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Fabrication and Simulation of Glucose Sensor using Finite Element Method

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Abstract— Electrochemical glucose sensors use amperometric methods to measure the concentration of glucose in a sample. This example models the diffusion of glucose and ferri/ferrocyanide redox mediators in a unit cell of electrolyte above an interdigitated electrode. The sensor gives a linear response over a suitable range of concentrations. The Electro- analysis interface is used to couple the chemical species transport to the electrolysis at the working and counter electrodes, and the glucose is oxidized by the glucose oxidase enzyme in solution according to Michaelis-Menten kinetics.

Keywords— Glucose sensor, Finite Element Method, Model Geometry

I. Glucose Sensor

Glucose sensors used to measure the blood glucose concentration of a patient and are an important part of managing diabetes mellitus. Type 1 and type 2 diabetes are the most common forms of diabetes. Type 1 diabetes isusually diagnosed in children and young adults and ac- counts for about 5The majority of blood glucose sensors, or glucosemeters, are categorized as amperometric sensors.

Introduction

Glucose sensing is one of the most widespread and commercially successful uses of electro-analysis. In an electrochemical glucose sensor, the concentration of glucose in a sample is measured using amperometry; that is, the measurement of an electric current. An applied voltage causes the oxidation of glucose, and the current due to this oxidationis measured at the electrode. In a well-designed glucose sensor, there is a linear relationship between the glucose concentration and the current, enabling a calibrated measurement. Typically, the oxidation of glucose does not occur directly at the working electrode where current is measured. Instead, the reaction is accomplished by a chemical oxidant and accelerated by a biological enzyme such asglucose oxidase (GOx), which makes the sensor specific

to glucose and independent of the concentration of other oxidizable species that may be present in the analyte solution. The reduced form of the oxidant, after its reaction with glucose, can be re-oxidized directly at the electrode. In nature, the oxidant is oxygen, but this suffers from slow kineticsand the rate of oxidation is perturbed by the oxygen concentration dissolved from atmosphere into the analyte solution. In- steadan inorganic oxidant with fast electrode kinetics, such as the hexacyanoferrate (III) anion (commonly, "ferricyanide"), is suitable for use in a glucose sensor, since the measured currentis made independent of oxygen concentration and is notlimited by slow electrode kinetics (Ref.1). This example demonstrates a steady-state analysis of the current drawn in a unit cell of solution above an interdigitated electrode, where the counter electrode reacts ferricyanide to ferrocyanide. The linearity of the response of the sensor is demonstrated for a typical range of glucose concentrations.

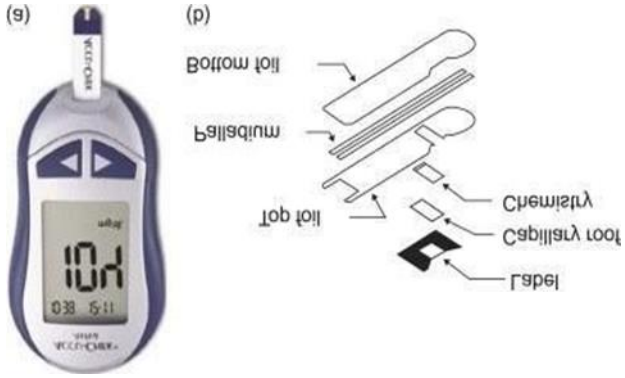

Fig.1. Glucose Meter.

In amperometric glucose sensors, reducing property of glucose is measured as a current. Sensors contain electrodes to measure the current generated by an enzymatic reactionusually between glucose, an enzyme, and a mediator. Use of glucose oxidase (GOx or GOD) has become the gold standard for glucose sensing [10,11]. The initial concept of glucose enzyme electrodes, where a thin layer of GOx was entrapped via a semipermeable membrane, was introduced by Clark and Lyons [12]. Sensing was based on the measurement of the oxygen consumed by the enzyme-catalyzed reaction In this method, glucose reacts with the enzyme GOx(ox). The reduced enzyme GOx(red)then reduces two mediator M(ox) ions to M(red), which is oxidized back to M(ox) at the electrode surface. Theoxidation process is measured as the current by the electrode. However, for this type of early glucose biosensors, a high operation potential is required to perform the amper- ometric measurement of hydrogen peroxide. Improved methods utilize artificial mediators in- stead of oxygen to transfer electrons between the GOx and the electrode [8]. Reduced mediators are formed and reoxidized at the electrode, providing an electrical signal to be measured.

