006-0020192-A1; U.S. Publication No. US-2006-0036143-A1; U.S. Publication No. US-2006-0036140-A1; U.S. Publication No. US-2006-0019327-A1; U.S. Publication No. US-2006-0020186-A1; U.S. Publication No. US-2006-0020189-A1; U.S. Publication No. US-2006-0036139-A1; U.S. Publication No. US-2006-0020191-A1; U.S. Publication No. US-2006-0020188-A1; U.S. Publication No. US-2006-0036141-A1; U.S. Publication No. US-2006-0020190-A1; U.S. Publication No. US-2006-0036145-A1; U.S. Publication No. US-2006-0036144-A1; and U.S. Publication No. US-2006-0016700A1.

Methods and devices that are suitable for use in conjunction with aspects of the preferred embodiments are disclosed in U.S. application Ser. No. 09/447,227 filed Nov. 22, 1999 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS"; U.S. application Ser. No. 11/280,672 filed Nov. 16, 2005, and entitled "TECHNIQUES TO IMPROVE POLYURETHANE MEMBRANES FOR IMPLANTABLE GLUCOSE SENSORS"; U.S. application Ser. No. 11/280,102 filed Nov. 16, 2005, and entitled "TECHNIQUES TO IMPROVE POLYURETHANE MEMBRANES FOR IMPLANTABLE GLUCOSE SENSORS"; U.S. application Ser. No. 11/201,445 filed Aug. 10, 2005 and entitled "SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA"; U.S. application Ser. No. 11/335,879 filed Jan. 18, 2006 and entitled "CELLULOSIC-BASED INTERFERENCE DOMAIN FOR AN ANALYTE SENSOR"; U.S. application Ser. No. 11/334,876 filed Jan. 18, 2006 and entitled "TRANSCUTANEOUS ANALYTE SENSOR"; U.S. application Ser. No. 11/333,837 filed Jan. 17, 2006 and entitled "LOW OXYGEN IN VIVO ANALYTE SENSOR".

All references cited herein are incorporated herein by reference in their entireties. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention as embodied in the attached claims.

What is claimed is:

1. A transcutaneous implantable continuous analyte sensor, comprising:
- a working electrode configured to be transcutaneously implanted; and
- a membrane disposed over at least a portion of the working electrode, the membrane comprising a blend, the blend comprising a silicone-containing polymer and a hydrophilic polymer;
- wherein the membrane is configured to reduce or block passage therethrough of acetaminophen, whereby when:
  - (1) the sensor is placed in a 2L bath filled with phosphate buffered saline, continuously stirred, brought to a temperature of 37° C., allowed to equilibrate for 1 hour until the sensor reaches a flat line continuous baseline signal; and
  - (2) acetaminophen is then added to the bath to a dilution of 3.8 mg/dL and the sensor is then allowed to equilibrate over 1 hour while measurements are continuously recorded from the sensor;
- the signal does not change by more than 1%.

2. The implantable continuous analyte sensor of claim 1, wherein the silicone-containing polymer is cross-linked with the hydrophilic polymer.

3. The implantable continuous analyte sensor of claim 1, wherein the hydrophilic polymer has a molecular weight of at least about 1,000 g/mol.

4. The implantable continuous analyte sensor of claim 1, wherein the hydrophilic polymer has a molecular weight of at least about 10,000 g/mol.

5. The implantable continuous analyte sensor of claim 1, wherein the hydrophilic polymer has a molecular weight of at least about 15,000 g/mol.

6. The implantable continuous analyte sensor of claim 1, wherein up to 25% of the silicone-containing polymer is covalently linked to the hydrophilic polymer.

7. The implantable continuous analyte sensor of claim 1, wherein up to 15% of the silicone-containing polymer is covalently linked to the hydrophilic polymer.

8. The implantable continuous analyte sensor of claim 1, wherein up to 5% of the silicone-containing polymer is covalently linked to the hydrophilic polymer.

9. The implantable continuous analyte sensor of claim 1, wherein the hydrophilic polymer comprises a material selected from the group consisting of polyvinylpyrrolidone, polyhydroxyethyl methacrylate, polyvinylalcohol, polyacrylic acid, polyethers, and copolymers thereof.

10. The implantable continuous analyte sensor of claim 1, wherein the membrane is configured to inhibit transport of an interfering species therethrough.

11. The implantable continuous analyte sensor of claim 1, wherein the membrane is configured to reduce a flux of an analyte therethrough.

12. The implantable continuous analyte sensor of claim 1, wherein the membrane comprises an enzyme configured to react with an analyte.

13. The implantable continuous analyte sensor of claim **1**, wherein the membrane further comprises a polyanionic polymer.

14. A transcutaneous implantable continuous analyte sensor, comprising:

a working electrode configured to be transcutaneously implanted; and

a membrane disposed over the working electrode, the membrane comprising:

a first domain comprising a blend of a silicone-containing polymer and a hydrophilic polymer, the first domain configured to reduce permeability of acetaminophen;

a second domain comprising an enzyme configured to react with an analyte; and

a third domain comprising ionic components configured to reduce permeability of the third domain to an interfering species;

wherein the first domain is configured to reduce or block passage therethrough of acetaminophen, whereby when:

(1) the sensor is placed in a 2L bath filled with phosphate buffered saline, continuously stirred, brought to a temperature of 37° C., allowed to equilibrate for 1 hour until the sensor reaches a flat line continuous baseline signal; and

(2) acetaminophen is then added to the bath to a dilution of 3.8 mg/dL and the sensor is then allowed to equilibrate over 1 hour while measurements are continuously recorded from the sensor;

the signal does not change by more than 1%.

