

Dynamics of Computational Islet Simulations: Islets with Majority Mutated Open K_{ATP} Channels Retain Bursting

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Abstract

The study of pancreatic beta-cells comprises a crucial part of the study of the group of diseases known as diabetes. These cells exist in groups known as islets of Langerhans and are responsible for storing and producing insulin. They exhibit electrical bursting behavior during insulin production that correlates with the rate at which insulin is secreted into the bloodstream. Coupling is a natural process within islets that enables the cells to communicate with one another and transfer various ions and electrical currents; coupling of both voltage and metabolites can occur. We model multicellular islets using an existing system of seven ordinary differential equations to model beta cell function. We simulate cells with mutated K_{ATP} channels that remain open indefinitely, which have been described in experimental studies but not yet modeled. Simulations run with these mutations reveal the existence of a bursting death threshold, described by the least percentage of cells in the islet that must be mutated for electrical bursts to completely disappear. We determine that this threshold is independent of coupling strengths, cell distribution, and possibly islet dimension; however, we also determined that this threshold is dependent on the glucose influx rate.

Keywords: Beta cell model, computational islet, glycolytic oscillations

1 Introduction

Diabetes mellitus, commonly known as diabetes, is a group of diseases in which the body either does not have the capabilities of producing insulin or is not capable of producing sufficient amounts of insulin to compensate for the glucose that enters the body. According to the American Diabetes Association (ADA), this set of diseases affects the lives of approximately 8.3% of the United States

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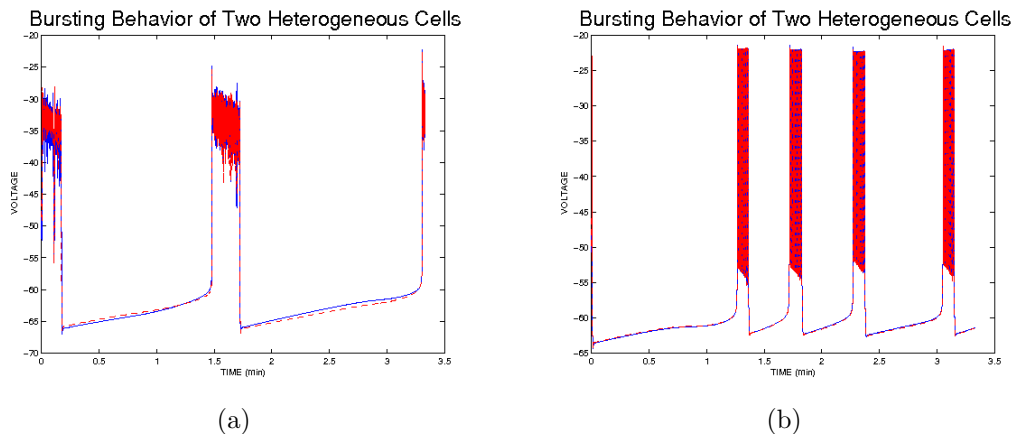


Figure 1: (a) Oscillation behavior of two coupled beta-cells with an electrical coupling value of 0.01 pS. (b) Oscillation behavior of the beta-cells with an electrical coupling value of 0.1 pS.

population of all ages and racial backgrounds [6]. However its prevalence is scattered across all regions of the world. Normally, when blood sugar levels are increased by the consumption of glucose, a healthy human body would naturally produce adequate amounts of insulin to remove excess glucose that could potentially be harmful if maintained. The biological units that are responsible for the secretion of insulin are identified as beta-cells [14], which are one of four hormone-producing cells located in the pancreas. Clusters of beta-cells are known as islets of Langerhans, which depend on other islets within the pancreas to successfully carry out the production of insulin.

While Type I Diabetes involves the immune system directly attacking the beta-cells, Type II Diabetes is caused by the increasing resistance that the body has towards the effects of insulin rather than the lack of beta-cells directly. In order to have a better understanding of diabetes in the hopes of finding effective methods to treat it, it is necessary to analyze the behavioral patterns exhibited by pancreatic beta-cells.

Previous studies have observed that beta-cells undergo voltage oscillations during the course of insulin secretion. Once glucose enters the beta-cell, the cell itself experiences an increase in ATP, which leads to the depolarization of the beta-cell, allowing calcium to enter and insulin to be released into the bloodstream [10]. The frequency at which insulin is secreted correlates to the oscillating behavior of the cells. Oscillations are grouped in bursts of electrical activity.

Coupling is a natural process that occurs between cells within the islets of Langerhans. Gap junctions serve as pathways for the coupling that occurs between these cells, allowing for effective communication from cell to cell, including the transfer of ionic currents and calcium ions [1]. Previous findings have supported the notion that certain variations of coupling play a vital role in facilitating the production of insulin [14]. This behavior can be seen primarily in the bursting patterns that the cells experience.

Figure 1 displays the oscillation behaviors of two heterogeneous beta-cells when they are electrically coupled with one another. Both plots display continuous voltage alterations between rapid spiking behavior and stages of gradual increase. The rapid voltage oscillations denote the bursting action of the beta-cells, signifying the release of insulin. The smooth lines following these rapid spiking phases represent the periods of rest before insulin is secreted again.