A blood glucose test is typically performed by pricking the finger to draw blood, which is then applied to a disposable "test-strip". Figurure shows a typical glucose meter and a teststrip. Each strip includes layers of electrodes, spacers, immobilized enzymes assembled in a small package. Continued research and development have worked to reduce the overall size of the sensor itself and reduce the amount of blood required for an accurate measurement (L)

A. GLUCOSE METER

A glucose meter is a medical device for determining the approximate concentration of glucose in the

blood. It can also be a strip of glucose paper dipped into a substance and measured to the glucose chart. It is a key element of home blood glucose monitoring (HBGM) by people with diabetes mellitus or hypoglycemia. A small drop of blood, obtained by pricking the skin with a lancet, is placed on a disposable teststrip that the meter reads and uses to calculate the blood glucose level. The meter then displays the level in units of mg/dl or mmol/l.

Since approximately 1980, a primary goal of the management of type 1 diabetes and type 2 diabetes mellitus has been achieving closer-to-normal levels of glucose in theblood for as much of the time as possible, guided by HBGMseveral times a day. The benefits include a reduction in the occurrence rate and severity of long-term complications from hyperglycemia as well as a reduction in the short-term,potentially life-threatening complications of hypoglycemia.

There are several key characteristics of glucose meterswhich may differ from model to model:

- Size: The average size is now approximately the size of the palm of the hand, although hospital meters can be the size of a remote control. They arebattery-powered.
- strips: A consumable element containing chemicalsthat react with glucose in the drop of blood is used for each measurement. For some models this element is a plastic test strip with a small spot impregnated with glucose oxidase and other components. Each strip is used once and then discarded. Instead of strips, some models use discs, drums, or cartridges that contain the consumable material for multiple tests.
- Coding: Since test strips may vary from batch to batch, some models require the user to manually enter in a code found on the vial of test strips or on a chip that comes with the test strip. By entering the coding or chip into the glucose meter, the meter willbe calibrated to that batch of test strips. However, ifthis process is carried out incorrectly, the meter reading can be up to 4 mmol/L (72 mg/dL) inaccurate. The implications of an incorrectlycoded meter can be serious for patients actively managing their diabetes. This may place patients at increased risk of hypoglycemia. Alternatively, some test stripscontain the code information in the strip; others havea microchip in the vial of strips that can be inserted into the meter. These last two methods reduce the possibility of user error. One Touch has standardized their test strips around a single code number, so that, once set, there is no need to further change the code in their older meters, and in some of their newer meters, there is no way to change thecode.
- Volume of blood sample: The size of the drop of blood needed by different models varies from 0.3 to1 l. (Older models required larger blood samples, usually defined as a ”hang- ing drop” from thefingertip.) Smaller volume requirements reduce the frequency of un- productive pricks.
- Alternate site testing: Smaller drop volumes have enabled ”alternate site testing” – prick- ing the forearms or other less sensitive areas instead of the fingertips. This type of testing should only be used when blood glucose levels are stable, such as when before meals, when fasting, or just before going to sleep.[9] Testing times: The times it takes to read a test strip may range from 3 to 60 seconds for different models.
- Display: The glucose value in mg/dl or mmol/l is displayed on a digital display. The preferred measurement unit varies by country: mg/dl are preferred in the US, France, Japan, Israel, and

India. mmol/l are used in Canada, Australia and China. Germany is the only country where medical professionals routinely operate in both units of measure. (To convert mmol/l to mg/dl, multiply by 18. To convert mg/dl to mmol/l, divide by 18.) Manymeters can display either unit of measure; there have been a couple of published in- stances[citation needed] in which someone with diabetes has been misled into the wrong action by assuming that a reading in mmol/l was really a very low reading in mg/dl, or the converse. In general, if a value is presented with a decimal point, it is in mmol/l,without a decimal it is most likely mg/dl.

