Published in final edited form as:

Anal Bioanal Chem. 2010 October ; 398(4): 1695–1705. doi:10.1007/s00216-010-4097-6.

Modeling the relative impact of capsular tissue effects on implanted glucose sensor time lag and signal attenuation

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Abstract

Little is known mechanistically about why implanted glucose sensors lag behind blood glucose levels in both the time to peak sensor response and the magnitude of peak sensor response. A mathematical model of glucose transport from capillaries through surrounding tissue to the sensor surface was constructed to address how different aspects of the tissue affect glucose transport to an implanted sensor. Physiologically relevant values of capsule diffusion coefficient, capsule porosity, cellular glucose consumption, capsule thickness, and subcutaneous vessel density were used as inputs to create simulated sensor traces that mimic experimental instances of time lag and concentration attenuation relative to a given blood glucose profile. Using logarithmic sensitivity analysis, each parameter was analyzed to study the effect of these variables on both lag and attenuation. Results identify capsule thickness as the strongest determinant of sensor time lag, while subcutaneous vessel density and capsule porosity had the largest effects on attenuation of glucose that reaches the sensor surface. These findings provide mechanistic insight for the rational design of sensor modifications that may alleviate the deleterious consequences of tissue effects on implanted sensor performance.

Keywords

Biomaterials; Biosensors; Modeling

Introduction

The Center for Disease Control estimates that over 23 million Americans suffer from diabetes and reports that more than 200,000 diabetics die each year from disease-related complications, making diabetes the seventh leading cause of death in the United States [1]. Those afflicted also live with an increased risk of heart disease, stroke, high blood pressure, blindness, kidney failure, and neurological disorders [1].

The standard of care for managing diabetes is monitoring blood glucose levels using the “finger prick” method. Unfortunately, reports have shown that only 30% of type 1 diabetics and 20% of type 2 diabetics on insulin treatment regularly check their blood glucose levels more than once a day [2]. Additionally, single finger prick measurements are dependent on the time of administration. Measurements taken during the waking hours cannot identify trends in blood glucose levels nor can they identify hypoglycemic events that typically occur during sleep.

Achieving reliable continuous glucose monitoring using implanted glucose sensors has been a goal of the diabetes community for decades, as percutaneous sensors for continuous glucose monitoring have been marketed to the public for years. Although percutaneous glucose sensor technology has shown robust selectivity and sensitivity in calibration tests, obstacles still exist in making it a viable alternative to finger prick systems. The Food and Drug Administration (FDA) has yet to approve invasive technologies for longer than a week. Medtronic’s current measurement paradigm, the implantable CGMS System Gold™ has been approved for 3-day use by the FDA [3,4]. Similarly, sensing systems from Abbott Labs and DexCom have only been approved for 5 and 7 days, respectively [3,4]. In addition to concerns about route to infection, an increasing body of evidence suggests that interaction between the sensor and the surrounding tissue also has a deleterious effect on percutaneous sensor lifetime [5–10].

In order to develop a sensor that can measure glucose concentrations with high sensitivity for a prolonged amount of time, the interaction between the sensor and the surrounding tissue must be considered. Once implanted, no sensor will exist as an inert object in the body since all implants will alter the surrounding environment. However, minimizing the effects of the sensor on the tissue will reduce errors associated with inflammation. A more thorough account of the foreign body response to implanted materials is presented by Anderson [11].

Figure 1a is a histological image from Yu et al. showing blood vessels embedded in a foreign body capsule that formed around an implanted glucose sensor 2 weeks post-implantation [12]. H&E staining shows the presence of red-stained blood vessels, blue-stained cells (mostly fibroblasts), and pinkstained extracellular matrix. Relative to cells and ECM, blood vessels typically occupy only a small percentage of the total tissue area surrounding an implant [10]. Figure 1b is an image from Koschwanez et al. showing a Masson’s trichrome stain of fibrous tissue that surrounded a glucose sensor 3 weeks post-implantation, with blue-stained ECM, red-stained cells, and no apparent evidence of vascularity [13]. Of particular note is the distinct layer of what is most likely inflammatory cells that lined the sensor surface. While no two encapsulation tissues exhibit the exact same histology they do share some common characteristics: (1) a porous network dominated by the extracellular matrix network, (2) little to no blood vessels, and (3) the presence of metabolically active cells.

Glucose sensors implanted or inserted in subcutaneous tissue measure interstitial glucose, which causes the glucose concentrations measured by the sensor to lag behind the peak blood glucose concentration both in terms of time and amount. Possible effects that the foreign body capsule may have upon sensor lag time and attenuation are the presence of underdeveloped microvascular networks for limited glucose delivery, local glucose consumption by metabolically active inflammatory cells, and decreased diffusion through the dense, collagen-rich capsule [10,12–14]. There is also considerable speculation that the initial biofouling layer plays a significant role in limited sensor performance [5,15].