Cases in which the cells contain stronger electrical coupling strengths eventually become synchronized. Figure 1 contains the results that are obtained when the electrical coupling strength is increased by a factor of 10. It can be observed that the oscillations between the two cells are more harmonized, which suggests that the bursting behaviors between the two heterogeneous cells are similar.

Recent experiments (Benninger et al. [2], Nguyen et al. [11]) show that mutations in a potassium

channel (K_{ATP}) that reduces sensitivity to ATP:ADP ratios as well as trafficking to the beta-cell membrane can impact the influx of calcium and the resultant secretion of insulin. The method used to impart this mutation was a transgene that alters the functional K_{ATP} channels but not in all of the beta-cells in an islet. Furthermore, the electrical coupling strength between the beta-cells of an islet can coordinate otherwise heterogeneous beta-cells. Both Benninger et al. and Nguyen et al. reduce coupling in an islet and unmask heterogeneity in K_{ATP} channel mutated islets by releasing mutated or unmutated cells to burst depending on closed or open form of the K_{ATP} channel mutation. We have developed a computational islet [10] that we use to mutate mathematically K_{ATP} channels in a fraction of islet cells. Here we observe the level of open K_{ATP} channel mutation necessary for loss of islet bursting.

2 Mathematical Model

To approach this problem, we represent a computational islet using an $N \times N \times N$ lattice of beta-cells, where N represents the dimensions of the lattice measured in number of cells.

One of the main focuses of our project was using these models to study the factors that provoke oscillation deaths. The term “death” is used to signify the loss in slow metabolic oscillations that the beta-cells exhibit. We looked at cases with distributions containing a certain proportion of mutated cells, in which the K_{ATP} channels of the cells are always open. Similar to what we did for the first part of our research, we observe the bursting behaviors that result from the addition of these mutated cells. We also determine the specific proportion of mutated channels that serve as a threshold between oscillating patterns and oscillation deaths. Specific distributions of these mutated cells can be found in Section 3.1.

After running tests that focused on manipulating the coupling strengths and varying the proportions of cells with mutated K_{ATP} channels, we were able to gain a clearer understanding on how these parameters play a role in the oscillating behavior of the cells. When determining the types of initial conditions that caused metabolic oscillations in beta-cells, we found that certain combinations of coupling at specific ranges of coupling strengths cause gradual reduction in metabolic oscillations. Furthermore, we noticed that having greater than 74% mutated cells in the distribution causes metabolic oscillation death regardless of the conditions of the other parameters. Details on specific inputs and results we obtained can be found in Section 4. Final conclusions are made in Section 5.

Oscillations in voltage and metabolites, such as glucose 6-phosphate (G6P) and fructose 1-6-bisphosphate (FBP), occur when glucose enters beta-cells through special protein channels in the cell membrane called glucose transporters (e.g., GluT1 or GluT2) via facilitated diffusion. This only occurs when the concentration of glucose outside the beta-cell is high. The cell then metabolizes the glucose in the mitochondria and produces adenosine triphosphate (ATP). Increases in the concentration of ATP triggers depolarization of beta-cell membranes by closing channels of ATP-sensitive (K_{ATP}) channels, which causes calcium to enter the cell. The subsequent influx of calcium and increase in [Ca] causes the release of vesicles containing insulin into the blood stream. Glucose levels are then decreased due to the release of insulin and the beta-cell resets itself [9]. The reaction rate of glucokinase (called R_{GK}) reflects the level of glucose stimulation and does not change during the course of a simulation.

The K_{ATP} channels that facilitate membrane depolarization are the main regulator of electrical activity in the islet, and glucose-stimulated insulin secretion relies on the sensitivity of these channels to ATP-inhibition. Mutations that render K_{ATP} channels insensitive to ATP-inhibition suppress glucose-stimulated insulin secretion and alter voltage levels in the islet. Mutations of these channels can occur such that they remain either open or closed.

In each cell, the beta-cell model uses glycolytic dynamics initially developed by Smolen [12], combined with electrical dynamics by Bertram et al. [3], and studied by Tsaneva-Atanasova et al. [14]. The model’s dependent variables are voltage V , fraction of open potassium channels n , and

five other chemical concentrations. The equations form a stiff system of seven coupled ordinary differential equations (ODEs). The equations are

$$\frac{dV}{dt} = -\frac{I_K + I_{Ca} + I_{K(Ca)} + I_{K(ATP)}}{C_m}, \quad (1)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}, \quad (2)$$

$$\frac{d[Ca]}{dt} = f_{\text{cyt}}(J_{\text{mem}} + J_{\text{er}}), \quad (3)$$

$$\frac{d[Ca_{\text{er}}]}{dt} = -\sigma_V f_{\text{er}} J_{\text{er}}, \quad (4)$$

$$\frac{d[ADP]}{dt} = \frac{[ATP] - [ADP] \exp\left\{(r + \gamma)\left(1 - \frac{[Ca]}{r_1}\right)\right\}}{\tau_a}, \quad (5)$$

$$\frac{d[G6P]}{dt} = k(R_{\text{GK}} - R_{\text{PFK}}), \quad (6)$$

$$\frac{d[FBP]}{dt} = k(R_{\text{PFK}} - 0.5R_{\text{GPDH}}), \quad (7)$$

where $[XX]$ denotes the concentration of XX in the cytosol for calcium (Ca), Adenosine diphosphate (ADP), glucose-6-phosphate (G6P), fructose-1,6-bisphosphate (FBP), and in the endoplasmic reticulum (ER) for calcium (Ca_{er}). The forms for consumption of G6P due to phosphofructose kinase R_{PFK} and dehydrogenase consumption of FBP R_{GPDH} can be found in [3].

