Investigating How Calcium Diffusion Affects Metabolic Oscillations and Synchronization of Pancreatic Beta Cells

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Abstract

In order to further understand diabetes mellitus, it is necessary to investigate the dynamics of insulin secretion in the bloodstream. Diabetes is a disease characterized by improper concentrations of blood glucose due to irregular insulin production. Beta cells are responsible for the production and regulation of insulin based on changes in glucose levels. Clusters of these cells, known as islets of Langerhans, are part of the endocrine system in the pancreas. Ultimately, insulin secretion occurs because of changes in the calcium concentration levels in beta cells. This dynamical process is composed of electrical, metabolic, and mitochondrial components that work together to release insulin into the blood. A mathematical model has been developed that captures the full dynamics of insulin secretion including the fast- and slow-bursting behavior from electrical and glycolytic oscillations, respectively.

Using the Dual Oscillator Model, we will examine how calcium handling within individual pancreatic beta cells affects the synchronization of metabolic oscillations within electrically coupled islets. Calcium permeability was implemented into the Dual Oscillator Model, and numerical solutions of the system were obtained via Matlab using a modified ordinary differential equation solver for stiff systems and the Automatic Differentiation for Matlab software. A synchronization index has been developed to quantitatively describe the synchronization of variables between nearest neighboring cells and throughout the islet as a whole. We consider how calcium diffusion between heterogeneous cells affects the behavior of metabolic oscillations and their synchronization. In particular, we want to examine fructose-1, 6-bisphosphate and glucose-6-phosphate. Our research will show whether calcium diffusion between cells enhances, diminishes, or terminates metabolic oscillations.

Key words. Pancreatic beta cells, calcium diffusion, diabetes, synchronizations, metabolic oscillations, Dual Oscillator Model.

1 Introduction

Diabetes mellitus, a group of diseases related to glucose levels in the blood stream, affects over 29 millions Americans and over 380 million people worldwide. Furthermore, the population of people with diabetes is expected to double by the year 2030, posing a major threat to the human race [1]. There are two major forms of diabetes, type 1 diabetes and type 2 diabetes. Both types rely on insulin production in the pancreas to regulate high glucose levels. Type 1 diabetes is an autoimmune disorder where insulin cannot be produced because the immune system attacks and destroys beta cells. Type 2 diabetes occurs when insulin is insufficiently produced to regulate the glucose levels [1]. Both types result in unhealthy glucose levels in the bloodstream. The growing number of cases of diabetes requires a deeper understanding of the pancreas, where insulin is produced. A brief explanation of the physiology of β-cells is discussed in Section 2, along with a look at the Dual Oscillator Model. Our methodology is described in detail in Section 3 and our results are examined in Section 4. And finally, we draw our conclusions in Section 5.

2 Background

2.1 Physiology

As mentioned above, insulin is produced in the pancreas. The pancreas consists of clusters of cells called islets of Langerhans. Each islet contains three different types of cells: α-cells, β-cells, and δ-cells. Our research focused on β-cells and the metabolic oscillation process that occurs within these β-cells [2]. As our title suggests, we were interested in researching how calcium affects the synchronization of cells within an islet. But first, it is necessay to understand the oscillation process in order to model synchrony within an islet.

An in-depth look at β-cells reveals a sophisticated and complex system of metabolic and electrical oscillations, cell coupling, and synchronization. Insulin is produced to control glucose levels. This multi-step process begins when glucose enters a β-cell, which starts the glycolysis process. As glucose is metabolized in the mitochondria, adenosine triphosphate (ATP) is created, and adenosine diphosphate (ADP) produces energy. As a result, K_{ATP} channels close. Next, the β-cell depolarizes which then permits calcium to enter the β-cell. Continuing on, insulin is secreted as ATP levels drop and ADP levels rise. Finally, K_{ATP} channels open again and this signifies the end of the depolarization process. The length of this process depends on whether the islet consists of mostly fast-bursting cells or mostly slow-bursting cells. If it is a fast-bursting islet, the metabolic oscillation will execute within tens of seconds. If it is a slow-bursting islet, these oscillations will progress over four to six minutes [6].

As mentioned above, we are interested in the oscillation synchrony and cell communication made possible through gap junctions. β-cells are connected by channels, called gap junctions, which allow metabolites and ions to be transferred between the cells. As one cell experiences the bursting process, the cell communicates to its neighboring cells, affecting the bursting process. This results in the synchronization of β-cells and the islets they comprise.