Different sensor surface modifications and drug release schemes have been developed to resist biofouling, attenuate inflammation, increase vascular density, and/or minimize foreign body capsule thickness [13,16,17]. However, all of these treatments have been developed in the absence of mechanistic understanding of how different aspects of the foreign body reaction affect glucose transport to the sensor surface.

Here, we present a computational model that examines the effects of the characteristic aspects of encapsulation tissue on the transport of glucose from the microvessels to the surface of a subcutaneously implanted sensor after a bolus injection of glucose into the systemic circulation. While others have modeled glucose transport through capsular tissue, the tissue has always been treated as a passive diffusive barrier [18,19]. In reality, the foreign body capsule is a perfused material comprised of a complex porous network that is both a diffusive barrier and a bioactive consumer of glucose that is subject to the influence of at least five variables: foreign body capsule thickness, foreign body capsule porosity, blood vessel density, density of glucose-consuming cells, and the capsular diffusion coefficient of glucose. Greater understanding of these effects should lead to a more effective design of surface treatments intended to extend sensor performance.

Methods

Two-compartment transport model

Glucose transport through the tissue that encapsulates an implanted sensor was modeled as a two-compartment, unidimensional diffusion-reaction problem (Fig. 2). The first outer compartment modeled native subcutaneous tissue as a porous environment rich in blood vessels and resident mesenchymal cells (e.g., adipocytes and fibroblasts). The second inner compartment modeled fibrous tissue, representing an avascular, porous environment with a presence of inflammatory cells. The layer of adsorbed protein at the sensor surface was neglected in this analysis.

The governing equation for glucose concentration in the outer native subcutaneous tissue (C_{tis}) is a non-linear, unidimensional diffusion-reaction equation in cylindrical coordinates through a porous medium (Eq. 1).

$$\frac{\partial C_{tis}(r, t)}{\partial t} = \frac{D_{tis}}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{tis}(r, t)}{\partial r} \right) + \Phi_b - Q_{tis}(r, t) \quad (1)$$

Φ_b and Q_{tis} represent the rate of glucose transport from the lumen of microvessels to the interstitial space of the subcutaneous tissue and the consumption rate of glucose by native adipocytes in the subcutaneous space. Φ_b is defined as the rate of glucose transport per unit volume from blood vessels into the interstitial space of the tissue, making it the source of glucose for the tissue compartment. It is described by a modified version of the Kedem–Katchalsky equation, where P is the microvascular permeability of the vessel wall to glucose

(cm/s), $\frac{S}{V}$ is the density of blood vessels in terms of the microvessel surface area per unit volume of the tissue (cm²/cm³), C_p is the concentration of glucose in the blood (μmol/cm³), and ϵ_{tis} is the porosity of the native tissue (unitless; Eq. 2)[20].

$$\Phi_b = \frac{PS}{V} \left(C_p(t) - \frac{C_{tis}(r, t)}{\epsilon_{tis}} \right) \quad (2)$$

Q_{tis} is defined as the uptake of glucose by native adipocytes and is represented by Michaelis–Menten kinetics, where $V_{max, tis}$ is the maximum rate of glucose consumption (μmol/(cell s)), $K_{M, tis}$ is the Michaelis constant (μmol/L), ϵ_{tis} is the porosity of the native tissue (unitless), and z_{cell} is the volume of a native cell (L/cell; Eq. 3)[21]. This term represents a glucose sink, as uptake of the analyte by cells removes it from the system.

$$Q_{\text{tis}}(r, t) = \frac{V_{\text{max,tis}} C_{\text{tis}}(r, t)}{K_{\text{M,tis}} \varepsilon_{\text{tis}} + C_{\text{tis}}(r, t)} \left(\frac{1 - \varepsilon_{\text{tis}}}{z_{\text{cell}}} \right) \quad (3)$$

The inner fibrous capsule compartment was modeled as an avascular area, which is consistent with histological findings that show a decreased presence of blood vessels relative to native tissue [19]. As a result, the governing equation describing glucose concentration in the fibrous capsule (C_{FBC} ; Eq. 4) has no source term in addition to the diffusion terms, and only a sink term to describe uptake by inflammatory macrophages that is similar to the uptake expression in the native tissue compartment.

$$\frac{\partial C_{\text{FBC}}(r, t)}{\partial t} = \frac{D_{\text{FBC}}}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{\text{FBC}}(r, t)}{\partial r} \right) - Q_{\text{FBC}}(r, t) \quad (4)$$

Q_{FBC} is defined as the rate of glucose uptake by inflammatory macrophages in the capsule and is modeled by Michaelis–Menten kinetics, where $V_{\text{max,FBC}}$ is the maximum rate of consumption ($\mu\text{mol}/(\text{cell s})$), $K_{\text{M,FBC}}$ is the Michaelis constant ($\mu\text{mol}/\text{L}$), ε_{FBC} is the porosity of the native tissue (unitless), and z_{cell} is the volume of an inflammatory cell (L/cell ; Eq. 5) [22]. This term represents a glucose sink in the capsule, as uptake of the analyte by cells removes it from the system.

