Modeling and Optimization of a Bioartificial Implant to Alleviate Diabetes

Ben Hung, Alex Fe, and Greg Schmidt

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I. Executive Summary

Diabetes is a chronic disease that is characterized by a person having too high blood sugar levels due to the deficiency of insulin. If left untreated, there is serious risk for development of cardiovascular diseases, renal failure, blindness, nerve damage, etc. Currently, this condition is treated by constant monitoring combined with insulin injection. Given that the various forms of this treatment have negative effects on overall quality of life, this paper focuses on modeling a different type of treatment that can potentially reduce the need for constant blood monitoring and reduce the need for insulin supplementation. The treatment involves surgically implanting a shunt with β-islet cells next to a blood vessel in the body [1]. Here, the β-islet cells release insulin that follows a bell-shaped curve when graphed vs. time [2], and this insulin diffuses across a semi-permeable membrane and into the bloodstream. After analyzing the results of the model, it was determined that insulin levels with the implant matched very closely with natural physiological levels, making this treatment a viable one. This treatment also showed the ability to emit a variety of insulin levels making it suitable for a wide variety of patients. This makes this a potentially important avenue of research and worthy of further study.

Key words: diabetes, beta-cells, insulin delivery

II. Introduction and Design Objectives

2.1. Introduction and Background

Diabetes is a chronic disease that is characterized by a person having too high blood sugar levels due to the deficiency of insulin. If left untreated, there is serious risk for development of cardiovascular diseases, renal failure, blindness, nerve damage, etc. Currently, there is no permanent cure for the disease. In order to restore normal insulin levels, patients suffering from diabetes can take daily insulin injections, but this treatment requires one to have a very structured lifestyle in order to control blood glucose levels. Another alternative would be to use an insulin pump, which can automatically infuse insulin depending on the levels of glucose in the blood. This is an improvement over the daily injections, but again the user is relegated to participating in less strenuous activities that limit damage to the pump. There is also the risk that the pump could stop working, which could cause many inconveniences. Given that currently all possible treatments affect one's normal life greatly, this paper focuses on modeling a different type of treatment that potentially has the same positive benefits as an insulin pump but is much less invasive in one's life. That treatment involves surgically implanting a shunt with β-islet cells next to a blood vessel in the body [1]. Here, the β-islet cells release insulin that follows a bell-shaped curve when graphed vs. time [2], and this insulin diffuses across a semi-permeable membrane and into the bloodstream. Axisymmetry is assumed, so the membrane and bloodstream are modeled as a slab. Another design was considered where a microsphere instead of a shunt was used to store the β-islet cells, but the model ended up not being feasible (see Appendix 5.3 for more details).

2.2. Design Objectives

We will model the insulin production of implanted β-islet cells and its mass transfer across a semipermeable membrane. The amount of insulin transferred into the bloodstream from this membrane must match normal physiological levels as much as possible. The device must also be a minimum length to facilitate implantation into diabetic patients. Satisfying these two main constraints is the main objective of the following model.

2.3. Problem Schematic

Our focus is the modeling in COMSOL of the intravascular arteriovenous shunt, implanted with β-islet cells. Schematics of the device are shown in Figure 2.1. A complete schematic of our model with all relevant boundary conditions and properties can be found in the appendix under mathematical statement of the problem.

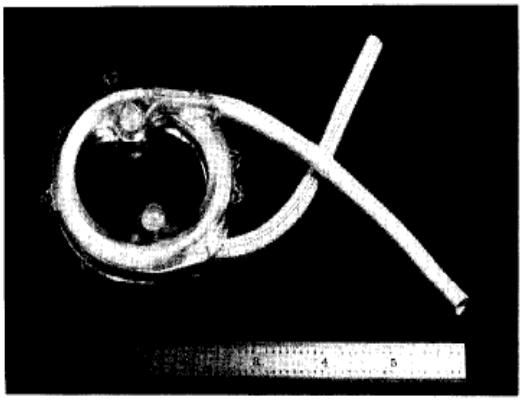


Fig. 2.1: Schematics of the intravascular arteriovenous shunt. The figure shows the physical shunt as discussed in [1]. Our model is shown in Appendix 5.1

III. Results and Discussion

3.1. Insulin Flow Profiles

As a representative display of insulin concentration profiles in the membrane and in the blood, surface plots (see Appendix) were taken at 7200 s, the midpoint of the time window being investigated. The flux is at a maximum at this time. There are three plots – one for the area where blood enters the implant (Figure 5.5), one for an area further downstream (Figure 5.6), and one for the area where the blood exits the implant (Figure 5.7). There is very little insulin observed in the blood, but that makes sense as the blood is actively carrying the insulin away by convection. Note that while the plots are labeled moles per meter cubed, the problem was run implicitly replacing meters with millimeters (so the correct units are moles per millimeter cubed).

Figure 3.1 below is the main focus of the results. It shows the variation of insulin flux out of the membrane as a function of time, from 0 to 14400 s. Insulin output from a normal pancreas will vary with many different factors such as glucose and insulin content – all of these factors vary with time. This means correct insulin output as a function of time is characteristic of a normal and healthy pancreas, and as discussed in our design objectives, we want our shunt to mimic the pancreas as much as possible. This graph indicates that our shunt achieved the desired goal of physiologically significant levels of insulin flux.