2.2 Mathematical Model

$$\frac{dV}{dt} = -\frac{I_{\mathrm{K}} + I_{\mathrm{Ca}} + I_{\mathrm{K(Ca)}} + I_{\mathrm{K(ATP)}}}{C_m} \tag{2.1}$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \tag{2.2}$$

$$\frac{d[\mathrm{Ca}]}{dt} = f_{cyt}(J_{mem} + J_{er}) \tag{2.3}$$

$$\frac{d[\mathrm{Ca_{er}}]}{dt} = -f_{\mathrm{er}}\sigma_V J_{er} \tag{2.4}$$

$$\frac{d[\mathrm{ADP}]}{dt} = J_{hyd} - \delta J_{ANT} \tag{2.5}$$

$$\frac{d[\mathrm{G6P}]}{dt} = k(J_{GK} - J_{PFK}) \tag{2.6}$$

$$\frac{d[\mathrm{FBP}]}{dt} = k(J_{PFK} - \frac{1}{2}J_{GPDH}) \tag{2.7}$$

The Dual Oscillator Model consists of seven differential equations, each with one independent variable: $V, n, [\mathrm{Ca_{er}}],\ [\mathrm{Ca_{er}}], [\mathrm{ADP}], [\mathrm{G6P}], [\mathrm{FBP}]$. The model can be separated into three components: electrical, mitochondrial, and glycolytic. The first four equations (2.1)-(2.4) comprise the electrical component, the fifth equation (2.5) characterizes the cell's mitochondria activity. The last two equations (2.6) and (2.7) describe the glycolytic activity occurring in the cell.

2.3 Electrical Component

Equation 2.1 represents membrane potential V is calculated by summing up the following ionic currents (2.8)-(2.11) and dividing them by the membrane capacitance, C_m.

$$I_k = \bar{g}_k n(V - V_k) \tag{2.8}$$

$$I_{Ca} = \bar{g}_{Ca} m_\infty (V - V_{Ca}) \tag{2.9}$$

$$I_{K(Ca)} = g_{K(Ca)}(V - V_K) \tag{2.10}$$

$$I_{K(ATP)} = g_{K(ATP)}(V - V_K) \tag{2.11}$$

such that,

$$g_{K(Ca)} = \bar{g}_{K(Ca)} \left(\frac{Ca^2}{K_D^2 + Ca^2} \right) \tag{2.12}$$

$$g_{K(ATP)} = \bar{g}_{K(ATP)} O_\infty(ADP, ATP) \tag{2.13}$$

In equation (2.2), n is the activation variable for the voltage dependent K channels, while equation (2.3) represents the free cytosolic Ca^{2+} concentration. In equation (2.4) the concentration of Ca^{2+} in the endoplasmic reticulum is represented by Ca_{er}. The variables [ADP], [G6P], and [FBP] in equations (2.5)-(2.7) represents the [ADP], [G6P], and [FBP] concentrations, respectively.

The free cytosolic Ca^{2+} equation, (2.3), relies on the following equations,

$$J_{mem} = -(\alpha I_{Ca} + k_{\text{PMCA}} Ca) \tag{2.14}$$

$$J_{er} = J_{leak} - J_{\text{SERCA}} \tag{2.15}$$

such that

$$J_{leak} = p_{leak}(Ca_{er} - Ca) \tag{2.16}$$

$$J_{\text{SERCA}} = k_{\text{SERCA}} Ca \tag{2.17}$$

where the fraction of free to total cytosolic Ca^{2+} is represented by, the flux of Ca^{2+} across the plasma membrane is denoted by J_{mem}, the flux of Ca^{2+} out of the endoplasmic reticulum is referred to as J_{er}, the leakage permeability is referred to as p_{leak}, and k_{SERCA} refers to the SERCA pump rate.

A more detailed look into the DOM can be found in [6] and [10].

3 Numerical Methods

Implementation of the Dual Oscillator Model (DOM) occurred in a two-fold process: through a single cell model and an islet model. The single cell model represents the intracellular dynamics of a single β-cell within each islet. The system of seven ordinary differential equations described in (2.1)-(2.7) states the relationship between the electrical, glycolytic, and mitochondrial activity that occurs within a β-cell. The full islet model was implemented by inserting the single cell model into a larger dynamical system based on a collection of Matlab files utilized in previous work at the University of Maryland, Baltimore County High Performance Computing Facility [3], [4], [5].

The culmination of our work involves the inclusion of Ca^{2+} diffusion via gap junctions between individual β-cells. By implementing Ca^{2+} diffusion in the full islet model we were able to investigate the role of calcium in the metabolic oscillations in the face of heterogeneity and the overall synchronization of an islet. Heterogeneity was introduced into the islet model in one of two ways: by varying the initial conditions between individual cells or by modeling two types of slow cells with different glucokinase reaction rates, J_{GK}. Variation in initial conditions was achieved by drawing independently from a standard normal distribution scaled around the mean initial conditions with a standard deviation of 20 percent of the mean initial conditions. Lastly, a synchronization index adapted from [11] was developed

and implemented to measure synchronization across an islet. More details regarding the details of the synchronization index implementation can be found at the end of this section.

The Dual Oscillator Model (DOM) described in equations (2.1–2.7) was formally implemented using the dynamical systems software XPPAUT in the form of an `.ode` file [9]. Bertram successfully solved the system of equations and provided phase planes for each of the seven variables using initial conditions and parameter values found in [9]. Using the same initial conditions and parameter values, we implemented the DOM into Matlab. This was accomplished by vectorizing the DOM such that

$$\frac{dy}{dt} = f(t, y), \tag{3.1}$$

where

$$y = (V, n, Ca, Ca_{er}, ADP, G6P, FBP)^T. \tag{3.2}$$

It can be observed that equation (3.2) is a vector of the seven state variables, and the rate of change of the system as described in equation (3.1) holds the right hand side of equations (2.1–2.7).