$$Q_{\text{FBC}}(r, t) = \frac{V_{\text{max,FBC}} C_{\text{FBC}}(r, t)}{K_{\text{M,FBC}} \varepsilon_{\text{FBC}} + C_{\text{FBC}}(r, t)} \left(\frac{1 - \varepsilon_{\text{FBC}}}{z_{\text{cell}}} \right) \quad (5)$$

Boundary conditions

Boundary conditions were specified at the sensor surface ($r=a$), the interface between the tissue and capsule compartments ($r=a+L$), and a location far away from the sensor ($r \rightarrow \infty$). At the sensor surface, the rate of glucose diffusion in the capsule compartment is equal to the rate of glucose uptake by the sensor, Q_{sensor} (Eq. 6). It was assumed that the consumption rate was proportional to the glucose concentration at the sensor surface with λ being the proportionality constant ($\text{mol}/(\text{mM s})$). The sensitivity of the sensor to glucose may decay with time. To account for this occurrence, a nondimensional parameter, α , was introduced. It is defined as the sensor efficiency and ranges from zero to unity. For this case, the sensor is assumed to be perfectly efficient, with $\alpha=1$. A_{sensor} is defined as the total surface area of the sensor available for glucose transport and a is the radius of the sensor [23].

$$D_{\text{FBC}} A_{\text{sensor}} \frac{\partial C_{\text{FBC}}}{\partial r}(r=a, t) = Q_{\text{sensor}} = \frac{\alpha \lambda C_{\text{FBC}}(r=a, t)}{\varepsilon_{\text{FBC}}} \quad (6)$$

At the interface between the tissue and capsule compartments, it is assumed that glucose is conserved and no glucose accumulates or disappears at the interface, so both concentrations and fluxes are matched (Eqs. 7 and 8).

$$\frac{C_{\text{FBC}}(r=a+L, t)}{\varepsilon_{\text{FBC}}} = \frac{C_{\text{tis}}(r=a+L, t)}{\varepsilon_{\text{tis}}} \quad (7)$$

$$D_{\text{FBC}} \frac{\partial C_{\text{FBC}}}{\partial r}(r=a+L, t) = D_{\text{tis}} \frac{\partial C_{\text{tis}}}{\partial r}(r=a+L, t) \quad (8)$$

In tissues far away from the sensor, it is assumed that the concentration in the tissue is the same as that in the blood (Eq. 9).

$$C(t, r \rightarrow \infty) = \varepsilon_{\text{tis}} C_p(t) \quad (9)$$

Blood glucose concentration

Blood glucose profiles used in simulations were numerical fits of actual experimental intravascular glucose infusion data taken from the published literature. The glucose infusion and sensor response data of Koschwanez et al. was employed to demonstrate that the program generated realistic and typical dose–response behavior of a subcutaneously implanted sensor [13]. For parametric sensitivity analysis, the glucose infusion data of Armour et al. were employed because the blood glucose data are from an intravascular sensor that may measure instantaneous changes in blood glucose more reliably than data from a discrete finger prick test [24]. The raw infusion data from Armour et al. were fit to a sum of three Gaussian curves (Eq. 10). The fitted values for the constants in Eq. 10 are given in Table 1.

$$C_p(t) = a_1 e^{-\left(\frac{t-b_1}{c_1}\right)^2} + a_2 e^{-\left(\frac{t-b_2}{c_2}\right)^2} + a_3 e^{-\left(\frac{t-b_3}{c_3}\right)^2} \quad (10)$$

Transport and kinetic parameters

In order to accurately mimic a fully formed capsule, the physiologically relevant values of model constants listed in Table 2 were used in numerical simulations. However, it should be noted that chronic inflammation and wound healing processes may lead to changes in these values; a condition that was not considered in this study.

Diffusion coefficient values (D) were obtained from the study of glucose transport in subcutaneous tissue and the fibrous capsule, respectively. The V_{max} and K_M values in the capsule were based upon the data of macrophage uptake of glucose while those in the native tissue were based upon adipocyte uptake of glucose, thereby accounting for the fatty nature of the human subcutis. Capsule thicknesses (L) vary based upon the type of implant, how it is implanted, and what is classified as a foreign body capsule. Results for subcutaneously implanted sensors can vary anywhere from 30 to 750 μm , in extreme cases [9,12,19]. The thickness was chosen to be 75 μm since it was a typical value for a well-formed capsule. The surface area of the sensor was measured for a Medtronic MiniMed sensor.