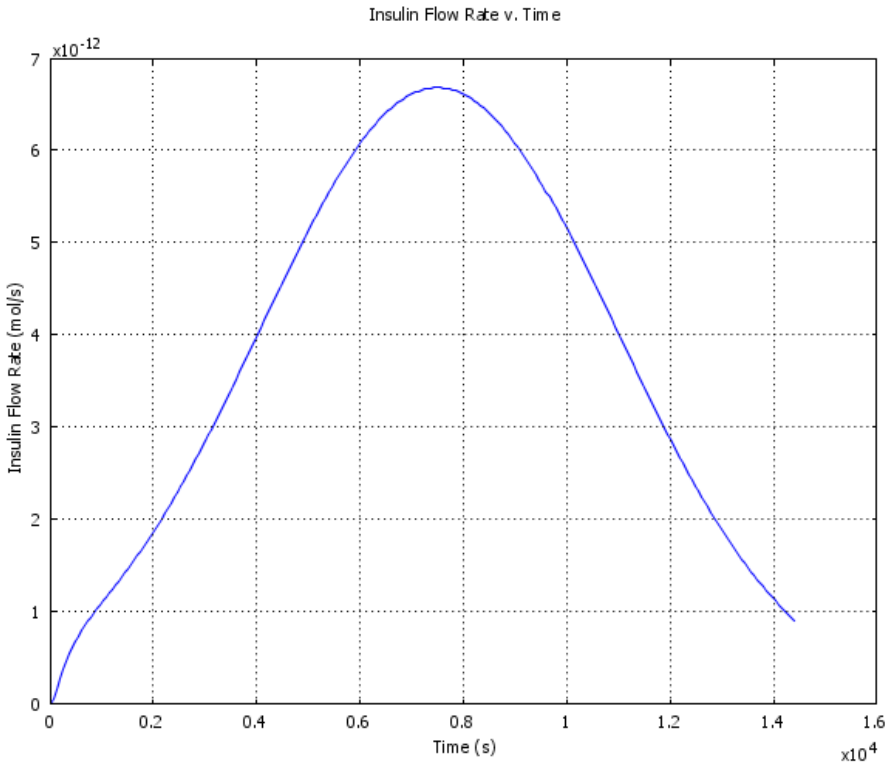


Fig. 3.1: A plot of insulin flow rate out of the device and into the blood flow versus time. This plot must match regular physiological levels for the design to be verified.

3.2. Sensitivity Analysis

In doing any modeling, the sensitivity of the system to variation in the input parameters is always an issue of interest [5]. With this in mind, we set out to conduct a sensitivity analysis and find the uncertainty in our predicted insulin flow rates as well as find the range over which alterations in the model were possible.

We chose to vary three parameters in our sensitivity analysis: the flux function at boundary 7, the diffusivity of insulin in the membrane, and the diffusivity of insulin in the blood. We chose to change each parameter twice – once to a low value and again to a high value. We then graphed the insulin flow rate for all three cases. The dashed line represents the lower bound, the solid line represents the original mean value, and the dotted line represents the upper bound.

The flux function we used was $\phi_m = \left(8.71 \times 10^{-15}\ {}^{mol}/_{mm^2 \cdot s}\right) e^{-\left(\frac{t-(7200s)}{(4870s)}\right)^2}$. This came from us fitting a Gaussian bell curve to a graph derived in literature [2]. MatLab was used to fit this curve, and it gave 95% confidence intervals for the three parameters it fit. We chose to vary only the first parameter (the coefficient of the exponential) because the other two (the values inside the exponent) control the shape of the curve, which will stay more or less constant as that is dictated by the glucose levels in the body. The coefficient, however, controls the magnitude of the insulin flux entering the body, and that is more important to examine. So,

we changed the coefficient to $8.2 \times 10^{-15}\ {}^{mol}/_{mm^2 \cdot s}$, the lower bound in the confidence interval, and then changed it to $9.23 \times 10^{-15}\ {}^{mol}/_{mm^2 \cdot s}$, the upper bound.

The diffusivity of insulin in the blood we got from a paper [3] that used the Einstein-Stokes equation we used in BEE 350 – for some reason, most research in this area uses the diffusivity of insulin in water as an approximation and this was the closest we could find. This, however, means we weren't given a range of values. We arbitrarily decided to go up and down $8.4 \times 10^{-5}\ {}^{mm^2}/_{s}$ in our sensitivity analysis. The original value of this diffusivity was $D_{IB} = 1.16 \times 10^{-4}\ {}^{mm^2}/_{s}$.

The diffusivity of insulin in our membrane was from a paper [4] that gave a range of values, so we used their limits, $1.26 \times 10^{-5}\ {}^{mm^2}/_{s}$ and $3.61 \times 10^{-5}\ {}^{mm^2}/_{s}$. The original value used was $D_{IM} = 2.43 \times 10^{-5}\ {}^{mm^2}/_{s}$.

The graphed results of the analysis are shown below (in the same order as presented above, from left to right and then down). The insulin flow rate through the membrane and into the blood seems to be particularly sensitive to the diffusivity of insulin in the blood. Varying the diffusivity in the membrane does not seem to change the flow much (the dotted line in the graph is almost invisible as it is almost exactly in line with the solid line), and the system shows an intermediate sensitivity to the flux function.