The built-in Matlab solver `ode15s` was chosen to obtain numerical solutions for the individual DOM model since the system can be categorized as a stiff system of differential equations. In a stiff system such as this, calculations within the system are occurring on wide time scales. Some interactions take milliseconds to complete, while others are on the scale of minutes. The built-in solver `ode15s` utilizes backward difference numerical differentiation methods to approximate the derivatives, selects the most efficient initial time step, and updates the Jacobian and time interval as needed throughout the iterations to achieve optimal results [7]. Numerical solutions to the islet model utilized a modified version of Matlab's `ode15s` function to accommodate for memory issues [6]. Additionally, the Automatic Differentiation for Matlab software was implemented to provide a symbolic Jacobian matrix to the ordinary differential equation solver [5].

Islets of Langerhans were simulated as cubes of $N \times N \times N$ cells, where the islet configuration of β-cells was chosen based on the type of simulation. For simulations with varying initial conditions, the configuration consisted entirely of slow-bursting cells that had identical bursting parameter values. For simulations with two types of slow-bursting cells, the configuration consisted of alternating layers of each type of slow cell. In the latter simulation, a 50-50 ratio of the two types of slow cells was used.

To simulate a slow-bursting cell, the parameter values for J_{GK}, $\bar{g}_{K(Ca)}$, and $\bar{g}_{K(ATP)}$ were selected using an exploratory parameter space method. In this study bursting parameter values were chosen to ensure J_{GK} lies within a region where metabolic oscillations are independent of calcium oscillations or "calcium independent" region where

$$0.045 < J_{GK} < 0.15,$$

approximately [9]. To simulate two types of slow-bursting cells, the value for J_{GK} was varied by ten percent. One slow cell type is denoted by having $J_{GK} = 0.143$ and the other slow cell type with $J_{GK} = 0.133$. Values for the glucokinase flux were chosen at the upper bound of the calcium independent region to ensure the bursting period stayed within a reasonable time

frame. The values chosen accomplished this given the sensitivity of the system dynamics to changes in J_{GK}.

In order to realistically simulate β-cell islets, coupling was introduced into the model to represent the movement of ions between cells. Voltage coupling and calcium permeability were implemented into the DOM by introducing an adjacency matrix, G, such that

$$\frac{dy}{dt} = f(t, y) + Gy. \tag{3.3}$$

Matrix G contains values of either one or zero: elements equal to one represent a connection between neighboring cells, and elements equal to zero represent no connection. The product of the adjacency matrix and a vector containing the coupling strengths results in the matrix used in equation (3.3). Simulations involving no coupling, only voltage coupling, and voltage coupling paired with calcium diffusion were performed. When coupling was introduced to the system, an assortment of coupling strengths for both voltage (1, 5, 10, 50, 100, and 500 pS) and calcium (0.1, 0.011, 0.01, and 0.009 ms^{-1}) was implemented.

3.1 Synchronization Indexing

A synchronization index was developed to quantitatively describe the synchronization of the voltage, V, free cytosolic calcium concentration, $[Ca]$, and the fructose-1,6-bisphosphate concentration, $[FBP]$ throughout the islet. The Pearson correlation matrix was used to determine the pairwise correlation between nearest neighboring cells. Next we find the minimum row mean of the correlation matrix. This is accomplished by taking the averages across each row in the matrix. Then the minimum of each of the averages was chosen as the synchronization index for the islet.

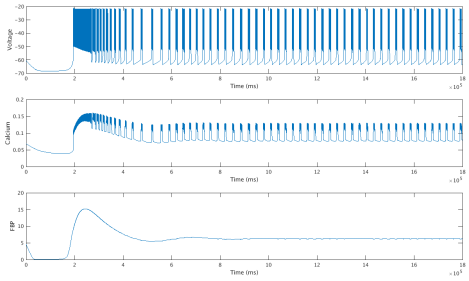
4 Results

In contrast with previous years, our modifications incorporate calcium diffusion along with voltage coupling and allow us to study how calcium handling between individual β-cells affects the oscillations and synchronization within pancreatic islets, particularly in FBP. Using these modifications, we simulate and describe how varying parameters and the heterogeneity of cells change oscillations within a multicellular islet. See Section 3 for further techniques used in the objectives of our studies.

4.1 Single β-cell Model Results

After implementing the original DOM file from XPPAUT to Matlab, we compared the results between the two to ensure that we converted the model accurately. We compared the oscillations for all variables and confirmed that the oscillations were equivalent between the two files. Figure 4.1 shows the voltage, calcium, and FBP oscillations for slow- and fast-bursting β-cells produced by the Matlab version of the DOM.

(a) Fast-bursting β-cell



(b) Slow-bursting β-cell

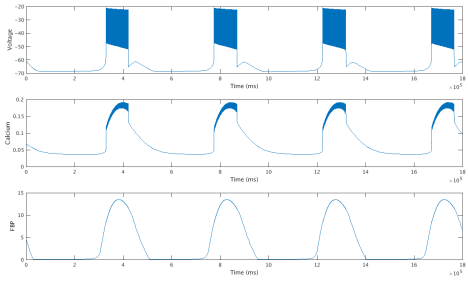


Figure 4.1: Single cell traces obtained from the revised DOM in Matlab for the (a) fast-bursting and (b) slow-bursting β-cells in a 30 minute period.