Parametric sensitivity analysis

Aspects of the fibrous capsule that had the greatest effect on either time lag or sensor signal attenuation were determined by running the simulation for a range of values for each parameter, while keeping all other parameters constant. The parameters to be considered were capsule diffusion coefficient (D_{FBC}), capsule porosity (ε_{FBC}), vessel surface area per unit volume of

subcutaneous tissue $\left(\frac{S}{V}\right)$, maximum rate of glucose uptake by macrophages ($V_{\text{max,FBC}}$) and capsule thickness (L). Table 3 shows the range of values that were input for the sensitivity study. For every simulation that was executed for a value of a given parameter, the model predicted both an associated output lag time and an attenuation value. Therefore, for an input

range of N values of a given parameter, there would be N associated lag times and N associated attenuation values.

The sensitivities of these output values to their input values of the model parameters were calculated using logarithmic sensitivity analysis [25]. The representative equation for a logarithmic sensitivity, S_i , of an output value, l , for a given input parameter, x , is given in Eq. 11.

$$S_i = \frac{\Delta l}{\Delta x} \frac{x_i}{l_i} \quad (11)$$

Δl is defined as the difference between outputs over the range of input values and Δx is defined as the difference between the input values. x_i is defined as the midpoint of the input range, and l_i is the output associated with the input, x_i . For a range of input and output values, one could calculate a range of sensitivities by decreasing Δx . By calculating sensitivity in this way, the differences in absolute magnitude are not considered. Instead, only the relative change in response to the relative change in the input is considered.

For this specific series of simulations, ranges of values for the capsule diffusion coefficient

(D_{FBC}), capsule porosity (ε_{FBC}), subcutaneous vessel density ($\frac{S}{V}$), cellular uptake of glucose ($V_{\text{max,FBC}}$), and capsule thickness were entered into the model. When testing one parameter, all others were held constant to see how the changes within each parameter affect simulated sensor performance.

Assessing glucose sensor performance

Lag times were calculated as the difference between the time at which glucose concentration peaked in the blood glucose profile and the time glucose concentration peaked at the sensor surface. Attenuation of glucose concentration due to capsule formation was calculated as one minus the ratio of the peak sensor surface value divided by the peak blood glucose value (Eq. 12).

$$\text{Attenuation} = 1 - \frac{\max \{C_{\text{FBC}}(t, r=a)\}}{\max \{C_p(t)\}} \quad (12)$$

Numerical methods

The governing partial differential equations were discretized into a series of ordinary differential equations using the finite difference method. These discretized equations were then solved using the differential equation solver, ode15s, in MATLAB (The Mathworks, Natick, MA). Curve fitting for the blood glucose profile was performed using the Curve Fitting Toolbox in MATLAB.

Results

Numerical approximation of experimental sensor data

The individual data points in Fig. 3 are rat tail prick blood glucose values following a tail vein injection of 0.5 mL of 50% dextrose measured using a commercial blood glucose meter (filled circle), and the corresponding values from a MiniMed sensor implanted for 24 h in the dorsal subcutis of the same rat as reported by Koschwanez et al. (filled square) [13]. The dashed line superimposed on the experimental blood glucose values (dash-dot line) is the best fit of Eq. 10

to the blood glucose values, which was then used as a model input to generate the simulated glucose sensor response (broken line). This trace can then be compared to the solid line fitted to the experimental sensor data. Figure 3 also indicates the sensor time lag (Δt_{est}) and the sensor attenuation (ΔC_{est}) for the simulated data that was used in subsequent sensitivity analyses. The experimental lag (Δt_{exp}) and attenuation (ΔC_{exp}) from Koschwanez et al. are also reported in Fig. 3 [13].

Overall, Fig. 3 shows that the program was able to approximate the temporal profile of the experimental data from the implanted sensor. The simulated sensor response had a lag time of ~3 min and the sensor signal was 76% of the blood glucose signal for a signal attenuation of 24% [13]. With regards to attenuation, the simulated trace produces a peak that is 97% of the measured sensor peak and only minimally overestimates attenuation. Lag times are less similar between the experimental and simulated data, with the simulated trace recording a lag of 2.87 min, underestimating the experimental lag of 5.28 min. It should be noted that attenuation and lag are less pronounced in this simulation because model parameters were based upon the local environment at 24 h post-implantation, which is before a mature capsule has formed. While subsequent studies in this manuscript will describe transport through a fully formed capsule, this example demonstrates the ability of the model to describe different temporal regimes of the post-implantation environment when compared to experimental data.

Sensor lag time and attenuation of glucose concentration

Values of time lag and glucose attenuation were calculated using the physiologically representative literature values in Table 2 where five of these variables—capsule diffusion coefficient, capsule porosity, maximum cellular uptake rate for glucose in the capsule, vascular density in surrounding native tissue, or the capsule thickness—were allowed to vary independently as listed in Table 3. These calculations resulted in the two sets of five plots presented in Figs. 4 and 5, respectively. In each case, the results were normalized to the benchmark values of time lag and attenuation calculated using the values in Table 2. The normalized benchmark values are represented by the horizontal dashed lines in Figs. 4 and 5. This allowed direct comparison of the fractional effects of independently varying one of the five parameters listed in Table 3.