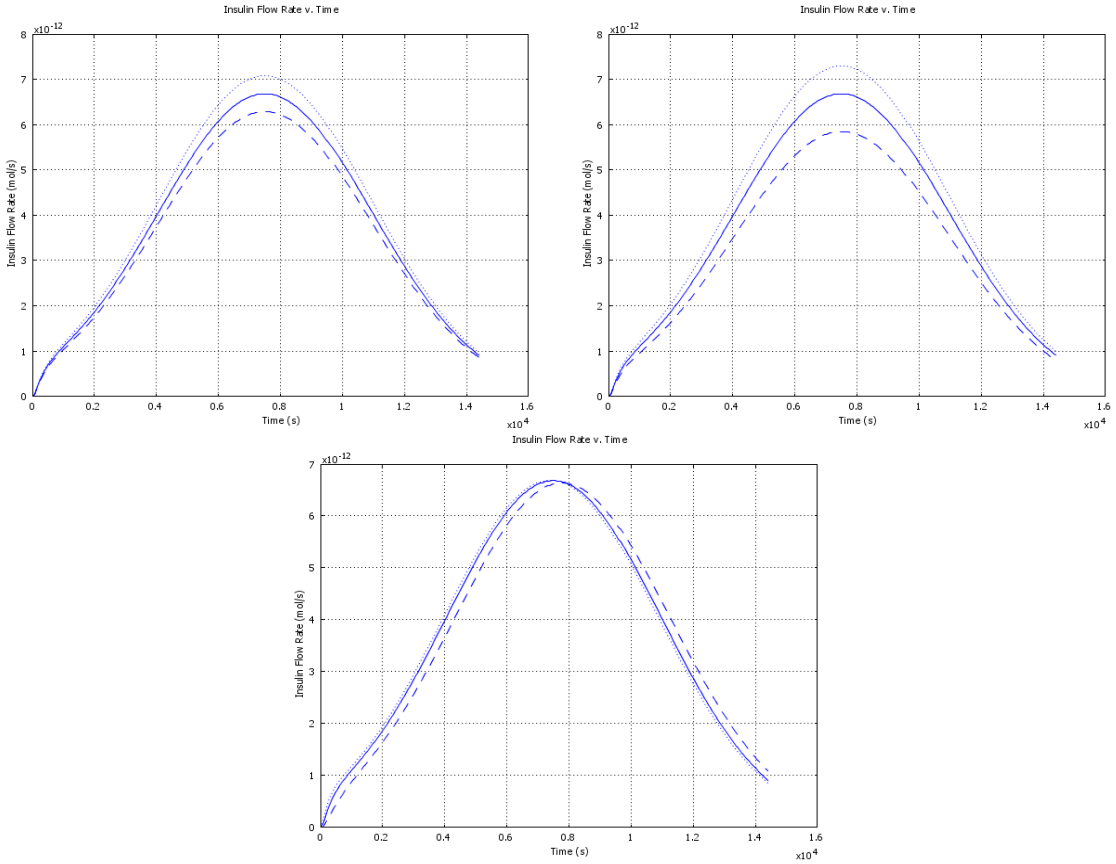


Fig. 3.2: Results of the sensitivity analysis. The solid line is the original flow function as shown in Fig. 3.1. The dashed line represents the flow when using the lower bound of the parameter; the dotted line is the same for the upper bound. The upper left, upper right, and lower graphs are the sensitivity analyses for the flux function, the diffusivity of insulin in the blood, and the diffusivity of insulin in the membrane, respectively.

The results of our analysis are also in line with what we'd expect. Increasing the flux or the diffusivity of insulin in the blood increases the total insulin flow into the blood. Increasing the diffusivity of insulin in the membrane shifts the curve left, as it takes less time for the insulin to enter the blood.

Continuing the analysis, we chose to use the flow at t = 7200 s to find the total sensitivity of flow to changes in these three input parameters. In doing so, we used Eqn. (1):

$$d\dot{m} = \sqrt{\left(\left(\frac{d\dot{m}}{da}\right)da\right)^2 + \left(\left(\frac{d\dot{m}}{dD_{IB}}\right)dD_{IB}\right)^2 + \left(\left(\frac{d\dot{m}}{dD_{IM}}\right)dD_{IM}\right)^2} \qquad (1)$$

where $\dot{m}$ is the insulin flow rate, a is the coefficient of the flux function, D_{IB} is the diffusivity of insulin in the blood, and D_{IM} is the diffusivity of insulin in the membrane. In doing this analysis, we used only the upper bounds and the lower bounds of the parameters (i.e. we did not use the mean values used in the original model, except for the parameters not being varied – so, for

instance, as *a* was being varied, the diffusivities were kept at their mean values). The results are tabulated in Figure 3.3.

Parameter	Value	$\dot{m}$
a	$8.20 \times 10^{-15}\ {}^{mol}/_{mm^2 \cdot s}$	$6.26 \times 10^{-12}\ {}^{mol}/_{s}$
a	$9.23 \times 10^{-15}\ {}^{mol}/_{mm^2 \cdot s}$	$7.05 \times 10^{-12}\ {}^{mol}/_{s}$
D_{IB}	$3.20 \times 10^{-5}\ {}^{mm^2}/_{s}$	$5.82 \times 10^{-12}\ {}^{mol}/_{s}$
D_{IB}	$2.00 \times 10^{-4}\ {}^{mm^2}/_{s}$	$7.27 \times 10^{-12}\ {}^{mol}/_{s}$
D_{IM}	$1.258 \times 10^{-5}\ {}^{mm^2}/_{s}$	$6.54 \times 10^{-12}\ {}^{mol}/_{s}$
D_{IM}	$3.61 \times 10^{-5}\ {}^{mm^2}/_{s}$	$6.68 \times 10^{-12}\ {}^{mol}/_{s}$

Fig. 3.3: The second part of the sensitivity analysis. The values shown are at the *t* = 7200 *s*, when the insulin flux is maximal. Parameters not being varied in each test were set to their original mean values in obtaining the displayed values.

As was mentioned before, $da = 5.14 \times 10^{-16}\ {}^{mol}/_{mm^2 \cdot s}$, $dD_{IB} = 8.4 \times 10^{-5}\ {}^{mm^2}/_{s}$, and $dD_{IM} = 1.174 \times 10^{-5}\ {}^{mm^2}/_{s}$. Using Eqn. (1) then gives $d\dot{m} = 8.23 \times 10^{-13}\ {}^{mol}/_{s}$.

This value is the most the flow varies (at the peak of insulin flow, *t* = 7200 *s*). It is moderately high, mostly due to the high variation seen with the diffusivity of insulin in blood. A future step may be to pay special attention to that particular parameter.

3.3. Accuracy Check

As the exact method of providing insulin we have proposed is a relatively cutting-edge design, finding adequate peer-reviewed research on this subject is extremely difficult. However, diabetes in general is one of the more well-researched conditions in modern society and while our exact method may not be as extremely well researched, there are several other methods of insulin supply that provide an appropriate analogue. One of these methods is the use of an insulin pump. An insulin pump is subcutaneously inserted into the body and then allowed to release a pre-determined amount of insulin. This is essentially the same goal as in our project; however, our design is actually physically implanted as opposed to merely being attached under the skin. The appropriate rate we were trying to achieve is what is known as the body's basal insulin rate. Basal, in this case, refers to a low level of secretion of insulin that is happening

continuously throughout the day. While basal insulin rate can vary extraordinarily from person to person, an average value would be between 1-2 units of insulin per hour [6].