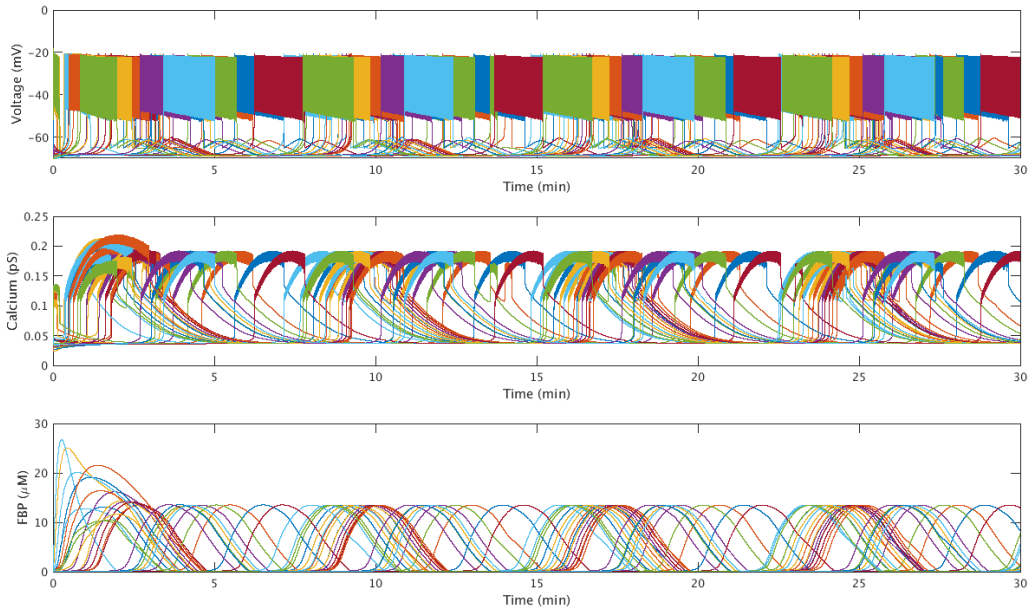


Figure 4.2: Voltage, calcium, and FBP traces for $3 \times 3 \times 3$ islet containing hetergeneous β-cells with voltage coupling = 0 pS and calcium diffusion = 0 ms^{-1}.

4.2 Coupling Between Individual β-cells

We extend our studies further by observing how voltage coupling and calcium diffusion effects the metabolic oscillations and synchronization of a $3 \times 3 \times 3$ pancreatic islet. The islet consists of only slow-bursting β-cells with initial conditions drawn independently from a normal distribution with 20 percent standard deviation and plotted over the course of 30 minutes.

(a) Voltage Coupling Only (b) Voltage Coupling & Calcium Diffusion

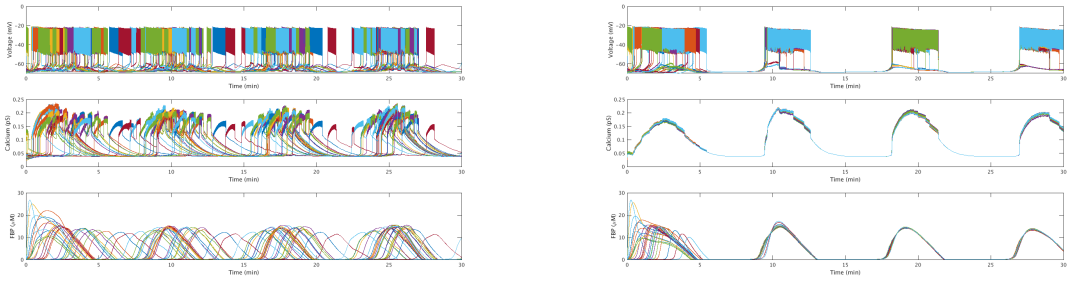


Figure 4.3: Electric and metabolic oscillations with voltage coupling = 5 pS and calcium diffusion = $\frac{5}{110}$ ms^{-1}

(a) Voltage Coupling Only (b) Voltage Coupling & Calcium Diffusion

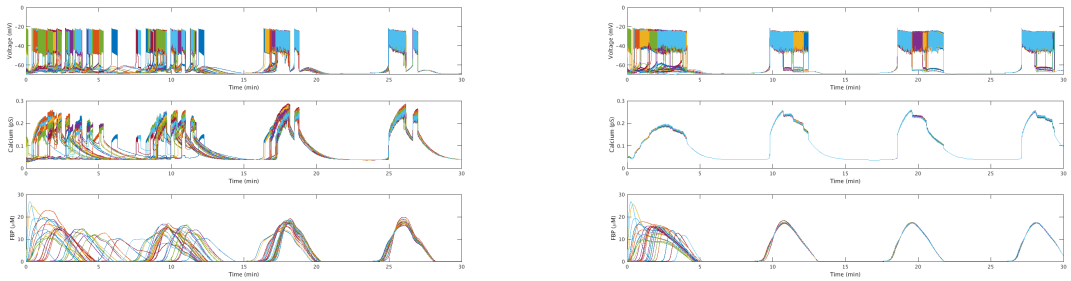


Figure 4.4: Electric and metabolic oscillations with voltage coupling = 10 pS and calcium diffusion = $\frac{10}{110}$ ms^{-1}