Figure 4 shows the relative temporal effects of varying (a) the capsule diffusion coefficient, (b) the capsule porosity, (c) the vascular density in surrounding native tissue, (d) the cellular uptake of glucose in the capsule, and (e) the capsule thickness on the sensor time lag—i.e., time lag between the appearance of peak glucose concentration in blood and the appearance of the peak glucose concentration at the sensor surface.

Increased capsular tissue glucose diffusion coefficient and vessel density both caused sensor lag times to decrease. Conversely, increased capsule thickness and increased capsule porosity both caused sensor lag times to increase. Increased cellular uptake of glucose had a marginal effect on lag time.

Figure 4 also shows the relative mass effects of varying (a) the capsule diffusion coefficient, (b) the capsule porosity, (c) the vascular density in surrounding native tissue, (d) the cellular uptake of glucose in the capsule, and (e) the capsule thickness on the attenuation of the sensor signal—i.e. attenuation of the peak glucose concentration at the sensor surface relative to the peak glucose concentration in blood.

Increased capsule diffusion coefficient, capsule porosity, and vessel density all lessened attenuation of peak glucose concentration at the sensor surface. Conversely, increased cellular uptake of glucose in the capsule and capsule thickness both increased attenuation of peak

glucose concentration at the sensor surface. In this case, changes in the diffusion coefficient and cellular uptake both had only modest effects.

Lag time and attenuation sensitivity analysis

Logarithmic sensitivity analysis was used to determine the sensitivity of a dependent variable, such as lag or attenuation, to variation in one independent variable while holding all other independent variables constant. Figure 5 shows box and whisker plots of logarithmic sensitivities for (a) the normalized lag time and (b) the normalized glucose attenuation values as a function of the five independent variables listed in Table 3.

Sensor lag time was shown to be highly sensitive to changes in capsule thickness, while only mildly sensitive to the other four variables. The minimum sensitivity due to capsule thickness change (0.4828) was more than twice that of the maximum sensitivity from the next highest value due capsule porosity change (0.2307).

The attenuation of blood glucose as it is transported to the sensor surface was most sensitive to two variables: the vessel density of the subcutaneous tissue and the capsule porosity. Glucose attenuation also appears to be mildly sensitive to capsule thickness, and essentially insensitive to capsule diffusion coefficient and cellular glucose uptake. Although vessel density did have the highest maximal sensitivity value of 1.01, it had a lower mean sensitivity than capsule porosity, and a minimum sensitivity value of 0.0515 that was similar in magnitude to the less sensitive parameters of capsule thickness, capsule diffusion coefficient and cellular glucose uptake.

Interestingly, increasing capsule thickness had a pronounced effect on increasing sensor lag time, but capsule thickness had only a modest effect on glucose attenuation; whereas increasing either vessel density or capsule porosity had pronounced effects on decreasing glucose attenuation, but neither vessel density nor capsule porosity had appreciable effects on sensor lag time. Furthermore, both sensor lag time and glucose attenuation were essentially insensitive to cellular uptake of glucose.

Discussion

Experimental studies have shown that if an implanted glucose sensor can withstand the 7–14 days that it normally takes to form a stable fibrous capsule, then it is more likely to remain functional in the body for months [26]. The current study used a transport model to simulate the behavior of an implanted glucose sensor surrounded by a fibrous foreign body capsule. The primary advantage of the modeling approach over experimentation was the ability to evaluate the effects of individual physiological parameters on glucose sensor response.

The goal of this study was twofold: (1) demonstrate that the transport model accurately reproduces implanted glucose sensor response by incorporating physiologically relevant tissue parameters, and (2) use the model to gain insight into aspects of the fibrous capsule and the surrounding tissue that most affect sensor lag time and glucose signal attenuation.

The suitability of the transport model was demonstrated by generating a simulated implanted glucose sensor response using a blood glucose profile from Koschwanetz et al. as the input (Fig. 3)[13]. The simulated sensor output was compared to the actual implanted sensor response to the input blood glucose profile. The model was able to reproduce the shape of the implanted sensor trace with an attenuation and lag time that are comparable to experimental data.

Table 2 lists the physiological modeling parameters used to describe a mature fibrous capsule that would surround a sensor a few weeks following subcutaneous implantation. These values

were used to generate a benchmark simulated sensor response for the sensitivity studies. Vessel densities were based on measured values at 3 weeks post-implantation in the subcutaneous tissue of rats. Cell metabolic values were based on those of macrophages, which are the dominant cell type in the fibrous capsule at that time. Capsule thicknesses were similarly based upon reported values at 3 weeks post-implantation, though thickness values vary considerably across the literature due to what is considered a capsule during experiments.