For an appropriate accuracy check of our results, the six insulin flux rates listed above, combined with an average flux over the entire time period and the delta value found were converted into international units per hour. The tabulated numbers are below.

	Insulin Flow	Insulin Flow	Int. Units
Peak Values	$6.26 \times 10^{-12}\ {}^{mol}/_{s}$	$2.25 \times 10^{-8}\ {}^{mol}/_{hr}$	$3.25\ {}^{1}/_{hr}$
	$7.05 \times 10^{-12}\ {}^{mol}/_{s}$	$2.54 \times 10^{-8}\ {}^{mol}/_{hr}$	$3.66\ {}^{1}/_{hr}$
	$5.82 \times 10^{-12}\ {}^{mol}/_{s}$	$2.10 \times 10^{-8}\ {}^{mol}/_{hr}$	$3.02\ {}^{1}/_{hr}$
	$7.27 \times 10^{-12}\ {}^{mol}/_{s}$	$2.62 \times 10^{-8}\ {}^{mol}/_{hr}$	$3.77\ {}^{1}/_{hr}$
	$6.54 \times 10^{-12}\ {}^{mol}/_{s}$	$2.35 \times 10^{-8}\ {}^{mol}/_{hr}$	$3.39\ {}^{1}/_{hr}$
	$6.68 \times 10^{-12}\ {}^{mol}/_{s}$	$2.40 \times 10^{-8}\ {}^{mol}/_{hr}$	$3.47\ {}^{1}/_{hr}$
Average Value	$3.00 \times 10^{-12}\ {}^{mol}/_{s}$	$1.80 \times 10^{-8}\ {}^{mol}/_{hr}$	$1.56\ {}^{1}/_{hr}$
Δ(Flow)	$8.23 \times 10^{-13}\ {}^{mol}/_{s}$	$2.96 \times 10^{-9}\ {}^{mol}/_{hr}$	$0.43\ {}^{1}/_{hr}$

Fig. 3.4: This is tabulated data showing the insulin flow into the bloodstream in the medical measurement of International Units per hour. The conversion factor used is 6.94 nmol = 1 IU.

This check indicates that our accuracy is quite satisfactory. As an average flow value of $3 \times 10^{-12}\ {}^{mol}/_{s}$ yields an effective basal rate of 1.56 IU per hour our model fits directly in the middle of the average range of basal rates with a change in flux being able to alter it enough in each direction by changing model parameters (the value of $3 \times 10^{-12}\ {}^{mol}/_{s}$ for flow is the approximate midpoint of the flux bell curves derived above). This indicates that our experiment seems to be appropriate for imitating a basal rate and reduces a diabetic's need for insulin injections. It should also be noted that the peak flux values would significantly decrease the need for insulin during meal times.

Also it should be noted that it is unnecessary to change these values to a concentration, as the basal rate of 1-2 IU per hour is given in terms of mass.

IV. Conclusions and Design Recommendations

4.1. Optimization and Potential of the Device

With the three conclusions above, of a model that outputs insulin at an accurate physiological level and is sensitive to alterations, the device can be optimized for other potential patients.

From our analysis in the accuracy check, we found that our device as modeled matched physiological levels almost perfectly. Due to the sensitivity of the body to insulin levels (as the reader can see, the required insulin levels are on the order of picomoles), any small change in

the length of the implant will alter the insulin flow enough change the effectiveness of the device. To show this, we reduced the length of the implant by one millimeter and plotted the resulting insulin flow in Figure 4.1 (the solid line is the original flow graph). The variation at the peak is 1.504% - again, this does not seem like much, but even a change of this magnitude can affect the functionality of the device.

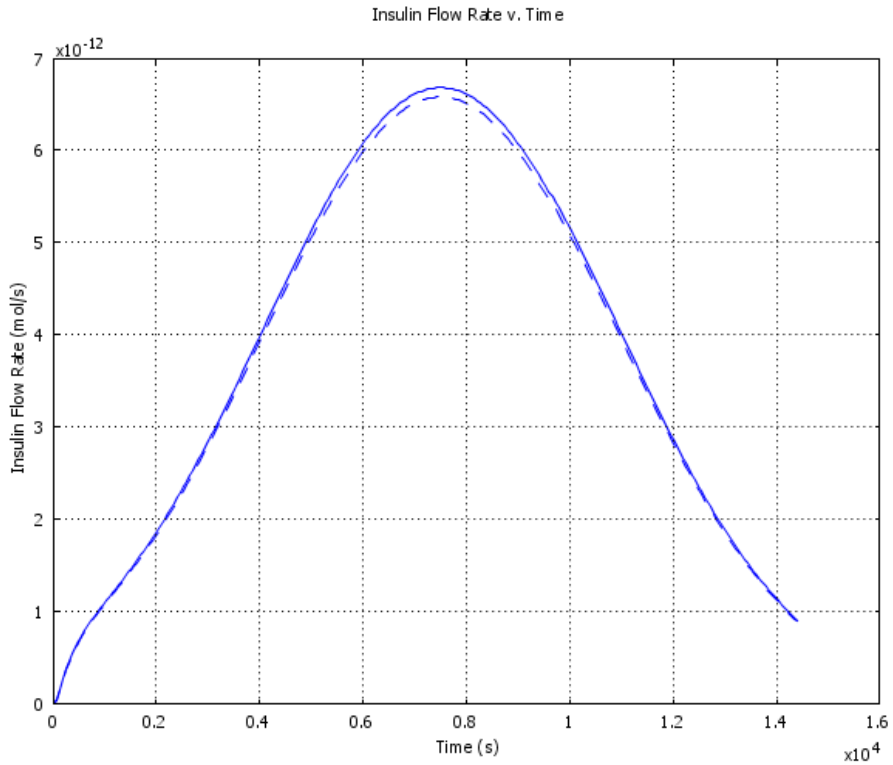


Fig. 4.1: Change in the insulin flow rate due to decreasing the length of the implant by 1 *mm*. The solid line is the original curve, while the dashed line is the curve after the reduction. The value at the peak decreases by 1.504%, which can be significant in the context of insulin production.