- Glucose vs. plasma glucose: Glucose levels in plasma (one of the components of blood)
- are higher than glucose measurements in whole blood; the difference is about 11
- Clock/memory: Most meters now include a clock that is set by the user for date and time and a memory for past test results. The memory is an important aspect of diabetes care, as it enables the personwith diabetes to keep a record of management and look for trends and patterns in blood glucose levels over days and weeks. Most memory chips can display an average of recent glucose readings. A known deficiency of all current meters is that the clock is often not set to the correct time (i.e., due to time changes, static electricity, etc.) and therefore has the potential to misrepresent the time of the past test results making pattern management difficult.
- Data transfer: Many meters now have more sophisticated data handling capabilities.

Many can be downloaded by a cable or infrared to a computer that has diabetes man- agement software to display the test results. Some meters allow entry of additional data throughout the day, such as insulin dose, amounts of carbohydrates eaten, or exercise. A number of meters have been combined with other devices, such as insulin injection devices, PDAs, cellular transmitters,[11] and Game Boys.[12] A radio link to an insulin pump allows automatic transfer of glucose readings to a calculator that assists the wearer in deciding on an appropriate insulin dose.

Many glucose meters employ the oxidation of glucose to gluconolactone catalyzed by glucose oxidase (sometimes known as GOx). Others use a similar reaction catalysed instead by another enzyme, glucose dehydrogenase (GDH). This has the advantage of sensitivity over glucose oxidase butis more susceptible to interfering reactions with other substances.

The first-generation devices relied on the same colorimetric reaction that is still used nowa- days in glucose test strips for urine. Besides glucose oxidase, the test kit contains a benzidine derivative, which is oxidized to a blue polymer bythe hydrogen peroxide formed in the oxidation reaction. The disadvantage of this method was that the test strip had to be developed after a precise interval (the blood had to be washedaway), and the meter needed to be calibratedfrequently.

Most glucometers today use an electrochemical method. Test strips contain a capillary that sucks up a reproducible amount of blood. The glucose in the blood reacts with an enzyme elec- trode containing glucose oxidase (or dehydrogenase). The enzyme is reoxidized with an excess of a mediator reagent, such as a ferricyanide ion, a ferrocene derivative or osmium bipyridyl complex. The mediator in turn is reoxidized by reaction at the electrode, which generates an electric current. The total charge passing through the electrode is proportional to the amount of glucose in the blood that has reacted with theenzyme. The coulometric method is a technique where the total amount of charge generated

by the glucose oxidation reaction is measured over a period of time. The amperometric method is used by some meters and measures the electric current generated at a specific point in time by the glucose reaction. This is analogous to throwing a ball and using the speed at which it is travelling at a point in time to estimate how hard it was thrown. The coulometric method can allow for variable test times, whereas the test time on a meter using the amperometric method is always fixed. Both methods givean estimation of the concentration of glucose in the initial blood sample.

The same principle is used in test strips that have been commercialized for the detection of diabetic ketoacidosis (DKA). These test strips use a beta-hydroxybutyrate-dehydrogenase enzyme instead of a glucose oxidizing enzymeand have been used to detect and help treat some of the complications that can result from prolonged hyperglycemia. Blood alcohol sensors using the same approach, but with alcohol dehydrogenase enzymes, have been tried and patented but have not yet been successfully commercially developed.

II. MODEL DEFFINATION

The model contains a single 2D domain representing a 100 m-wide unit cell of solution above an interdigitated electrode. The real geometry is a periodic repetition of this unit cell in the x-direction. The cell and electrode are assumed to extend sufficiently far out-of-plane of the model that the 2D approximation is suitable. At the top of the unit cell is a bulk boundary where the concentrations are assumed to equal those in the bulk solution of the analyte. At the bottom of the unit cell, the y 0 axis is divided by fourpoints into separate electrode and insulator boundaries. The anode (working electrode) is at the centerof the cell in the range

37.5 m ¡ x ¡ 62.5 m. unit cell contains half of each of the two neighboring cathodes (counter electrodes) in the ranges x ¡12.5 m and x ¿ 87.5 m. Between the anode and cathode surfaces, a solid insulating material is present.