It should be noted that the biofouling layer was neglected in the simulations. Generally, this stratum of protein and protein fragments ranges from 20 nm to 0.5 μm in thickness, which creates a negligible effect on transport, even when its permeability to glucose is drastically decreased (data not shown). These findings further support findings from Wisniewski et al. who found that the surrounding tissue offered substantially greater resistance to glucose transport than the biofouling layer [5]. While many believe that the proteins and proteolytic enzymes within the biofouling layer can damage the glucose sensitive membranes on sensor electrodes, those assertions are outside the scope of this study, which only considers biofouling from a transport perspective.

The transport model was utilized to examine how capsule formation affects the onset of lag times and signal attenuation. When exposed to a range of values for the five parameters of interest, lag times were most affected by changes to the thickness of the capsule. Lag times steadily increased in a linear fashion over a range of thicknesses. Such an effect upon lag time should be expected. First, a thicker capsule translates to larger length scale that allows for more random routes for transport of glucose molecules to the sensor surface [27]. Second, since the capsule was assumed to be avascular, the distance between source blood vessels and the target sensor has been increased. Therefore, capsule thickness cannot affect how much glucose is in the system but instead can only affect how fast the glucose reaches the sensor. By comparison, changes in lag time were not affected appreciably by changes in capsule porosity, capsule diffusion coefficient, or cellular uptake of glucose. From a biological perspective, this implies that the physical thickness of the capsule mattered more to inducing the lag time than did changes in the constituent parts of the capsule.

With respect to attenuation, capsule porosity and vessel density were found to have the largest effects on sensor response, though the ranges of sensitivity exhibited greater spread than those values in the lag time study. Attenuation sensitivity to vessel density ranged from an essentially insensitive factor of 0.0515 for low vessel densities to the most highly impactful factor for all parameters of 1.01. This finding is intuitive as blood vessels in the subcutaneous tissue are the only source of glucose in the model, i.e., a reduction in the source of glucose translates into a decreased amount of glucose that can even reach the sensor. The vessel density findings corroborate those of Sharkawy and Koschwanez, who have found that the presence of vessels can extend the useful life of the sensor [13,28].

Comparatively, influence of capsule porosity on attenuation had a higher median sensitivity and more narrow range of sensitivities, suggesting that it had a more consistent effect on attenuation than did vessel density. Low capsule porosity increased glucose attenuation because it reduced transport pathways, resulting in a diminished amount of glucose molecules reaching the sensor surface and an accumulation of glucose in the native tissue.

It should be noted that increasing the capsule thickness had a modest effect on glucose attenuation because of the transient behavior of blood glucose level after a bolus injection and the glucose consumption by macrophages. If both plasma clearance and cellular uptake of glucose in tissues are negligible, the capsule thickness should have no effect on glucose attenuation. In contrast, the diffusion coefficient of glucose in the capsule and the maximum rate of glucose uptake had little effect on the attenuation of the glucose signal.

It is interesting to note that high vessel density and high porosity have similar effects on glucose attenuation: porosity exhibits high attenuation sensitivity at high porosities ($\epsilon_{\text{FBC}} > 0.6$) and

vessel density exhibits high attenuation sensitivity at high vessel densities ($\frac{S}{V} > 60 \text{ cm}^{-1}$), both of which are likely to occur early following implantation. As capsule formation occurs, the capsule goes from a loosely organized protein and cell layer to a highly dense layer of cells and extracellular matrix. Therefore, the high sensitivity at high porosities denotes that capsule porosity has a large effect on attenuation at points early in the capsule formation process. Similarly, peak attenuation sensitivity occurs at vessel densities near pre-implantation values, which would indicate that it affects attenuation early in the capsule formation process as well. This finding suggests an initial synergistic effect of both the changing porosity and changing vessel density on attenuating sensor response early in the capsule process. However, as vessel density decreases through capsule formation, so does its sensitivity to attenuation, reaching a minimum at 0.0515. Though sensitivity due to capsule porosity also decreases as the capsule forming process continues and porosity decreases, its minimum is still much higher (0.278) than the maximum values of other parameters. For later times in capsule formation, porosity continues to dominate attenuation sensitivity. Attenuation sensitivity is initially affected by both vessel density and capsule porosity, with porosity dictating attenuation as the capsule continues to grow.

Ultimately, we are interested in the conditions that generate the best scenario for glucose transport to an implanted sensor. Figure 6 is a scatter plot that summarizes all of the lag time and glucose attenuation values generated for all of the conditions tested using the computational model. Vessel density (green), capsule porosity (blue), and capsule thickness (red) were labeled to see the lag time and attenuation trends among the highly sensitive model parameters. The benchmark point determined using the baseline values in Table 2 is labeled in magenta and represents the intersection of all other points in the simulation.