4.2.1 Voltage Coupling

We simulated islets with uniform, constant voltage coupling between nearest neighboring β-cells and various levels of voltage coupling, including 0, 1, 5, 10, 50, 100, 500 picosiemens (pS). In Figure 4.2, the absence of voltage coupling allows the cells to oscillate independently from

(a) Voltage Coupling Only (b) Voltage Coupling & Calcium Diffusion

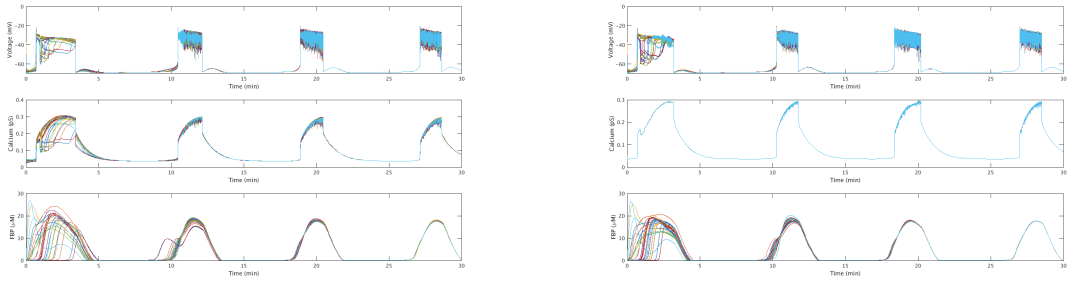
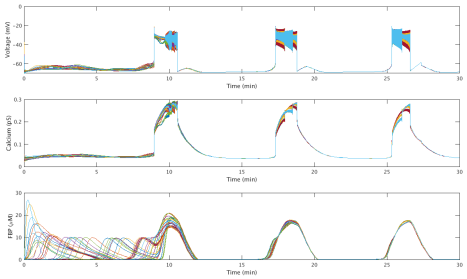


Figure 4.5: Electric and metabolic oscillations with voltage coupling =50 pS and calcium diffusion = $\frac{50}{110}$ ms^{-1}

(a) Voltage Coupling Only



(b) Voltage Coupling & Calcium Diffusion

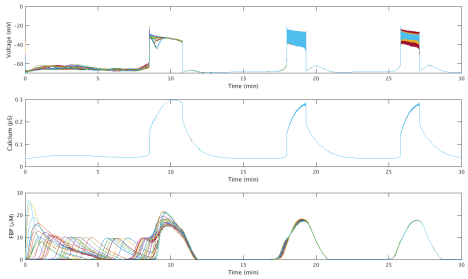


Figure 4.6: Electric and metabolic oscillations with voltage coupling =100 pS and calcium diffusion = $\frac{100}{110}$ ms^{-1}

one another and no synchronization between the cells is observed. As the amount of voltage coupling between the β-cells increases to 10 pS as shown in Figure 4.4(a), the oscillations slowly begin to synchronize. Increasing the voltage coupling even further to 50 pS, Figure 4.5 shows that a high amount of voltage coupling between cells allows for the oscillations to synchronize more rapidly than when the voltage coupling was lower. As the amount of voltage coupling increases, the synchronization of the oscillations within the pancreatic islet also increases. For islets that were uncoupled, and hence unsynchronized, a $3 \times 3 \times 3$ islet used about 26.27 minutes of computational time to simulate 30 min, whereas an islet that was highly synchronized took about 1.42 minutes.

4.2.2 Calcium Diffusion

In addition to adding voltage coupling to the pancreatic islet model, calcium diffusion was also incorporated into the code to observe if calcium handling had an effect on oscillations between β-cells. For each of the voltage coupling parameters, we simulated various levels of calcium diffusion as percentages of the voltages, including 0.9, 1, 1.1, and 10 percent. We only show traces for 0.9 percent of voltage coupling because we did not notice any different effects when the calcium diffusion value was higher than this. For simulations in which calcium diffusion was 100 or 1000 percent of the voltage coupling parameter, the oscillations did not change drastically, which suggests that calcium diffusion did not kill the oscillations as mentioned by [8]. As seen in Figure 4.3, when calcium diffusion was added, the oscillations become more synchronized in comparison to when there was only voltage coupling present. This phenomenon can also be seen in Figure 4.4 where voltage coupling plays a larger role, but calcium diffusion also synchronizes the oscillations further. When voltage coupling is around 50 pS, as shown in Figure 4.5, there is not very much difference between Figure 4.5(a) when only voltage coupling present and Figure 4.5(b) when there is an addition of calcium diffusion. As voltage increased higher than 50 pS, calcium diffusion did not affect the synchronization of the oscillations as much as when the voltage coupling was lower.