DOMAIN EQUATIONS

A large quantity of supporting electrolyte is present. This is inert salt added in electroanalytical experiments to increase the conductivity of the electrolyte without otherwise interfering with the reaction chemistry. Under these conditions, the resistance of the solution is sufficiently low that the electric field is negligible, and we can assume a constant electrolyte potential l = 0. The Electroanalysis interface implements chemical species transport equations to describe the diffusion of the chemical species. The domain equation is the diffusion equation (also known as Fick's 2nd law). At steady-state, this reduces to: Dici= 0 for each species

i. In this model three species are modeled: the active redox couple— ferricyanide and ferrocyanide anions—as well as theconcentration of the glucose analyte.

Here, the parameter Vmax is the maximum rate of the enzyme-catalyzed reaction, depending on the quantity of enzyme available, and the parameter Km is a characteristic Michaelis-Menten coefficient. At large glucose concentration, the rate becomes independent of the glucose concentration and solely depends on the enzyme kinetics.

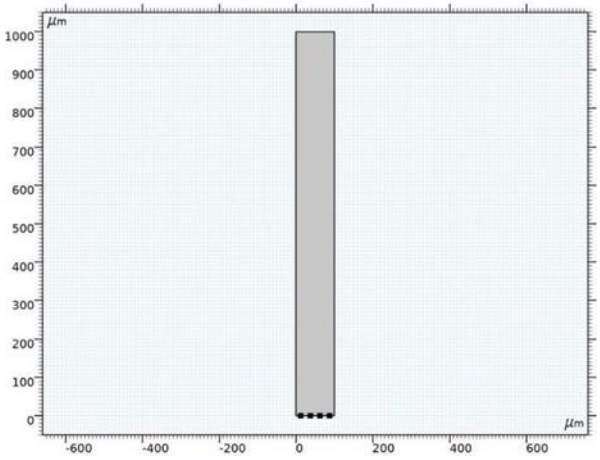

Fig. 2 Model Geometry.

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$$\nabla \cdot (D_i \nabla c_i) = 0$$

for each species i. In this model three species are modeled: the active redox couple— ferricyanide and ferrocyanide anions—as well as the concentration of the glucose analyte species. We ignore the products of the glucose oxidation since they do not affect the behavior of the sensor. The enzyme-mediated reaction of the glucose with the ferricyanide anion occurs in the solution phase above the electrode:

The rate of this reaction (mol/m3) is given by a Michaelis–Menten rate law as

$$v = \frac{\mathrm{d[P]}}{\mathrm{d}t} = \frac{V_{\max}[\mathrm{S}]}{K_{\mathrm{M}} + [\mathrm{S}]}.$$

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BOUNDARY EQUATIONS

At the bulk boundary (y = 1 mm), we assume a uniform concentration of each chemical species equal to its bulk concentration. The glucose concentration here is equivalent to that in the an- alyte mixture being measured; the ferricyanide:ferrocyanide ratio here is 50 000:1, with the ferricyanide anion present in bulk in a concentration of 50 mM. Because the analytical pro- cess is oxidizing with respect to the glucose analyte, more oxidant must be supplied. At the insulating (inert) surfaces, the

normal fluxes of all species are equal to zero, since this surface is impermeable and no species reacts there. At the electrode boundaries, current is drawn from the interconversion of ferrocyanide and ferricyanide. By convention, electrochemical reactions are written in the reductive direction: ferri + e– ferro The stoichiometric coefficient is –1 for ferri- cyanide, the "reactant" in the reductive direction, and +1 for ferrocyanide, the "product" in the reductive direction. This formulation is consistent at the anode also, although here the reaction proceeds favorably in the opposite, oxidative direction. The number of electrons transferred, n, equals one. The current density for this reaction is given by the electroanalytical Butler–Volmer equation for an oxidation:

RT RT in which k0 is the heterogeneous rate constant of the reaction, c is the cathodic transfer coefficient, and is the overpotential at the working electrode. According to Faraday's laws of electrolysis, the flux of the reactant and product species are proportional to the current density drawn: i –n J = ————- nF This is expressed in the Electrode Surface boundary condition. The total current recorded at the electrode can be extracted by integrating the local current density across the electrode surface. It is not sufficient to simply multiply by the area of the electrode, because the current density may be non- uniform. An Integration Component Coupling is used to define an electrode current variable according to: Iel = ilocdA where the integration is performed over the area of theworking electrode. The working electrode (anode) is held at

+0.4 V vs. the ferro/ferricyanide redox couple. The counter electrode is constrained to deliver an opposite current to the anode.