The quadrant on the bottom left of Fig. 6 represents low attenuation (<0.5) and low lag (<5 min). Of all the conditions entered into the model, only vessel density between 60 and 166.3 cm^2/cm^3 produced a low attenuation and low lag environment. Attenuation dropped fourfold from nearly avascular conditions to a highly vascular tissue typical of subcutaneous tissue. This finding demonstrates the importance that adequate vessel density has on effective implantable sensor readings in vivo and corroborates previous assertions by Ward et al. about the importance of vasculature in sensor performance [29]. The upper right quadrant represents the worst case scenario of high lag time and high attenuation. Only high capsule thicknesses generated this situation with lag times increasing steadily from nearly 0 s to nearly 10 min with a 50-fold increase in capsule thicknesses, further showing the deleterious effects of a thick capsule on sensor performance. Most results resided in the upper left quadrant of low lag and high attenuation, suggesting that most of the conditions tested affected attenuation more than lag time. Thus, lag was attributed almost exclusively to capsule thickness, while attenuation was affected by multiple factors. No points resided in the lower right quadrant, suggesting that changes in the model parameters will not create a situation where a sensor will have a high lag time and low attenuation.

Finally, this modeling study made two key assumptions: (1) that each parametric variable could be changed independently without affecting the others, and (2) that the system can be described as a straightforward two-compartment transport model. Clearly, the assumption of variable independence is problematic because a number of transport parameters are in fact interrelated. For example, the diffusion coefficient for the capsule is not just the diffusion coefficient of glucose in the void space of the capsule, but the effective diffusion coefficient of glucose in the capsule matrix that would be affected by altering the porosity or the cellular glucose uptake. However, this study is just asking what happens when one parameter is changed. This study

is more concerned with what happens to the output when a parameter changes, not necessarily how it changes constituent parts.

The possible omission of additional mitigating variables from the model is also of concern. This finding may be most apparent in that most conditions yielded a lag time of approximately 2 min, except for cases of very thin or very thick capsules. Such a finding is in contrast to the 5-min or longer time lags typically reported in the literature for implanted glucose sensors, even in cases where the sensor has been implanted for short time periods before any fibrous capsule could form. This may suggest that factors like metabolic activity of inflammatory cells and the formation of the biofouling layer should be taken into greater account in future iterations. An additional factor that may help to account for time lag is the change in microcirculation patterns in tissues during inflammation and wound healing. Besides the obvious changes in vessel density, there is also a decrease in the length and diameter of vasculature in wound healing tissue as well as a decrease in red blood cell velocity [30]. Smaller diameters of the existing vessels in the tissue will create a higher resistance to blood flow and may shunt blood flow to a different collection of vessels. Therefore, not only the number of patent blood vessels, but also the geometry of those vessels will affect the delivery of glucose to the subcutaneous space. Future computational studies will have to account for such changes to create a more complete portrait of the post-implantation environment.

Conclusions

This study describes a computational model of glucose transport through native tissue and across the foreign body capsule to a sensor surface that was used to examine how different transport parameters affect sensor time lag and attenuation of glucose to reach the sensor surface. Sensitivity analysis showed that sensor lag is mainly attributable to changes in capsule thickness and sensor attenuation is primarily affected by changes in vessel density and capsule porosity. Another interesting point was the observation that the capsule diffusion coefficient and cellular uptake of glucose did not affect the different modes of sensor failure. To exclude certain features of capsule formation allows for more focused designs and experiments in the future. The work presented here will allow for more rational design of modified sensor surfaces to control immune responses, ultimately extending the useful life of implantable glucose sensors.

Acknowledgments

This work was supported by an NIH Biotechnology Predoctoral Fellowship, T32 GM 8555 (MTN) and NIH Grant DK 54932 (WMR). The authors thank Mr. Robert D. Kirkton, Dr. Nima Badie, and Dr. Charles S. Wallace for valuable feedback on the manuscript.

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Fig. 1.

a Histological image of a foreign body capsule that has formed around an implanted glucose sensor at 14 days post-implantation. H&E staining demonstrates lack of vasculature (*red*) relative to cells (*blue*) within capsule. Image borrowed from [12]. **b** Masson's trichrome stain of a cross-section of fibrous tissue 3 weeks post-implantation shows presence of extracellular matrix (*blue*) as well as cells (*red*) within capsule tissue. Provides basis for modeling capsule as dense, avascular network composed of inflammatory cells and extracellular matrix. Image borrowed from [13]

Fig. 2. Schematic representation of model for diffusion of glucose through native tissue and the fibrous capsule

Fig. 3.