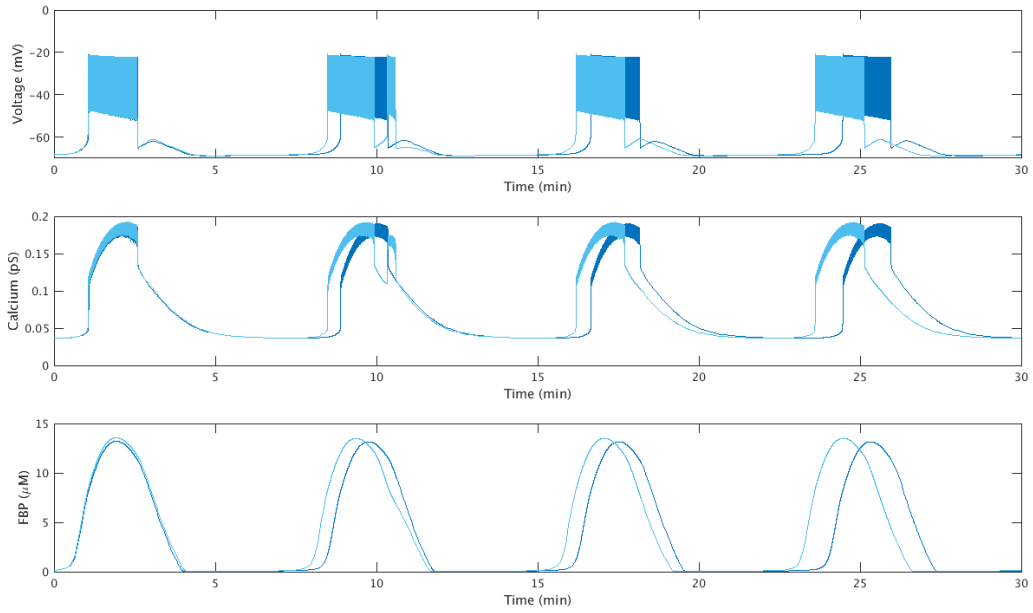


Figure 4.7: Voltage, calcium, and FBP traces for $3 \times 3 \times 3$ islet containing two different slow β-cells with voltage coupling = 0 pS and calcium diffusion = 0 ms^{-1}.

(a) Voltage Coupling Only

(b) Voltage Coupling & Calcium Diffusion

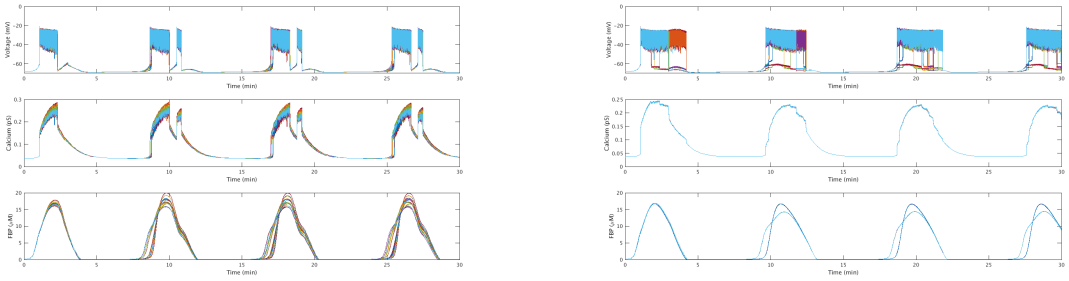


Figure 4.8: Electric and metabolic oscillations for varying J_{GK} experiment with voltage coupling = 10 pS and calcium diffusion = 1 ms^{-1}.

4.3 Varying J_{GK} in Slow β-cells

Beyond only varying the initial conditions of the β-cells, we also chose two different J_{GK} values to simulate how two different types of slow cells interact with one another when voltage coupling and calcium diffusion is introduced. Figure 4.7 represents the oscillations when there is no voltage coupling or calcium diffusion involved. Unlike the varying initial condition experiments, the two different kinds of cells begin at the same initial conditions, but continue to oscillate at their own respective rhythms. When introducing voltage coupling, represented in Figures 4.8 and 4.9, the electrical and metabolic oscillations synchronize over time, but it is still possible to see that the traces are not completely overlapped. However,

(a) Voltage Coupling Only (b) Voltage Coupling & Calcium Diffusion

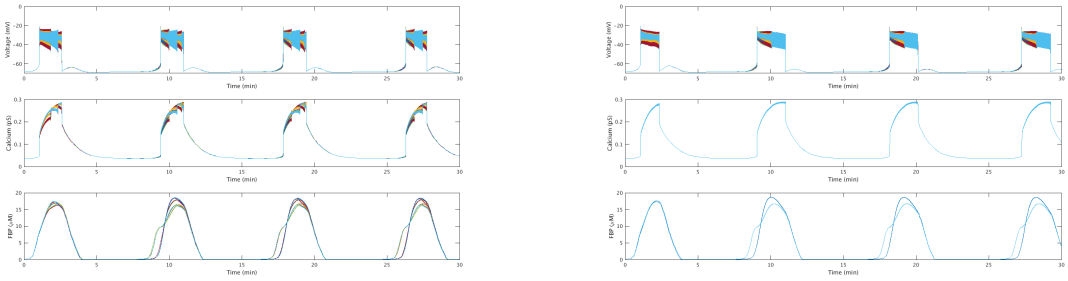


Figure 4.9: Electric and metabolic oscillations for varying J_{GK} experiment with voltage coupling = 100 pS and calcium diffusion = 10 ms^{-1}.