Additional definitions are

$$\begin{aligned} I_K &= \bar{g}_K n (V - V_K), \\ I_{Ca} &= \bar{g}_{Ca} m_\infty (V) (V - V_{Ca}), \\ I_{K(Ca)} &= g_{K(Ca)} (V - V_K), \\ g_{K(Ca)}([Ca]) &= \frac{\bar{g}_{K(Ca)}([Ca])}{1 + \left(\frac{K_d}{[Ca]}\right)^2}, \\ I_{K(ATP)} &= g_{KATP} (V - V_K), \\ g_{KATP} &= \bar{g}_{K,ATP} o_\infty([ADP]), \\ m_\infty(V) &= \frac{1}{1 + \exp\left[-\frac{20+V}{12}\right]}, \\ J_{\text{er}} &= 0.0002([Ca_{\text{er}}] - [Ca]) - 0.4[Ca], \\ J_{\text{mem}} &= (4.5 \times 10^{-6})I_{Ca} - 0.2[Ca], \end{aligned}$$

where

$$o_\infty([ADP]) = \frac{0.08(1 + 2\frac{0.165[ADP]}{17}) + 0.89(\frac{0.165[ADP]}{17})^2}{(1 + \frac{0.165[ADP]}{17})^2(1 + \frac{0.135[ADP]}{26}) + 0.05[ATP]}. \quad (8)$$

The potassium channel has current, I_K , with maximal conductance, \bar{g}_K , and gating variable n driven by the potential's difference from the channel's Nernst potential, V_K . Similarly, the calcium, calcium-sensitive potassium, and ATP-sensitive potassium channel with currents, I_{Ca} , $I_{K(Ca)}$, and $I_{K(ATP)}$, each have a maximal conductance $\bar{g}_{K(Ca)}$, \bar{g}_{Ca} , and $\bar{g}_{K(ATP)}$. Each also has conductance dynamics defined by $m_\infty(V)$, $\frac{[Ca]}{1 + \left(\frac{K_d}{[Ca]}\right)^2}$ with sensitivity parameter K_d , and $o_\infty([ADP])$, respectively.

Calcium enters the cytosol via the membrane, J_{mem} , or from the ER, J_{er} . A corresponding amount is lost from the ER, $-J_{\text{er}}$. Each calcium dynamic is scaled by f_{cyt} or f_{er} representing buffering in the respective compartment, and σ_V is the ratio of cytosol to ER volumes. The parameter k scales

the rates of metabolism reactions. The factor $\exp\left\{(r + \gamma)\left(1 - \frac{[\text{Ca}]}{r_1}\right)\right\}$ captures calcium feedback onto the production of ADP produced with a time constant, τ_a . We use constants: $C_m = 5300$ fF, $V_K = -75$ mV, $g_K = 2700$ pS, $\tau_n = 20$ ms, $g_{\text{Ca}} = 1000$ pS, $V_{\text{Ca}} = 25$ mV. Note that R_{GK} , $\bar{g}_{\text{K}(\text{Ca})}$, and $\bar{g}_{\text{K,ATP}}$ are parameters that impact bursting rates of electrical potential (voltage). For example, in Fig. 1 the fast bursting cell has $R_{\text{GK}} = 0.4$, $\bar{g}_{\text{K}(\text{Ca})} = 25000$ pS, and $\bar{g}_{\text{K,ATP}} = 600$ pS, while the slow bursting cell has $R_{\text{GK}} = 0.2$, $\bar{g}_{\text{K,CA}} = 27000$ pS, and $\bar{g}_{\text{K,ATP}} = 100$ pS. In the rest of the work, the cell heterogeneity is due only to changes in $o_\infty([\text{ADP}])$.

In order to couple the cells together, we define a matrix G that contains the coupling strengths between each pair of cells. The matrix G will be defined such that the coupling is diffusive ($\alpha(V_i - V_j)$ where α is the coupling strength, V_i is the neighboring cell and V_j is the current cell). Thus the differential equation can be written as

$$\frac{dy}{dt} = f(t, y) + G y, \quad (9)$$

where $y = (V, n, [\text{Ca}], [\text{Ca}_{\text{er}}], [\text{ADP}], [\text{G6P}], [\text{FBP}])^T$ is a vector of length $7N^3$ (with component vectors $V = [V_1, \dots, V_{N^3}]^T$, etc. of length N^3), $f(t, y)$ is the right hand side of equations (1)–(7). G is a sparse block diagonal connectivity matrix with 7×7 blocks defined as

$$G = \begin{pmatrix} C_V & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & \cdots & 0 & C_{G6P} & 0 \\ 0 & 0 & \cdots & 0 & 0 & C_{FBP} \end{pmatrix},$$