Of course, each patient is different, and so the optimal length of the implant will actually vary from case to case. As we mentioned, we based our model on a patient of mean 34 *yrs* and mean body mass index of 26.1 [2]. For patients in these ranges, then, a length of 76.2 *mm* will provide near perfect physiological insulin levels.

76.2 *mm* is actually quite long for an implant, however, and a possible way to circumvent this is to add more cells by making the cell chamber larger. The constraint in this case, however is the nutrient transport into the chamber and to the cells furthest from the blood. A similar model to ours, but using oxygen as the species in transport, would illuminate this optimization problem easily.

The diffusivity of the hydrogel to insulin is the second parameter we can optimize. Since our sensitivity analysis showed minimal sensitivity to this parameter, we believe any hydrogel with diffusivity around the value used in this model will suffice in terms of perfecting insulin flow rates. In worrying about the hydrogel, however, we must turn to a more serious problem,

one that plagues tissue engineering in general – the immune response to the implant, which usually depends heavily on the nature of the material used. Finding an optimal hydrogel, therefore, will require examining the mass transport of immunogenic particles such as IgG. Again, our model can be repeated, but using different immunogenic species (such as IgG) to accomplish this.

In short, our modeling technique for the intravascular arteriovenous shunt can be modified with different mass species to obtain an overall picture of the optimal parameters required.

This shows the flexibility of this model in its potential to improve the quality of life of a wide range of people suffering from Type I diabetes.

4.2. Realistic Constraints

While COMSOL is an incredibly powerful modeling software, it cannot recognize design impossibilities that are rooted in the physical reality of a problem. In the case of this implant, two of the biggest concerns for this kind of biologically active implant would be the patient's natural immune response and the problem of meeting the implant's nutrient needs.

As mentioned above, oxygen flux through the cells and membrane must be found because at a certain point the lack of oxygen would cause the implanted cells to die. This would be a severe design problem and one that has compounding ramifications when considered with other aspects of the implant's design.

Also, the body's immune response is increased with the body's increasing exposure to the implant. The size of our implant increases the likelihood of an immune reaction and this should be negated by reducing the area of our implant. However, this correspondingly would make oxygen diffusion through the tissue more difficult. These are realistic constraints which require more study in order to ensure that our implant can physically be realized and must be of an avenue of careful examination through more modeling or experimentation to ensure that the physical reality matches the modeled reality.

4.3. Conclusion

Diabetes is a condition affecting many Americans that can have life-threatening effects at worst or severely impact quality of lift at best. In this case, the primary goal of our model was to design something to improve overall patient quality of life by reducing the need for injection of insulin.

While significant amounts of research remain to be done, the basic feasibility of this implant to combat diabetes has been bolstered. With our generated insulin flux values matching mean basal rate levels, this implant shows potential to alleviate some of the symptoms of diabetes and is worthy of further research.

V. Appendix

5.1. Mathematical Statement of the Problem

We are using axisymmetry (therefore we are modeling a cylinder). In the membrane, our governing equation is the mass transfer equation in cylindrical coordinates with no reaction and convection:

$$\frac{\partial c}{\partial t} = D\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + \frac{\partial^2 c}{\partial z^2}\right) \quad (2)$$

In the blood, there are two governing equations – the mass transfer equation in cylindrical coordinates without reaction and the Navier-Stokes equation. The latter yields a velocity profile of this form:

$$\|\vec{v}\| = \|\vec{v}\|_0\left(1 - \frac{r^2}{r_0^2}\right) \quad (3)$$

In both the membrane and the blood, there is initially no insulin.

The boundary conditions used were as follows (Boundary 4 is internal and therefore excluded):

Boundary 1 (center axis of blood vessel): flux is 0 due to symmetry.

Boundary 2 (entrance of blood vessel): concentration is 0 because the blood has not picked up any insulin.

Boundary 3 (exit of blood vessel): convective flux boundary condition – the flux will be whatever it is at that point.

Boundary 5, 6 (edges of membrane): flux is 0 due to membrane attachment to impermeable material.

Boundary 7 (cell edge of membrane): flux specified by cells:

$$\phi_m = \left(8.71 \times 10^{-15}\ {}^{mol}/_{mm^2 \cdot s}\right) e^{-\left(\frac{t-(7200\,s)}{(4870\,s)}\right)^2}.$$

The property values used were as follows:

Diffusivity of insulin in membrane: $D_{IM} = 2.43 \times 10^{-5}\ {}^{mm^2}/_{s}$

Diffusivity of insulin in blood: $D_{IB} = 1.16 \times 10^{-4}\ {mm^2}/{s}$

Volumetric flow rate of blood: $\dot{V} = 8.33 \times 10^{3}\ {mm}/{s}$

Velocity profile of blood: $\|\vec{v}\| = (702\ {mm}/{s})\left(1 - \frac{r^2}{(2.5\ mm)^2}\right)$

