Modeling an Enzyme Based Electrochemical Blood Glucose Sensor

Stephen A. Mackintosh[*1], James I. Rodgers[1], Stephen P. Blythe[1]
[1]Lifescan Scotland Ltd, Inverness, IV2 3ED, Scotland.
*Corresponding author email: smackin3@its.jnj.com

Abstract: This paper describes the modelling of a blood glucose sensor using COMSOL Multiphysics. Chemical species interaction and diffusion, coupled with electrochemical oxidation of multiple blood species produced a powerful working model used in developing and refining a range of blood glucose sensors for the commercial market.

Keywords: diabetes, electrochemistry, diffusion, blood, biosensor

1. Introduction

Self monitoring blood glucose (SMBG) test systems are essential in the management and control of diabetes[1]. This paper describes the modeling of the glucose dependent, signal-generating, reactions that occur within the blood-filled reaction chamber of an example SMBG test strip during a blood glucose concentration measurement.

Figure 1. Blood Glucose Measurement using SMBG strip and meter

This model has built upon legacy work at Lifescan Scotland initially based around analytical solutions to partial differential equations on simplified domains and boundary conditions. Later work extended these models to include multiple species, chemical interactions and full electrochemistry. This COMSOL model has allowed additional flexibility in rapid model based prototyping, involving alternative chamber geometries and/or reagent compositions.

2. Model Development

2.1 Geometry and Reagents

The simplified geometry comprises two electrodes, a working and counter, over-coated with a thin deposited reagent layer composed of an oxidoreductase enzyme and a redox active electrochemical mediator, all located within a sample capillary volume, which is filled with a blood sample.

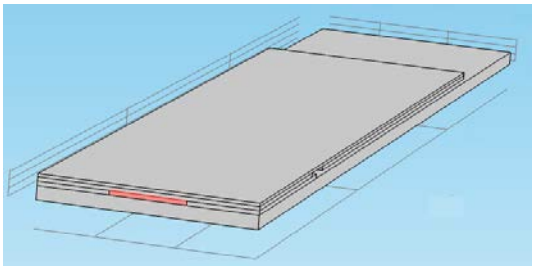

Figure 2a. Test strip with capillary volume highlighted in red.

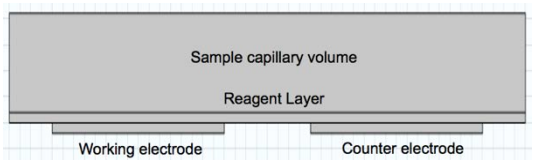

Figure 2b. 2D cross section of interior of capillary volume, comprising electrodes (working and counter), reagent layer and sample void.

2.2 Amperometric Reactions

The glucose analyte within blood is enzymatically oxidised to gluconolactone, with oxidised electrochemical mediator (potassium ferricyanide) being consumed, and reduced mediator (potassium ferrocyanide) being generated. This reduced ferrocyanide subsequently diffuses toward the polarized working electrode where it is electrochemically re-oxidised to ferricyanide, while an equivalent amount of the excess ferricyanide is simultaneously reduced at the counter electrode,

completing the circuit and producing an electrochemical current signal[2,3].

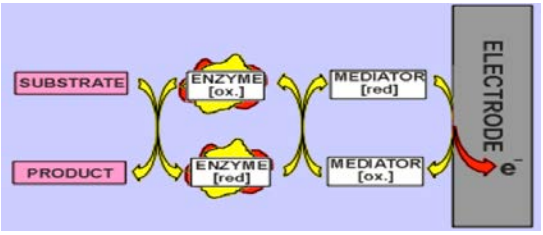

Figure 3. Mediated enzymatic electrochemical reaction.

2.3 Legacy work with analytical models

Early modeling work on this problem involved finding solutions (where possible) to partial differential equations with simplified domains and boundary conditions. Detailed chemical interactions and electrochemistry were ignored.

An example of this was the modeling of a gel layer assumed thin in comparison to the cavity height. The resulting PDE with simplified boundary conditions could be solved analytically via the application of Laplace Transforms. Here is the resulting current-time profile for such a solution:

$$I(t) = nFAC_0\sqrt{\frac{D_1}{\pi t}}\left[1+2\sum_{m=1}^{\infty}\alpha^m \exp\left\{-\frac{m^2 l^2}{D_1 t}\right\}\right]$$

Here D_1 is the diffusivity in the pad, l is the reagent thickness, A is the electrode area, F is Faraday's constant, n is the number of participating electrons, m is the summation index and

$$\alpha = \frac{1-\sqrt{D_1/D_2}}{1+\sqrt{D_1/D_2}}$$

Where D_2 is the diffusivity in the cell cavity.

The strength of this approach is the power and utility of a general solution that encapsulates the main variables of the system. The weakness is the rarity of simple solutions and the assumptions that might to be made in order to simplify domains and boundary conditions so that a solution can easily be computed.

When finite and/or complex geometries are required to describe the system, numerical models become more desirable.