where the (a, b) entry of the matrices C_V , C_{G6P} , C_{FBP} contains the coupling strength between the a th cell and the b th cell, g_V , g_{G6P} , and g_{FBP} , respectively. As in [10], a and b are indexed with $i + (j - 1)N + (k - 1)N^2$ being the one-dimensional index of the (i, j, k) -th cell with $1 \leq i, j, k \leq N$. Let $\nu = V, G6P, \text{ or } FBP$. Then, C_ν is a matrix with seven non-zero bands. In our model, the coupling strength is the same throughout the islet. So, the elements on the main diagonal of C_ν are the number of neighbors that each cell has multiplied by -1 and the coupling strength of the species ν . On the first superdiagonal and subdiagonal, N superdiagonal and subdiagonal, and the N^2 superdiagonal and subdiagonal are the coupling strength of the species ν .

3 Methodology

We now move to modifying the existing seven variable model for our study.

3.1 Simulating Mutations

In [2], Benninger experimentally studied the effects of mutated K_{ATP} channels on calcium oscillations in islets of beta-cells in mice. We extend the seven variable model so that it can handle cases in which a specified portion of cells in the islet have mutated K_{ATP} channels that remain fully open or fully closed (see Section 2). Although our code is capable of simulating both mutation types, we only investigate the open mutation case; closed mutations are a possible direction for further study.

From [14], we know that $o_\infty([\text{ADP}])$ from (8) controls the open and closed behavior of K_{ATP} channels; however, this number is not a fractional amount of open channels. In order to determine appropriate values for o_∞ in mutated cells, we numerically solved the ODEs (1) – (7) under different coupling conditions and distributions and observed the values of o_∞ during the run. Based on our observations, we set o_∞ to 0.0075 for the open mutation as the largest observed values for o_∞ .

Given these observations, we redefine $o_\infty([ADP])$ to

$$o_\infty([ADP]) = \begin{cases} 0.0075 & : \text{Open Mutation,} \\ \alpha([ADP]) & : \text{Normal Cell,} \end{cases} \quad (10)$$

where the steady-state open fraction from (8)

$$\alpha([ADP]) = \frac{0.08(1 + 2\frac{0.165[ADP]}{17}) + 0.89(\frac{0.165[ADP]}{17})^2}{(1 + \frac{0.165[ADP]}{17})^2(1 + \frac{0.135[ADP]}{26} + 0.05[ATP])}$$

now applies to normal cells.

For our investigations of islets with cells with open mutations, we are interested in two distributions with $m \leq N^3$ mutated cells and $N^3 - m$ non-mutated cells:

1. **Mutated Grouped:** Set cells 1 to m to be mutated cells and cells $m + 1$ to N^3 to be non-mutated cells.
2. **Mutated Spread:** Mutated Spread: Set cell 1 to be mutated then set cell N^3 to be mutated. Continue placing a mutated cell halfway between mutated cells and evenly distributed until there are m mutated cells (i.e., at cells 1, N^3 , $N^3/2$, $N^3/4$, $3N^3/4$, $N^3/8$, $3N^3/8$, $5N^3/8$, $7N^3/8$, etc.).

For the case of open mutations, the *burst death threshold* is the number of mutated cells in the islet required for no voltage bursts to be observed in the first 10 minutes of the simulation. The main focus of our mutation studies is to see how this threshold value is effected by different electrical and metabolic coupling, cell distributions, and R_{GK} values. The different studies we run for the $5 \times 5 \times 5$ islet are as follows:

1. **Electrical Coupling Study:** This study varies electrical coupling strength from 25 pS to 600 pS incrementing by 25 pS while holding G6P and FBP coupling constant at 0.0 ms^{-1} and R_{GK} at 0.2 s^{-1} for both types of distributions.
2. **FBP Coupling Study:** This study varies FBP coupling strength from 0 ms^{-1} to 0.1 ms^{-1} incrementing by 0.005 ms^{-1} while holding G6P coupling constant at 0.0 ms^{-1} , voltage coupling at 100 pS, and R_{GK} at 0.2 s^{-1} for both types of distributions.
3. **G6P Coupling Study:** This study varies G6P coupling strength from 0 ms^{-1} to 0.1 ms^{-1} in increments of 0.005 ms^{-1} while holding FBP coupling at 0.01 ms^{-1} , voltage coupling at 100 pS, and R_{GK} at 0.2 s^{-1} for both distributions.
4. **R_{GK} Study:** This study varies R_{GK} from 0 s^{-1} to 0.6 s^{-1} incrementing by 0.025 s^{-1} while holding voltage coupling at 100 pS, FBP coupling at 0 ms^{-1} , and G6P coupling at 0 ms^{-1} for both types of distributions.

We also run a sampling of these studies for the $3 \times 3 \times 3$ islet to see if and how varying islet size affects the threshold.