Length of implant: $\ell = 76.2\ mm$

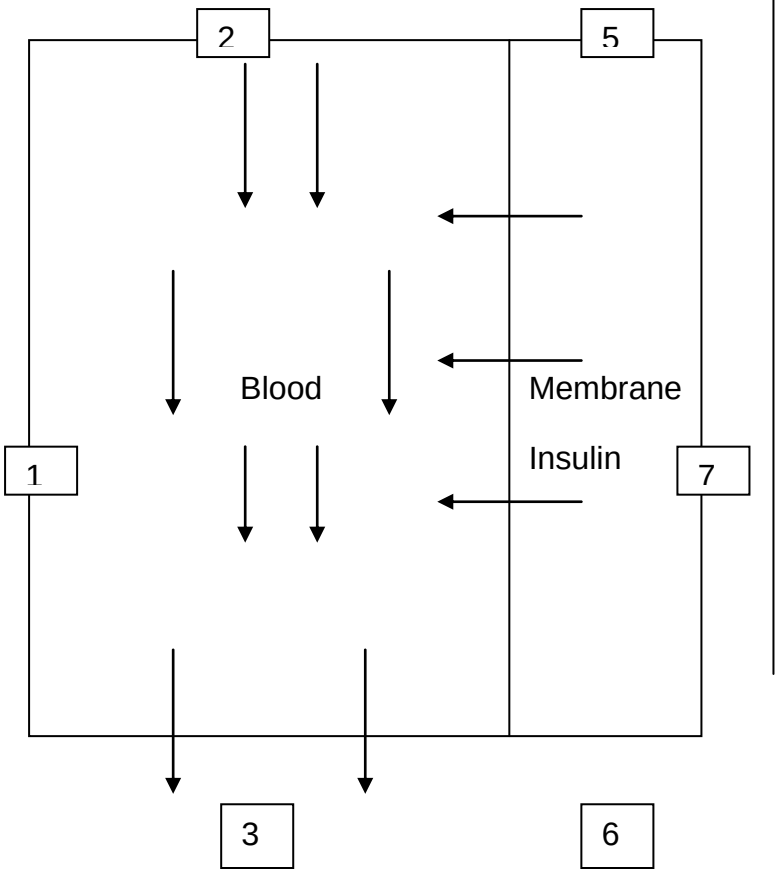
Inner radius of implant: $r_0 = 2.5\ mm$

Width of membrane: $dr = 0.12\ mm$

Volume of implant: $V = 147.1\ mm^3$

Average value of boundary 7 flux function: $\phi_{av} = 5.03 \times 10^{-15}\ {mol}/{mm^2 \cdot s}$

Time window modeled: $t(s) = 0{:}\,60{:}\,14400$



Governing Equation:

$$\frac{\partial c}{\partial t} = D\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + \frac{\partial^2 c}{\partial z^2}\right)$$

Initial Condition:

C = 0 @ time = 0

Boundary Conditions:

Defined by number above

Blood Velocity:

$$\|\vec{v}\| = \|\vec{v}\|_0\left(1 - \frac{r^2}{r_0^2}\right)$$

Properties:

Defined above

76.2 mm long

5.2. Technical Details

The direct (UMFPACK) solver was used to solve the problem. We chose a time step of one minute to be as precise as possible without overloading the computer memory. The

relative tolerance was 0.01 and absolute tolerance was 0.0010. Relative tolerance is indicative of the error relative to the quantity being calculated. For example, percent error is also a kind of relative tolerance as the calculated percentage is dependent on both a calculated value and a deviation from an accepted value. Absolute tolerance is different as simply the magnitude of a number is the only factor of concern. These values listed above were obtained from COMSOL and indicate tolerances within calculated output values and were calculated for our main variable of interest the blood insulin concentration.

5.3. Mesh Statistics for the Microsphere (fail)

As was mentioned in the report, we attempted to model a microsphere to compare it with the shunt (the main focus of the project). In doing this we modeled a sphere of radius 0.25 mm. In COMSOL this corresponds to an axisymmetric geometry using a half-circle. Because the spheres are not membrane-encapsulated, the boundary of the sphere has the time-dependent flux condition $\phi_m = \left(3.79 \times 10^{-16}\ {mol}/{mm^2 \cdot s}\right) e^{-\left(\frac{(t-(7200\,s))}{(4870\,s)}\right)^2}$. We arrived at this equation by using the original insulin flow equation and scaling down by volume.

We chose to model 2.25 mm of blood on one side of the sphere (so the sphere is in the exact center of the blood vessel) because this is the distance used in the other device. The equation for blood flow is the same. All boundaries have zero flux except for the exit, which is free.

The model described here has major flaws, the first being that such a small sphere will not remain stationary in the blood as the model suggests. Also, many such spheres are implanted, leading to more complex concentration profiles. Finally, as we found while doing mesh convergence, the tiny amounts of insulin involved actually gives the computer problems:

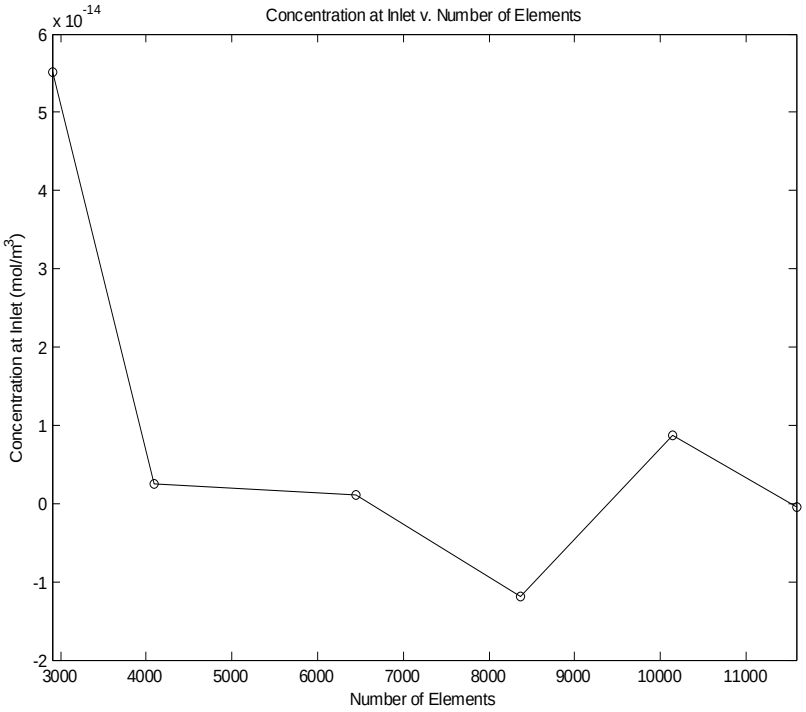


Fig. 5.1: Mesh convergence for the microsphere model. As of 11587 elements, the mesh not only does not converge, but fluctuates through positive and negative values, implying the computer cannot handle such small numbers.