(a) Varying Initial Conditions (b) Varying J_{GK} Values

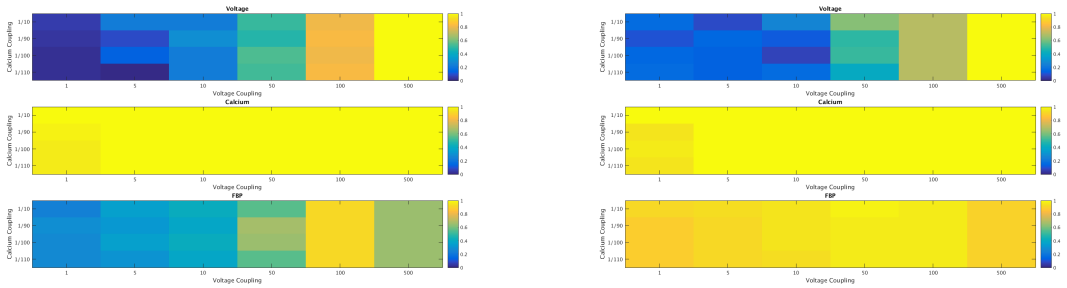


Figure 4.10: Plot showing scaled image data from a 2-D matrix containing synchronization indices of islets with corresponding voltage coupling and calcium diffusion parameters for varying (a) initial conditions and (b) J_{GK} values.

whenever calcium diffusion is introduced, the traces become synchronous in both cases. The addition of voltage coupling when varying the J_{GK} values has the same effects as seen when varying the initial conditions of the β-cells within an islet. When calcium diffusion is introduced in every case of voltage coupling, the traces become more synchronous, unless voltage coupling has already completely synched the traces.

4.4 Synchronization of Pancreatic Islets

To measure the synchronization of an islet as a whole, we performed the methods described in Section 3 and represented the synchronization of a $3 \times 3 \times 3$ multicellular islet with various voltage coupling and calcium diffusion parameters. In Figure 4.10, the yellow boxes indicate high synchronization, whereas the blue boxes represent low synchronization. Figure 4.10(a) represents the synchronization plots for the varying initial conditions experiments, whereas Figure 4.10(b) represents the synchronization plots for the two different J_{GK} value experiments. As seen in both figures in the voltage synchronization plot, as voltage coupling increased, regardless of the amount of calcium diffusion, the voltage oscillations became more synchronized within the islet. When the voltage coupling was a low value, the synchronization index of the voltage oscillations were close to zero, and therefore, not synchronized;

however, when calcium diffusion increased, the synchronization index of the voltage oscillations slightly increased. In both experiments, the calcium synchronization plots remained highly synchronized through all voltage coupling and calcium diffusion parameters with synchronization index values ranging from around 0.95 to 1. In the FBP synchronization plot, the same phenomenon was observed as in the voltage synchronization plot: as voltage coupling increased, the synchronization of the islet also increased. As calcium diffusion increased for low values of voltage coupling, the synchronization of the islet increased slightly. Within the FBP oscillations, it is important to note that in the experiments where we incorported two different slow cells within the islet, the range of the synchronization indices for the FBP plots was between approximately 0.85 and 1. When voltage coupling was very high, such as 500 pS, the synchronization of the islet seems to be lower. This occurred because we only simulated the oscillations for 30 minutes; when we run the simulations for longer times with voltage coupling at 500 pS, the FBP oscillations eventually synchronize.

4.5 Computational Challenges

Although there were many successes during our research project, we also faced several computational challenges while running simulations that we believe can be improved in the future. In the $5 \times 5 \times 5$ islet, there were specific cases where the cluster maya at the UMBC High Performance Computing Facility (HPCF) ran out of memory, despite only saving the variables V, Ca, and FBP, because there were too many time steps in the simulations. This occurred in cases when the islet's initial conditions were perturbed by 20 percent and when the coupling was low, resulting in low synchronization within the islet. We also attempted to run the pancreatic islet model containing $10 \times 10 \times 10$ cells, but this also proved to be too computationally challenging for the cluster maya as only the simulations that were completely synchronous finished running with results. As an example, for $3 \times 3 \times 3$ islets with varying initial conditions that were uncoupled, and hence unsynchronized, it took about 26.27 minutes to run completely, whereas an islet that was highly synchronized took about 1.42 minutes. For simulations that have many time steps, such as uncoupled $5 \times 5 \times 5$ and $10 \times 10 \times 10$ islets, these would not only take a long time to run, but also need a large amount of memory in order to save the traces for voltage, calcium, and FBP.

5 Conclusion

Utilizing a revised version of the Dual Oscillator Model we were able to better understand the effects of calcium diffusion between β-cells. The individual β-cells have gap junctions which allow Ca^{2+} to diffuse. By implementing Ca^{2+} diffusion in the full islet model, we were able to mainly focus on the role of calcium in the metabolic oscillations and synchronization.