3.2 Numerical Method

Given the different reaction rates of the system of differential equations (1)–(7), we have to treat this system as a stiff system of differential equations. We use a memory-modified version of MATLAB's ode15s with automatic differentiation developed in [7] to run our simulations. MATLAB's standard implementation of ode15s uses a version of Numerical Differentiation Formulas (NDF k), which is the standard method for stiff systems of differential equations. In order to solve the system, NDF k requires a Jacobian to be supplied, which MATLAB allows to be handled in multiple ways. We

supply a sparse Jacobian derived analytically using automatic differentiation, computed via the ADiMat software [4]. This is the optimal choice for our studies because it has a significant speedup compared to most other methods, as observed in [10] and confirmed for the particular case of this paper in Section 4.2, as well as allows us to make modifications to the model in our simulations without having to recompute the Jacobian by hand.

MATLAB's standard ode15s has significant speed and memory issues in solving the seven variable model even when supplied with a Jacobian found using automatic differentiation. The memory-modified version developed in [7] reduces the amount of memory allocated for each iteration of the process and removes the feature of ode15s which stores the gradient vector for each iteration since it is not used in any of the post-processing for our model. Efficiency tests in [10] show that there is a significant speedup when the combination of ADiMat and the memory-modified ode15s is used, which allows for more simulations.

In addition, usage of MATLAB's Parallel Computing Toolbox allowed for significantly higher simulation throughput. The command `parfor` is a parallel `for`-loop for studies with multiple runs of code, one for each of the `for`-loop values. Each `for`-loop parameter typically represents one parameter value, for which a run of the code is needed. On the cluster tara with 8 computational cores on each node, MATLAB distributes the job associated with each parameter value in the parallel `for`-loop to one of the 8 cores. Since these jobs are independent of each other and run simultaneously, the overall study can be completed 8 times as fast as a serial run.

3.3 Description of the Computing Environment

The computations for this study were performed using the MATLAB programming language (www.mathworks.com) under the Linux operating system on the cluster tara, located in the UMBC High Performance Computing Facility (www.umbc.edu/hpcf). The distributed-memory cluster tara consists of 86 nodes, with each node containing two quad-core Intel Nehalem X5550 processors (2.66 GHz, 8 MB cache) and 24 GB memory, thus up to 8 parallel processes can be run simultaneously per node. All nodes and the 160 TB central storage are connected by an quad-data rate InfiniBand interconnect.

4 Results

Using the extended capabilities of our model, we simulate and describe effects of varying parameters in a multicellular islet and extend our study to simulate islets in which some cells have mutated K_{ATP} channels.

4.1 Observing the Effects of Open K_{ATP} Channel Mutations

Our model considers cells with either of two types of K_{ATP} channel mutations: always open, which leads to hyperpolarized and unresponsive cells, and always closed, which forces cells to be consistently bursting. We investigate only the case of open mutations but have simulation capabilities of both cases in our model. These mutations alter the sensitivity of K_{ATP} channels to ATP-inhibition, which changes the value of the current $I_{K(ATP)}$ and, in consequence, the cell's voltage (see (1)). Based on this structure of influence within our model, we expect that the presence of mutated cells in the islet will affect voltage oscillations most severely. We expect the degree of influence to depend on the percentage of cells in the islet with channel mutations.

Figure 2 shows a detailed study of electrical oscillation behavior as open K_{ATP} channel mutations are introduced into a $5 \times 5 \times 5$ computational islet with an R_{GK} value of 0.2 s^{-1} in both types of cells. As the number of mutated cells increases, the number of voltage bursts observed in cells in the islet gradually decreases. Voltage bursts continue to reduce until they eventually disappear when 93