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$$j = j_0 \cdot \left\{ \exp\left[\frac{\alpha_a z F \eta}{RT}\right] - \exp\left[-\frac{\alpha_c z F \eta}{RT}\right] \right\}$$

$I_{el} = \int i_{loc} dA$

where the integration is performed over the area of the

working electrode. The working electrode (anode) is held at

+0.4 V vs. the ferro/ferricyanide redox couple. The counter electrode is constrained to deliver an opposite current to the anode.

Geometry

- This is the geometry of glucose sensor strip whichincludes
- Total 8 boundaries
- 4 edges
- It is positioned horizontally of x and yplane
- unit cell contains half of each of the two neighbouring cathodes (counter electrodes) in theranges x < 12.5 µm and x > 87.5 µm. Between theanode and cathode surfaces, a solid insulating material is present
- (for e.g.silica)

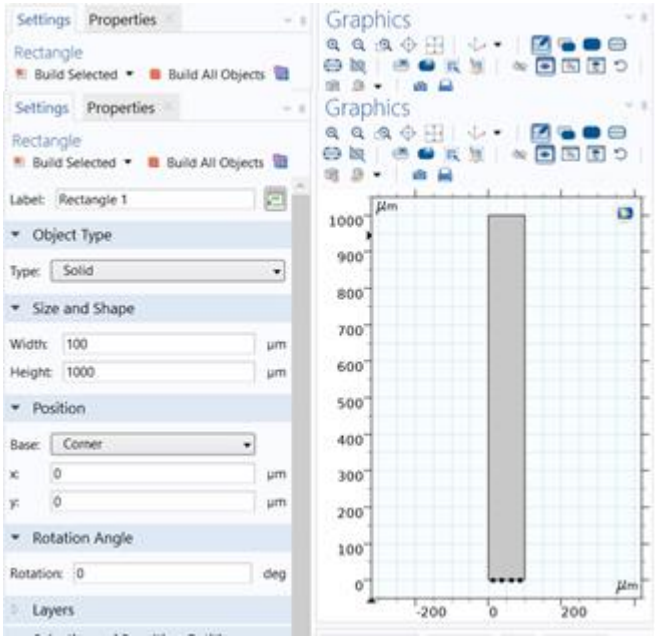