In the shunt, we got mesh convergence at ~500 elements. Here, we went to 11587 elements and the concentration is still changing; furthermore, it fluctuates between positive and negative values (this is the reason a mesh plot of the microsphere is not included in this text). From here we concluded that the microspheres cannot be modeled in COMSOL using the approach we used before. Instead, much more complex analyses must be done, and considering we only wanted to model this alternative device as a comparison to the main cylindrical device, given the time we have remaining in the project we felt continuing in this regard was not worth it.

5.4. Mesh Statistics for the Intravascular Arteriovenous Shunt (success)

Our mesh statistics are as follows (our mesh size is very small compared to our geometry, and so a mesh plot would appear uniformly gray even at the most zoomed-in):

Number of degrees of freedom	19669
Number of mesh points	4995
Number of elements (total)	4840
Number of elements (triangular)	0
Number of elements (quadrilateral)	4840
Number of boundary elements	418

Number of vertex elements	6
Minimum element quality	0.086
Element area ratio	0.48

The parameter used to find mesh convergence was the average concentration of insulin in the membrane. This value is almost completely irrelevant in the grand scheme of the project, but it provides a single variable from which to find mesh convergence.

In finding mesh convergence, the time-dependent boundary condition for flux was not used (because the average concentration was found at the last time step anyway). Instead, the average value of the flux function was used. The values for mesh convergence are as follows (the number of mesh elements only reflects the number of elements in the membrane subdomain, because that's where the integration was taking place):

$n_{elements}$	$n_{insulin}\ (mol)$	$c_{av}\left(mol/mm^3\right)$
20	1.902×10^{-9}	1.293×10^{-11}
80	1.906×10^{-9}	1.296×10^{-11}
320	1.913×10^{-9}	1.301×10^{-11}
440	1.926×10^{-9}	1.309×10^{-11}
660	1.926×10^{-9}	1.309×10^{-11}
720	1.926×10^{-9}	1.309×10^{-11}

Fig. 5.3: Numerical data for mesh convergence.

It can be concluded, therefore, that 440 mesh elements is sufficient for mesh convergence. The results are shown graphically here:

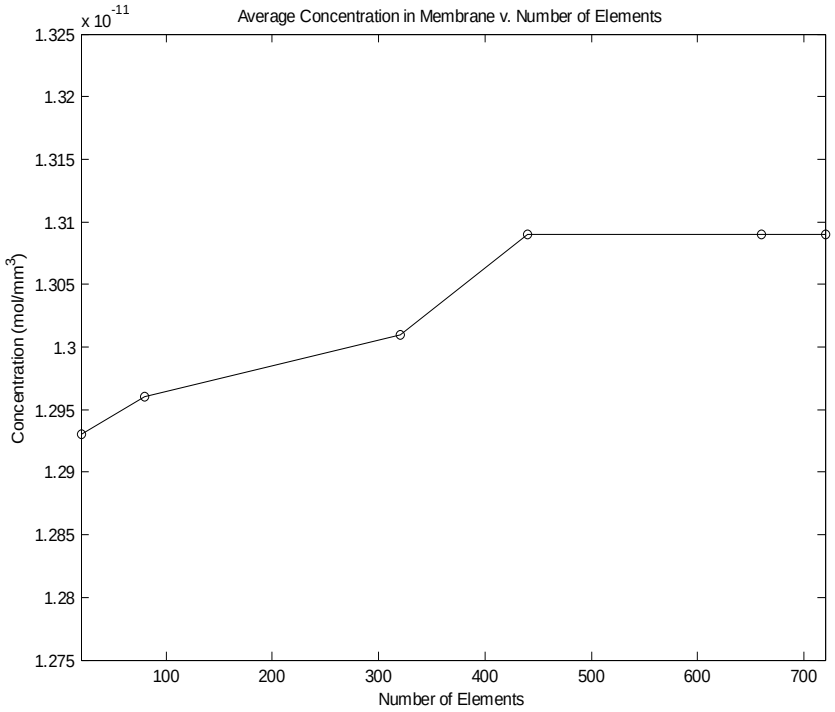


Fig. 5.4: Mesh convergence for the shunt. Convergence happened at 440 elements.