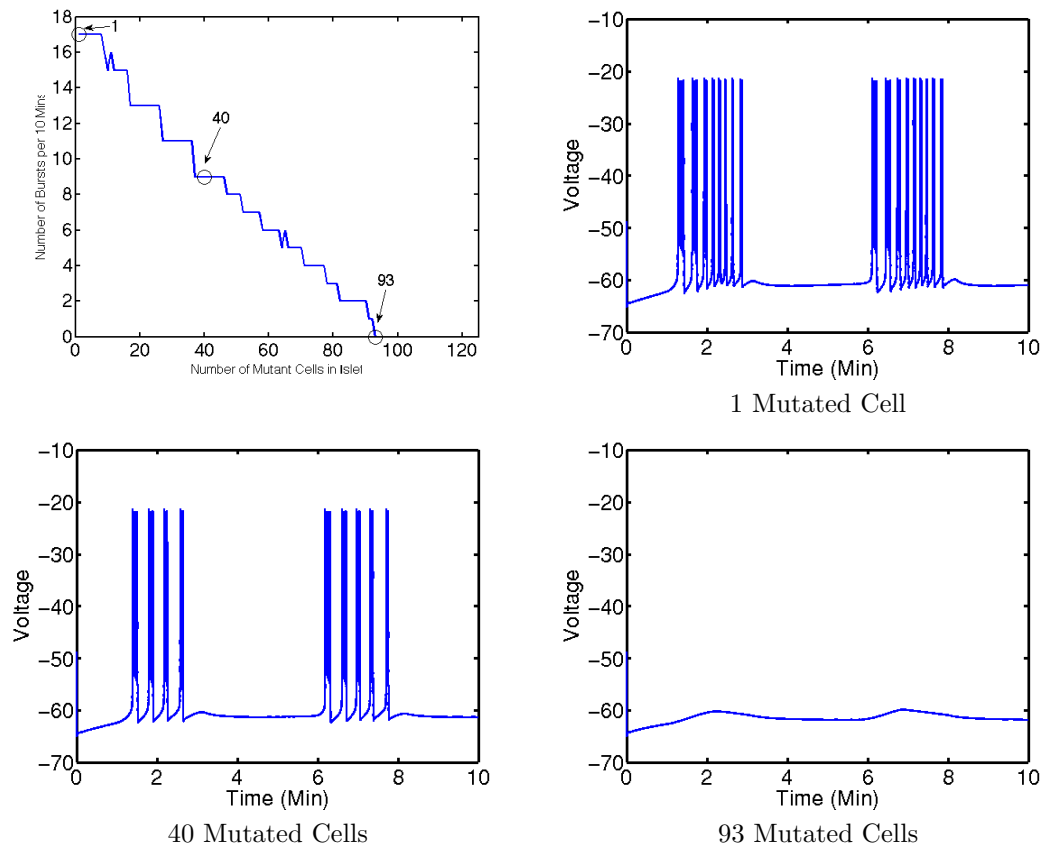


Figure 2: Voltage bursting as mutated cells are introduced into the $5 \times 5 \times 5$ islet. Coupling strengths kept constant at $g_V = 75$ pS, $g_{G6P} = 0$ ms^{-1} , and $g_{FBP} = 0$ ms^{-1} . R_{GK} is 0.2 s^{-1} .

of the 125 cells, or 74%, are mutated. Figure 2 shows the gradual loss of electrical bursting as the percentage of mutated cells in the islet increases. The behavior displayed corresponds to an islet coupled electrically but not metabolically; however, the behavior exhibited by islets with additional coupling parameters is analogous, which is analyzed in the next figure.

The studies in Figure 3 observe the number of electrical bursts over 10 minutes vs. the percentage of mutated cells in an $N \times N \times N$ islet with $N = 5, 6, 7, 8, 9, 10$. The cells are coupled electrically as well as metabolically ($g_{G6P} = 0.035$ ms^{-1} and $g_{FBP} = 0.01$ ms^{-1}). Figure 3 (a) gives the number of electrical bursts over 10 minutes vs. the percentage of mutated cells in a $5 \times 5 \times 5$ islet. Compare this to the top left plot in Figure 2; we see that the threshold of 93 of the 125 cells, or 74%, is the same in both computational islets. The studies in Figure 3 also confirm that the bursting threshold is independent of islet size by running this simulation for larger values of N .

Table 1 lists the number of simulations in the studies for Figure 3 along with the shortest and longest runtime among the runs for each study, which cover a range due to the different numbers of mutated cells in each simulation. Since the runtime of each simulation and the number of simulations required for a study both increase as N increases, the total runtime of studies for larger values of N are very long. By using the distributed-memory cluster tara, described in Section 3.3, to run the simulations in the studies for larger N simultaneously on several nodes, these studies become feasible in reasonable amount of time, when using the optimal memory-modified code with automatic differentiation, discussed in Section 3.2.

We conduct a study of the effect of R_{GK} values on oscillation death threshold in the islet with open channel mutations by varying the value of R_{GK} and documenting the number of mutated cells