Fig.3. Geometry of Glucose Sensor strip

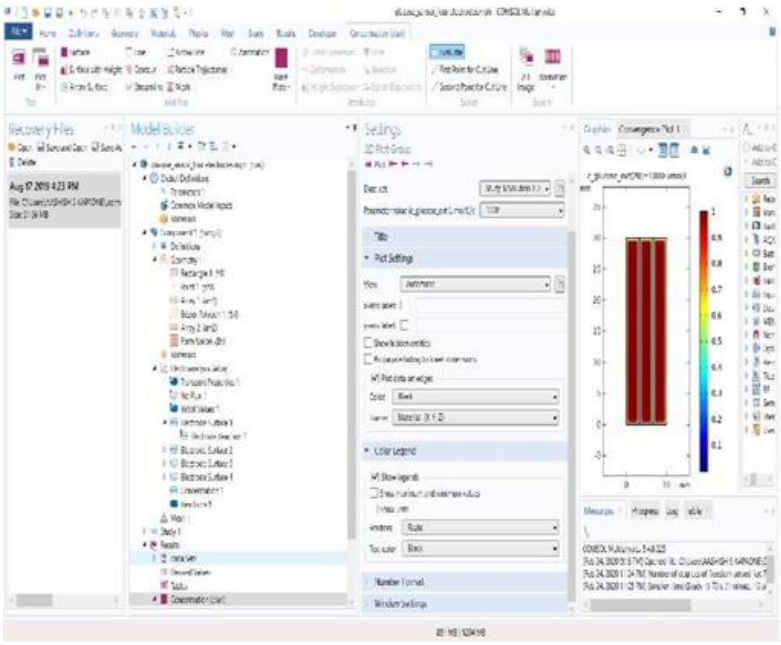

Fig.4. Redesigned Electrodes

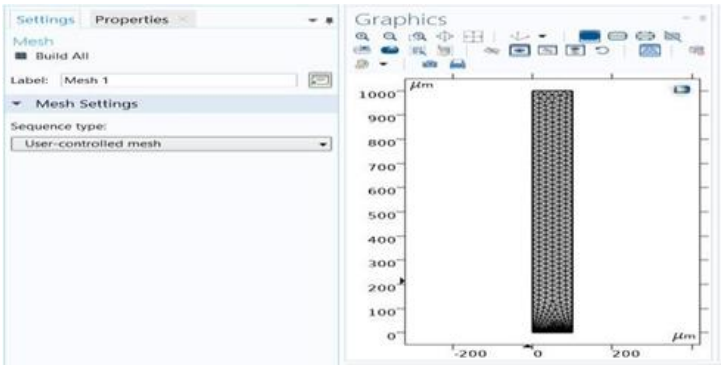

Fig.5. Meshing

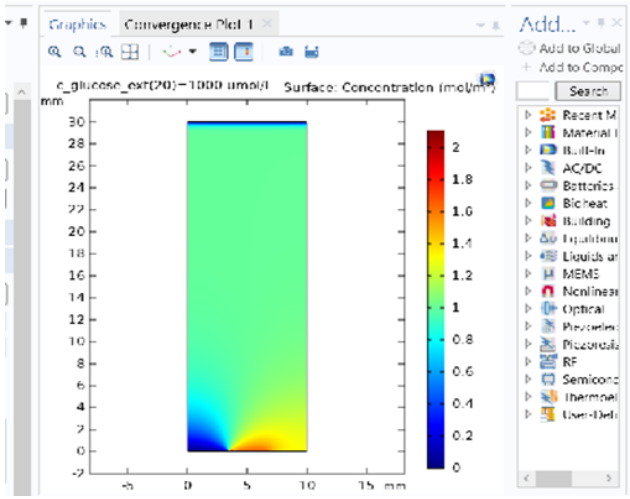

Fig.6. Ferrocyanide concentration for an external glucose concentration of 1 mol/m3.

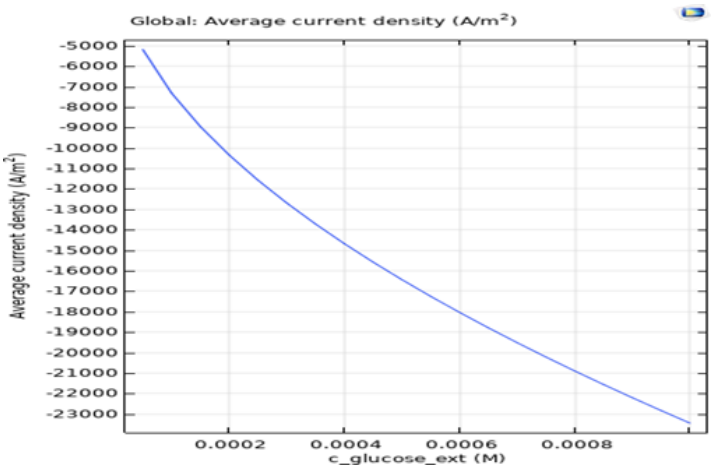

Fig. 7. Current density versus glucose concentration.

Results

Figure 6 shows a typical concentration profile for the ferrocyanide ion in the unit cell. Ferro-cyanide is generated in the solution between the electrodes and bulk by the enzyme- catalyzed oxidation of glucose. It react sat the anode in the center of the unitcell to provide the working electrode current used to measure the concentration of glucose. Ferrocyanide is regenerated at the cathode counter electrodes at the left and rightof the cell.

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