Simulated recreation of experimental glucose sensor traces. Raw blood glucose data (*filled circle*) was fit to a continuous curve, $C_{bg,experimental}$ (dash-dot line) and then input into the model to give a simulated glucose sensor trace, $C_{s,model}$ (dash line). This output was compared in shape to raw sensor data (*filled square*), which is fit by a solid line, $C_{bg,experimental}$. The raw sensor output data was converted from nanoamperes to micromolar using an experimentally determined standard curve relating the two, $C_{s,experimental} = 276i_{s,experimental} - 1130$ ($R^2=0.9993$, data not shown). The simulated trace produced a lag time (Δt_{est}) and attenuation (ΔC_{est}) and a shape similar to data in Koschwanez et al. [13]. The lag time and attenuation from [13] are represented in the figure by Δt_{exp} and ΔC_{exp} . All parameters used for this study were the same except for vessel density and capsule porosity. Vessel density was increased to $100 \text{ cm}^2/\text{cm}^3$ as a representation of how density has decreased from its subcutaneous value. Capsule porosity was calculated from a Darcy's Law constant for fibrin matrices to be 0.925, thus representing the loosely organized matrix early in inflammation (data not shown)

Fig. 4. Effect of **a** capsule diffusion coefficient, **b** capsule porosity, **c** vascular density in surrounding native tissue, **d** cellular uptake of glucose in the capsule, and **e** the capsule thickness on sensor lag times (*solid line*) and attenuation (*broken line*). Results have been normalized to baseline values in Table 2

Fig. 5. **a** Box and whisker plots of lag sensitivity to five different model parameters. **b** Box and whisker plots of attenuation sensitivity to five different model parameters. Sensitivities are represented as unitless values to allow for comparison across parameters

Fig. 6.

Scatter plot of sensor time lag vs. glucose attenuation for all of the conditions simulated with the transport model. The three variables that showed the greatest sensitivity—capsule thickness, vessel density, and capsule porosity—are represented by the *red*, *green*, and *blue circles*, respectively. The benchmark value of time lag and attenuation calculated using the variables in Table 2 is labeled in magenta. This data point is common to all simulation trials. The *open circles* clustered around the benchmark value are the results obtained for the less sensitive variables of capsule diffusion coefficient and cellular glucose uptake

Table 1

Constants for blood glucose expression for data from Armour et al. [24]

<i>a</i> (μM)			<i>b</i> (s)			<i>c</i> (s)		
<i>a</i> ₁	<i>a</i> ₂	<i>a</i> ₃	<i>b</i> ₁	<i>b</i> ₂	<i>b</i> ₃	<i>c</i> ₁	<i>c</i> ₂	<i>c</i> ₃
2,404.64	5,678.23	6,2449×10 ⁸	2,482.8	3,954	3.013×10 ⁶	733.8	1,303.8	8.562×10 ⁵

Table 2

List of all baseline model parameters

Model parameters	Parameter values		
	FBC	Native tissue	Citation
Diffusion coefficient (D) (cm ² /s)	1.87×10 ⁻⁶	3.5×10 ⁻⁶	[19]
Porosity (ε) (unitless)	0.5	0.6	— ^a
Vessel density (S/V) (cm ² /cm ³)	—	15.4	[23]
Capsule thickness (L) (μm)	75	—	[9,12,19]
Michaelis constant (K _M) (μM)	6.13×10 ³	6.2×10 ³	[21,22]
Maximal rate of cellular glucose uptake (V _{max}) (μmol/(cell s))	4.88×10 ⁻¹¹	3×10 ⁻¹¹	[21,22]
Vascular glucose permeability (P) (cm/s)	—	5×10 ⁻⁵	[20]
Conversion constant (λ) (mol/(mM s))	2.574×10 ⁻¹⁴	—	— ^b
Cell volume (z _{cell}) (L/cell)	9.5×10 ⁻¹³	9.5×10 ⁻¹³	— ^a
Glucose sensor radius (a) (cm)	0.07	—	[23]
Sensor surface area (A) (cm ²)	0.0058	—	[23]

^aModel assumptions

^bCalculated values with no previous citation

Table 3

Range of different parameters to be used for sensitivity analysis

Parameters					
	D_{FBC} (cm^2/s)	ε_{FBC} (unitless)	$V_{\text{max},FBC}$ ($\mu\text{mol}/(\text{cell s})$)	Vessel density (cm^2/cm^3)	Capsule thickness (μm)
1	1.87×10^{-7}	0.2	4.88×10^{-12}	2	15
2	3.74×10^{-7}	0.4	2.44×10^{-11}	5	75
3	9.35×10^{-7}	0.6	4.88×10^{-11}	15.4	150
4	1.87×10^{-6}	0.8	9.76×10^{-11}	60	375
5	3.74×10^{-6}	0.9	2.44×10^{-10}	120	750
6	—	—	4.88×10^{-10}	166.3	—

Values presented in italics represent benchmark values from Table 2