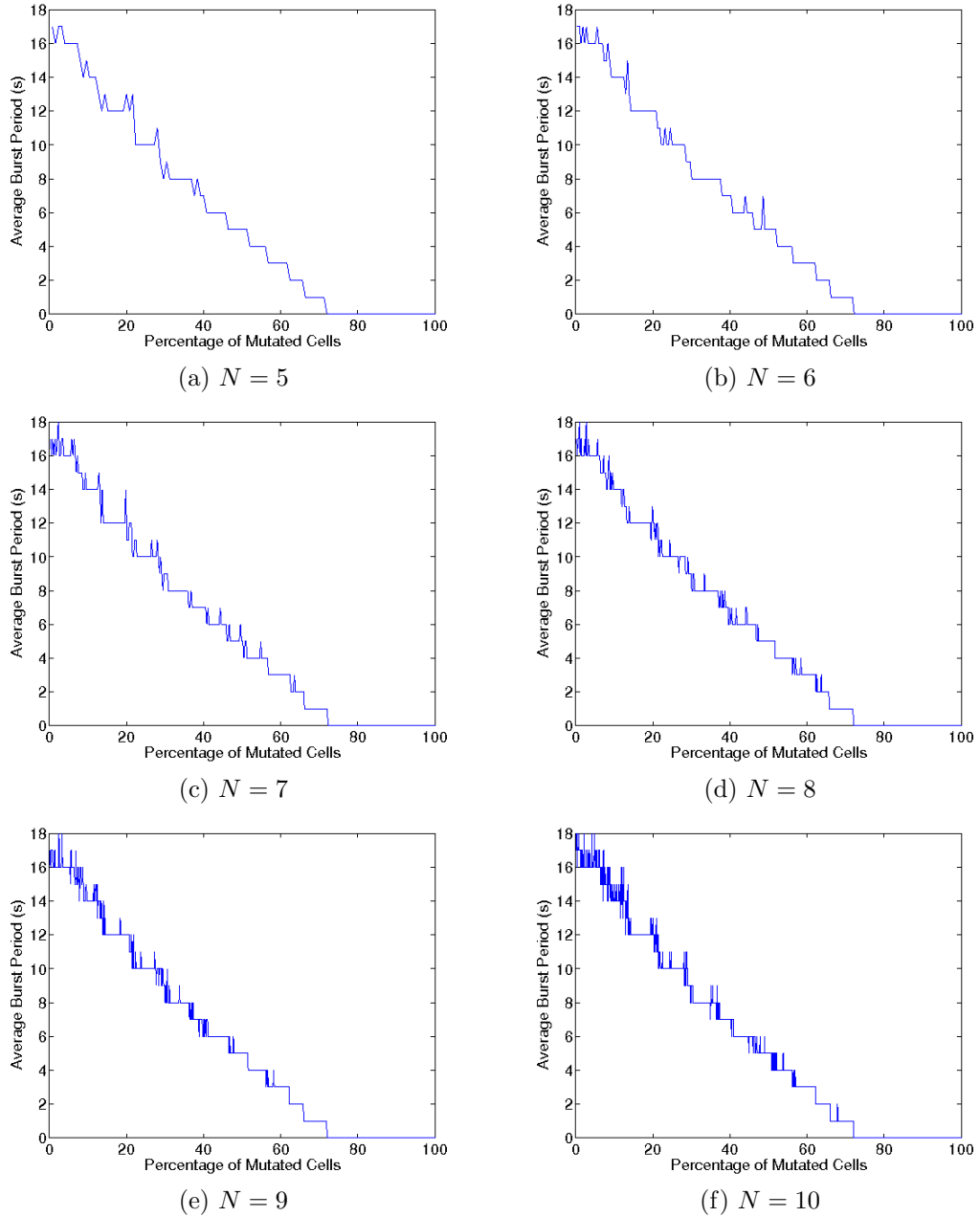


Figure 3: Average burst period vs. percentage of mutated cells in an $N \times N \times N$ islet with $n = 5, 6, 7, 8, 9, 10$. Coupling strengths kept constant at $g_V = 100$ pS, $g_{G6P} = 0.035$ ms^{-1} , and $g_{FBP} = 0.01$ ms^{-1} . R_{GK} is 0.2 s^{-1} .

Table 1: The number of runs, minimum runtime in HH:MM:SS, maximum runtime in HH:MM:SS for 600,000 ms with the range of islet dimensions $N \times N \times N$ considered in Figure 3 using the memory-modified ode15s code.

$N \times N \times N$	Number of runs	Minimum time	Maximum time
$5 \times 5 \times 5$	125	00:00:17	00:01:54
$6 \times 6 \times 6$	216	00:00:27	00:03:09
$7 \times 7 \times 7$	343	00:00:41	00:05:00
$8 \times 8 \times 8$	512	00:01:10	00:08:29
$9 \times 9 \times 9$	729	00:01:59	00:13:56
$10 \times 10 \times 10$	1000	00:03:03	00:22:22

for which electrical oscillations disappear. In this study, we hold coupling constant at $g_V = 100$ pS, $g_{G6P} = 0$ ms⁻¹, and $g_{FBP} = 0$ ms⁻¹ and do not consider heterogeneity in the values of R_{GK} in the two cell types. Figure 4 and Table 2 contain the bursting death thresholds for multiple R_{GK} values in the $5 \times 5 \times 5$ islet.

We observe through repeated runs with mutated cells with varied parameters that the threshold depends on R_{GK} values in the islet but is independent of electrical coupling, at levels above those for synchronization where we can identify a single islet behavior, and of metabolic coupling strengths as well as of mutated cell arrangement within the islet. This threshold exists in every computational islet we considered in which cells with open channel mutations were introduced and increased.

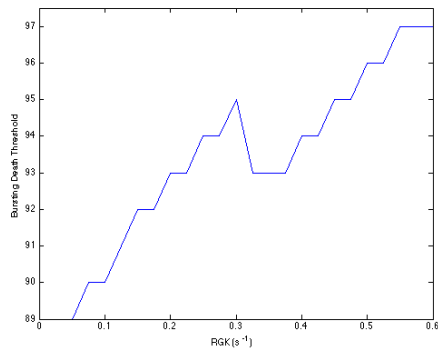


Figure 4: Bursting death threshold vs. R_{GK} .

Table 2: Bursting death threshold vs. R_{GK} .

R_{GK}	Threshold	R_{GK}	Threshold	R_{GK}	Threshold	R_{GK}	Threshold
0.050	89	0.200	93	0.350	93	0.500	96
0.075	90	0.225	93	0.375	93	0.525	96
0.100	90	0.250	94	0.400	94	0.550	97
0.125	91	0.275	94	0.425	94	0.575	97
0.150	92	0.300	95	0.450	95	0.600	97
0.175	92	0.325	93	0.475	95		

4.2 Numerical Study

Efficiency studies were performed in [10] to show that the numerical implementation we use is optimized. We compare the original ode15s method with the memory-modified version to justify its continued use when we introduce metabolic coupling capabilities and associated computations into the model. Table 3 gives the wall clock time in HH:MM:SS for a simulation with coupling strengths of $g_V = 75$ pS, $g_{G6P} = 0.01$ ms⁻¹, and $g_{FBP} = 0.001$ ms⁻¹ for 200,000 ms in the grouped distribution. Table 1 contains runtimes for studies with final time of 600,000 ms for a range of percentage of mutated cells using memory-modified ode15s, hence with a range of times. Table 3 reports actual runtimes for a particular study with a final time of 200,000 ms for a fixed percentage of mutated cells using both original ode15s and memory-modified ode15s as prototype example, using the ADiMat software in both cases.