The Dual Oscillator Model was created in a two-step process. The first step was the replication of the single cell model from XPPAUT to Matlab. Using the same initial conditions and parameter values in the XPPAUT file, we implemented the DOM into Matlab. The second step was creating the islet model. The full islet model was implemented by inserting the single cell model into a larger multi-cellular system on a 3-D lattice. We used the built in Matlab solver ode15s, which helped the model run faster by cutting down time in calculat-

ing derivatives and updating Jacobians. By introducing coupling between the cells, the cells started to develop synergy. In order to measure synchronization between cells in the islet, we successfully built on a previous synchronization index and developed and implemented an updated synchronization index. We were able to produce plots that show the effect of calcium diffusion in a 3x3x3 islet with initial conditions drawn individually from a normal distribution with 20 percent standard deviation.

Through multiple trials we came to a conclusion that calcium diffusion between β-cells in a pancreatic islet does indeed synchronize metabolic oscillations when voltage coupling is low. For example when voltage coupling is 1, 5, 10 pico siemens and calcium is applied, the β-cells have a higher synchronization index. However when voltage coupling is high (approximately 50 pS). The role of calcium in the synchronization of metabolic oscillations is overshadowed by voltage coupling. Although there were slight variation in the plots, there was no significant evidence that calcium diffusion plays a role when voltage coupling is high. Ultimately, calcium diffusion between pancreatic β-cells plays a role in the synchronization of metabolic oscillations.

Moving forward in this project it would be beneficial to use the same Dual Oscillator Model with a larger Islet (i.e. 10x10x10). Creating a larger islet would make sure that edge cells are not influencing the oscillations in any way. This would be done to produce a more intricate and accurate cell arrangement. It would also be interesting to study the synchronizations of islets in the pancreas with one another. This would allow future research to observe the cause of the synchronizations of islets.

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References

[1] "What Is Diabetes?" What Causes Diabetes? Web. 6 Aug. 2015.

[2] Annie Dai, David Palensky, Alex Piatski, Kendall Queen, Gina Vockeroth, Teresa Lebair, Bradford E. Peercy, Margaret Watts, Arthur Sherman. A spatial multi-cellular

model of the pancreatic islet including α-, β-, δ-cells. Technical Report HPCF-2014-13, UMBC High Performance Computing Facility, University of Maryland, Baltimore County, 2014.

[3] Sidafa Conde, Teresa Lebair, Christopher Raastad, Virginia Smith, Kyle Stern, David Trott, Matthias K. Gobbert, Bradford E. Peercy, and Arthur Sherman. Enabling physiologically representative simulations of pancreatic beta cells. Technical Report HPCF-2010-21, UMBC High Performance Computing Facility, University of Maryland, Baltimore County, 2010. (HPCF machines used: tara)

[4] Gemma Gearhart, Shuai Jiang, Thomas J. May, Jane Pan, Samuel Khuvis, Matthias K.Gobbert, Bradford E. Peercy, and Arthur Sherman. Investigating oscillation loss in computational islets. Technical Report HPCF-2013-14, UMBC High Performance Computing Facility, University of Maryland, Baltimore County, 2013. (HPCF machines used: tara).

[5] Samuel Khuvis and K Gobbert Matthias. Parallel performance studies for an elliptic test problem on the cluster maya. Technical report, Technical Report HPCF-2015-6, UMBC High Performance Computing Facility, University of Maryland, Baltimore County, 2015.

[6] Khuvis, S., Gobbert, M. K., Peercy, B. E. (2015). Time-stepping techniques to enable the simulation of bursting behavior in a physiologically realistic computational islet. *Mathematical Biosciences*, 263, 1-17.

[7] Lawrence F. Shampine and Mark W. Reichelt. The matlab ode suite. *SIAM Journal on Scientific Computing*, 18:1-22, 1997.

[8] Krasimira Tsaneva-Atanasova, Charles L Zimliki, Richard Bertram, and Arthur Sherman. Diffusion of calcium and metabolites in pancreatic islets: Killing oscillations with a pitchfork. *Biophysical Journal*, 90(10):3434-3446, 2006.

[9] Margaret Watts, Bernard Fendler, Matthew J Merrins, Leslie S Satin, Richard Bertram,and Arthur Sherman. Calcium and metabolic oscillations in pancreatic islets: Who's driving the bus? *SIAM Journal on Applied Dynamical Systems*, 13(2):683-703, 2014.

[10] Bertram, R., Satin, L., Zhang, M., Smolen, P., Sherman, A. (2004). Calcium and glycolysis mediate multiple bursting modes in pancreatic islets. *Biophysical Journal*, 87(5), 3074-3087.

[11] Min Zhang, Bernard Fendler, Bradford E. Peercy, Pranay Goel, Richard Bertram, Arthur Sherman, Leslie Satin, Long Lasting Synchronization of Calcium Oscillations by Cholinergic Stimulation in Isolated Pancreatic Islets, *Biophysical Journal*, 2008, 95(10):4676–88.