2.4 Theory

The physics used to build the more complete numerical models included Fick's diffusion law[4] coupled with Michaelis-Menten based chemical interactions[5]. A Bultler-Volhmer expression was used to provide concentration dependent changes to the base driving potential of the system[6]. Conservation of mass was implicit in the system with ferrocyanide and ferricyanide ions exchanging electrons and driving the base amperometric response.

$$\frac{\partial S}{\partial t} = \frac{\partial}{\partial x}\left(D_s(x).\frac{\partial S}{\partial x}\right) \quad [4]$$

Here S represents the concentration of one of potentially many diffusing species in the simulation (for example glucose), D_s is the diffusion coefficient of this species (which may vary across the spatial domain according to the materials employed), x is the generic space vector and t is time.

$$v = \frac{dP}{dt} = \frac{V_{max}S}{K_m + S} \quad [5]$$

Here P is the concentration of a generated product, V_{max} is the characteristic limiting rate of the enzyme-substrate reaction, K_m is the Michaelis-Menten constant for the enzyme-substrate combination and S is the concentration of substrate.

$$i_{loc} = i_0\left(C_R \exp\left(\frac{\alpha_a F\eta}{RT}\right) - C_O \exp\left(\frac{-\alpha_c F\eta}{RT}\right)\right) \quad [6]$$

Here i_o is the electrode-redox couple exchange current density, C_R is the concentration of reduced species, C_o is the concentration of oxidized species, R is the universal gas constant,

F is Faraday's constant, T is the temperature in kelvin, α is the transfer coefficient, η is the over-potential.

3. Use of COMSOL Multiphysics

Concentration of diluted species, secondary current distribution (battery and fuel cells), chemical reactions, and other boundary conditions using the custom mathematical equation editor were employed. Mesh generation was automated via Comsol's physics controlled mesh setting, with extra refinement nodes added near each electrode-electrolyte boundary.

1, 2 and 3D versions of the models were developed allowing rapid solutions for more simplified symmetric geometries. 2 and 3D versions were employed where specific detail was required to capture the impact of geometric anomalies on the system.

Solutions were always time dependent due to the finite test times required from commercial biosensors (typically 5 seconds or thereabouts).

4. Results

The model has been used to characterise existing and new biosensor geometries. Outputs such as the correlation between analyte concentration and current signal at different time periods, and using alternate layouts, has aided with cost effective optimisation of device chemistry and geometry. The detailed concentration gradients produced have increased understanding of signal features and the impact of design changes thereupon.

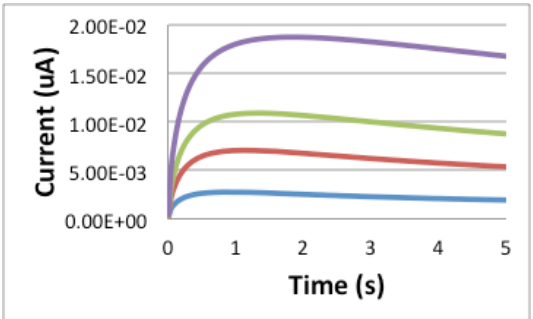

Figure 4. Model chronoamperometric response current at concentrations of 50, 150, 250 and 500mg/dL glucose. Higher concentrations show greater current response in the plot.

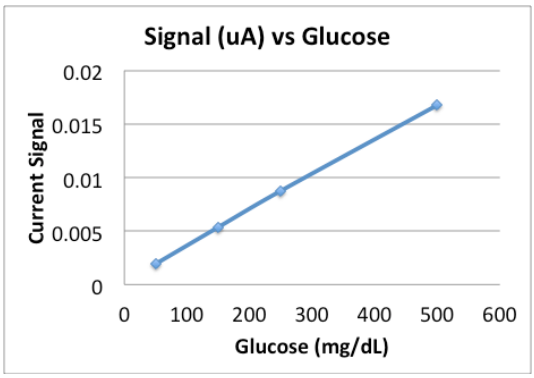

Figure 5. Linearity plot showing sensor response against glucose.

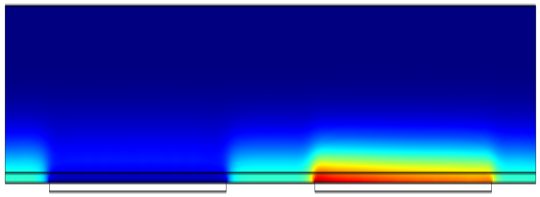

Figure 6. Concentration profile showing the distribution of ferrocyanide in the cell at a given time point. Local deficiency of ferrocyanide over the working electrode and its regeneration next to the counter electrode is clearly evident.

5. Conclusions

Results achieved in this simulation were in general agreement with experimental work using existing systems and prototypes. Whilst such models can never be used to facilitate decisions on the safety or efficacy of medical devices released to the public, they are expected to prove a useful tool in the design and optimisation of such devices in the future.

6. References

1. American Diabetes Association, Standards of Medical Care in Diabetes 2012, Section 5(c).

2. Asha Chaubey *, B.D. Malhotra, Mediated Biosensors, Biosensors & Bioelectronics 17 (2002) 441–456

3. Mediated Electrochemistry – A Practical Approach to Biosensing, Cardosi M F & Turner

APF in Advances in Biosensors Volume 1 (1991) JAI Press Ltd

4. A. J. Bard & L. R. Faulkner, Electrochemical Methods 2nd Ed, Page 148-155

5. Menten, L.; Michaelis, M.I. (1913), "Die Kinetik der Invertinwirkung", *Biochem Z* 49: 333–369

6. A. J. Bard & L. R. Faulkner, Electrochemical Methods 2nd Ed, Page 92-107

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