The results in Table 3 show significant improvement in simulation runtime, particularly as islet dimension N increases. Islets in the human body have approximately 1,000 beta-cells, which makes the performance of simulations run at $N = 10$ significant for biological applications.

Table 3: Runtimes in HH:MM:SS for 200,000 ms with the range of islet dimensions $N \times N \times N$ considered in our studies comparing the original ode15s and the memory-modified ode15s code.

$N \times N \times N$	Original ode15s	Memory-Modified ode15s
$3 \times 3 \times 3$	00:00:28	00:00:21
$4 \times 4 \times 4$	00:01:38	00:00:33
$5 \times 5 \times 5$	00:04:07	00:00:46
$6 \times 6 \times 6$	00:10:02	00:01:14
$7 \times 7 \times 7$	00:24:26	00:01:45
$8 \times 8 \times 8$	00:32:52	00:02:47
$9 \times 9 \times 9$	00:48:47	00:04:51
$10 \times 10 \times 10$	01:11:58	00:07:48

5 Conclusions

Through our studies, we gained a better understanding of the effects of coupling on the oscillation and bursting behaviors of pancreatic beta-cells.

When we ran simulations on islets containing cells with open K_{ATP} channel mutations, there was a clear reduction in electrical bursts as higher proportions of mutated cells were implemented in our islet. Through simulating islets with large proportions of mutated cells, we were able to determine a bursting death threshold describing the least number of mutated cells necessary for electrical bursting to be lost. In the case of our $5 \times 5 \times 5$ islet model ran with one possible set of parameter values (Section 4.1), we found this threshold to be 93 of the 125, or 74%. This percentage, though independent of coupling strengths, mutated cell arrangement, and possibly islet dimension, is not independent of R_{GK} values. However, the bursting death threshold was between 71% and 78% for the range of R_{GK} tested (see Table 2) with less glucose flux requiring a slightly higher percentage of excitable beta-cells to maintain bursting. These simulations provide an interesting prediction for islets adapted with transgenic expression of mutated K_{ATP} channels. Mutated islets that continue to burst should retain at least 29% excitable beta-cells, while those islets that do not burst would contain less than 22% excitable beta-cells. Furthermore, the bursting pattern may indicate the overall fraction of excitable cells with more dispersed spikes in a burst relating to fewer excitable cells and more dense bursting relating to greater numbers of excitable cells. We point out that it is somewhat remarkable in the model that up to 71% or greater of the K_{ATP} channels can be dysfunctional yet an islet may retain the power to burst, which illustrates the robustness of bursting

due to the high conductance of the K_{ATP} channel in the beta-cells of the coupled islet.

Benninger et al. [2] looks at the interplay in multiple components in islets (e.g. gap junctional coupling, KATP channels, paracrine interaction) to maintain effective bursting response. Specifically they mutate KATP channels by replacing the ATP/ADP sensitive tail of the KATP channel leaving the functional potassium channel intact but no longer metabolically sensitive and possibly lower numbers of proteins inserted in the membrane [5]. They mutate the gap junctional proteins to nearly eliminate electrical coupling between islet cells. They show combinations of these mutations for increasing glucose levels and see the KATP mutant and wild type islets have the same glucose response curve for active islet cells. However, once uncoupled combining the gap junctional and KATP channel mutations approximately 70% of islet cells are active even in low glucose. This suggests this type of mutation is equivalent to the closed form of the KATP channel, which we have not studied, but a reduced KATP channel conductance model has been considered in a single cell from whole islet model and a cubic lattice of cells in [13].

However, in recent work Nguyen et al. 2014 [11] look at the gain-of-function mutation that expresses open KATP channels in mice. With open potassium channels imbedded in an affected beta-cell membrane, these beta-cells will tend to remain hyperpolarized. Nguyen et al. address the hypothesis that coupling within the islet, which silences any spontaneous bursting, might also silence normal bursting with the open channel mutation. They show that wild type (no mutations) have about 80% active cells in 20mM glucose, which drops to about 5% of normal cells when coupled to those in an islet with cells having the open channel mutations. Uncoupling the islet rescues the percentage of normal active cells to about 60%. They measure about 50% mutated cells in an islet. In our model, to completely alleviate electrical bursting we find we need about 75%. However, it is possible that one or two spikes per burst is insufficient to induce the experimentally measured activity. They also show that calcium level in the coupled mutated islet is about half that of the wild type islet suggesting some electrical activity is present in otherwise mostly ineffective islets. So our threshold of about 75% for complete loss of electrical bursting may be an overestimate for fraction of mutated cells required for down stream calcium and insulin secretion reductions.

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