5.5. Figures not Included in the Text

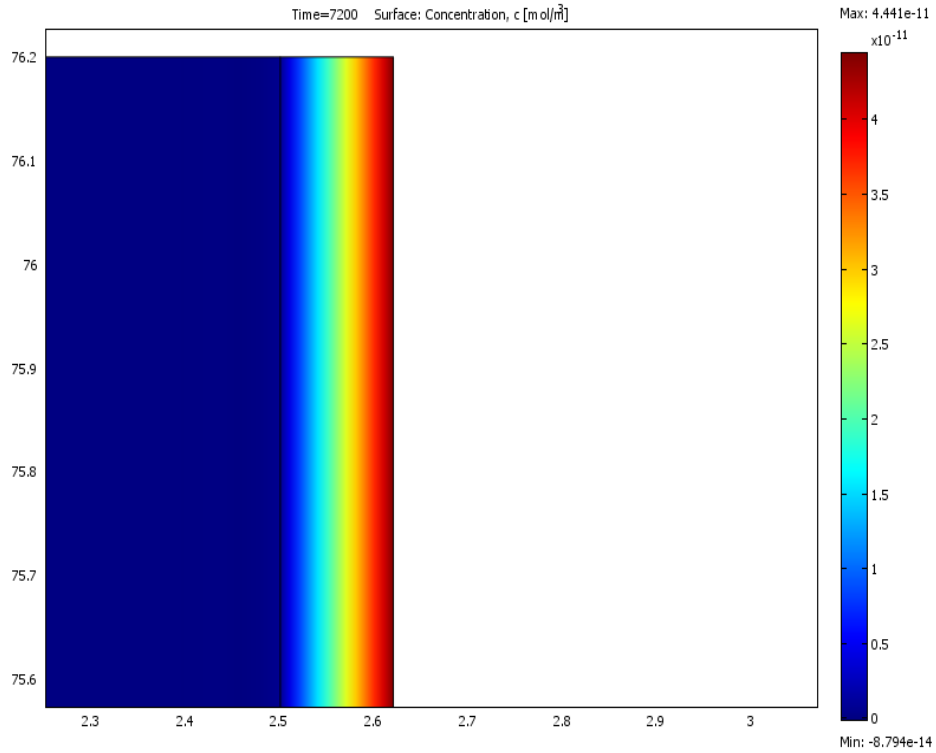


Fig. 5.5: Surface plot of insulin concentration at the area of the device where blood is exiting.

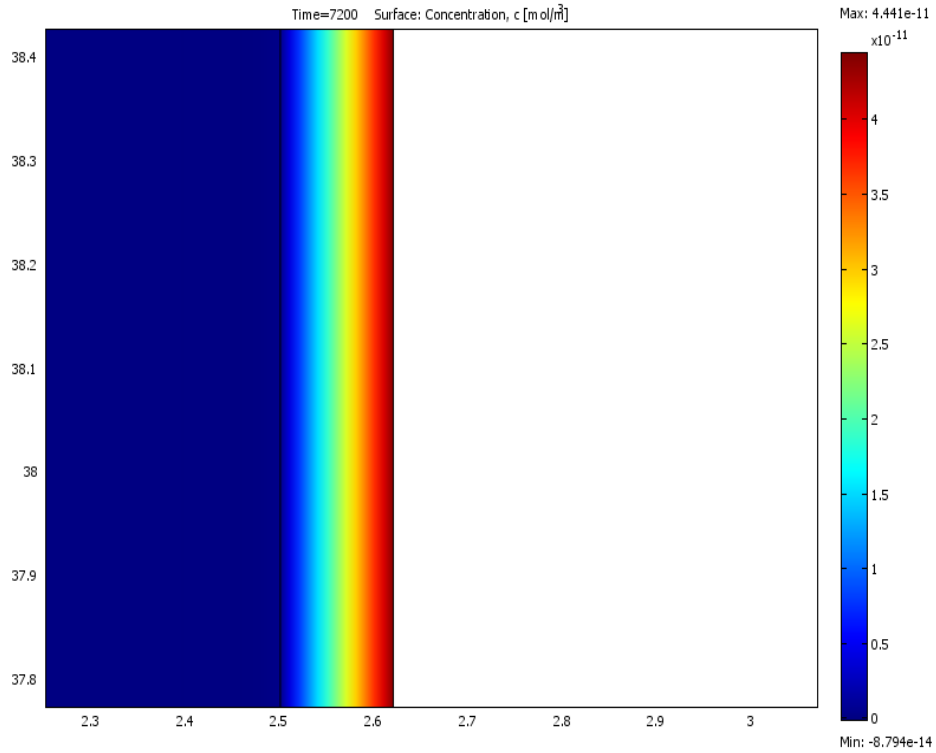


Fig. 5.6: Surface plot of insulin concentration at the middle of the device.

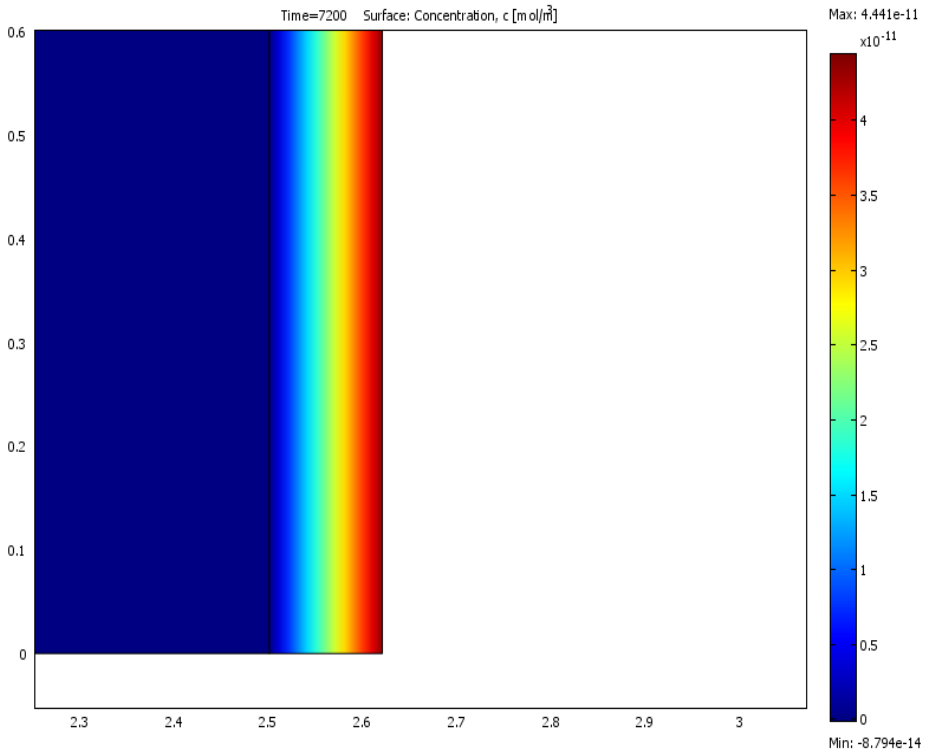


Fig. 5.7: Surface plot of insulin concentration at the area of the device blood is entering.

5.6. References

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