15. The implantable continuous analyte sensor of claim **14**, wherein the first domain is positioned more distal to the working electrode than the second domain, and wherein the second domain is positioned more distal to the working electrode than the third domain.

16. The implantable continuous analyte sensor of claim **14**, wherein the hydrophilic polymer comprises a material selected from the group consisting of polyvinylpyrrolidone, polyhydroxyethyl methacrylate, polyvinylalcohol, polyacrylic acid, polyethers, and copolymers thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,543,184 B2
APPLICATION NO. : 13/277997
DATED : September 24, 2013
INVENTOR(S) : Boock et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

In column 2 (page 7 item 56) at line 30, Under Other Publications, Change "hypoglycaemic" to --hypoglycemic--.

In column 2 (page 7 item 56) at line 46, Under Other Publications, Change "Senso" to --Sensor--.

In column 1 (page 8 item 56) at line 46, Under Other Publications, Change "implntable," to --implantable,--.

In column 1 (page 8 item 56) at line 51, Under Other Publications, Change "Enzymlology," to --Enzymology,--.

In column 1 (page 8 item 56) at line 71, Under Other Publications, Change "your and your patients." to --you and your patients.--.

In column 1 (page 9 item 56) at line 35, Under Other Publications, Change "ultrasmall" to --ultra-small--.

In column 1 (page 9 item 56) at line 43, Under Other Publications, Change "Aniodic" to --Anodic--.

In column 2 (page 9 item 56) at line 48, Under Other Publications, Change ":593-97." to --:S93-97.--.

In column 1 (page 10 item 56) at line 4, Under Other Publications, Change "Electronanalysis" to --Electroanalysis--.

In column 1 (page 10 item 56) at line 26, Under Other Publications, Change ":513-8." to --:S13-8.--.

In column 1 (page 10 item 56) at line 27, Under Other Publications, Change "amperometeric" to --amperometric--.

Signed and Sealed this
Thirteenth Day of May, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

In column 2 (page 10 item 56) at line 17, Under Other Publications, Change "Apllied" to --Applied--.

In column 2 (page 10 item 56) at line 62, Under Other Publications, Change "Bromedical" to --Biomedical--.

In column 1 (page 11 item 56) at line 49, Under Other Publications, Change "Subcutaenous" to --Subcutaneous--.

In column 1 (page 11 item 56) at line 66, Under Other Publications, Change "Membran," to --Membrane,--.

In column 2 (page 11 item 56) at line 31, Under Other Publications, Change "pancrease" to --pancreas--.

In column 1 (page 12 item 56) at line 3, Under Other Publications, Change "Membrance" to --Membrane--.

In column 1 (page 12 item 56) at line 51, Under Other Publications, Change "Tranducers" to --Transducers--.

In the Specifications

In column 4 at line 60, Change "andrenostenedione;" to --androstenedione;--.

In column 5 at line 8, Change "diptheria/" to --diphtheria/--.

In column 5 at line 15, Change "perioxidase;" to --peroxidase;--.

In column 5 at line 24, Change "sissomicin;" to --sisomicin;--.

In column 5 at lines 28-29, Change "Giardia duodenalisa," to --Giardia duodenalis,--.

In column 5 at line 36, Change "Trepenoma pallidium," to --Treponema pallidum,--.

In column 5 at line 37, Change "stomatis" to --stomatitis--.

In column 5 at line 58, Change "(barbituates," to --(barbiturates,--.

In column 9 at lines 15-16, After "Heller et al.;" delete "U.S. patent to".

In column 9 at line 20, Change "there" to --their--.

In column 10 at line 29, Change "(2H+)," to --($2H^+$),--.

In column 10 at line 29, Change "(2e-)," to --($2e^-$),--.

In column 17 at line 28, Change "SYNPERONICS®" to --SYNTRONICS®--.

In column 18 at line 1, Change "posses" to --possess--.

In column 19 at line 30, Change "phospazenes," to --phosphazenes,--.

In column 19 at line 34, Change "hydyoxyethyl" to --hydroxyethyl--.

In column 20 at line 39, Change "phospazenes," to --phosphazenes,--.

In column 20 at line 43, Change "hydyoxyethyl" to --hydroxyethyl--.

In column 22 at line 15, Change “phospazenes,” to --phosphazenes,--.

In column 22 at line 19, Change “hydyoxyethyl” to --hydroxyethyl--.

In column 28 at line 65, Change “stiffing” to --stirring--.

In column 29 at line 4, Change “stiffing” to --stirring--.

In column 31 at line 22, Change “US-2006-0016700A1.” to --US-2006-0016700-A1.--.

专利名称(译)	有机硅基膜用于植入式葡萄糖传感器		
公开(公告)号	US8543184	公开(公告)日	2013-09-24
申请号	US13/277997	申请日	2011-10-20
[标]申请(专利权)人(译)	德克斯康公司		
申请(专利权)人(译)	DEXCOM INC.		
当前申请(专利权)人(译)	DEXCOM INC.		
[标]发明人	BOOCK ROBERT RIXMAN MONICA		
发明人	BOOCK, ROBERT RIXMAN, MONICA		
IPC分类号	A61B5/05 A61B5/00		
CPC分类号	A61B5/14532 A61B5/14865 A61B5/6848 B33Y70/00 C08G77/12 C08G77/20 C08G77/46 C08L83/04 C08L2666/14		
其他公开文献	US20120035445A1		
外部链接	Espacenet USPTO		

摘要(译)

描述了包含硅氧烷聚合物的膜系统用于可植入分析物传感器。膜系统的一些层可包含硅氧烷聚合物与亲水聚合物的共混物，例如三嵌段聚（环氧乙烷）-聚（环氧丙烷）-聚（环氧乙烷）聚合物。这种聚合物共混物提供高氧溶解度和含水分析物溶解度。