The Effect of Unhealthy β-cells in Synchronized Insulin Secretion

Yang Pu[1], Saangho Lee[2], David C. Samuels[2], Layne T. Watson[1], Yang Cao[1]

[1]Department of Computer Science, Virginia Tech, Blacksburg, VA 24061
[2]Center for Human Genetics Research, Vanderbilt University, Nashville, TN 37232
Email: [1]{ypu, ltw, ycao}@cs.vt.edu, [2]{saangho.lee, david.samuels}@chgr.mc.vanderbilt.edu

***Abstract*—Insulin secreted by pancreatic islet β-cells is the principal regulating hormone of glucose metabolism. It plays a key role in controlling glucose level in blood. Impairment of the pancreatic islet function may cause glucose to accumulate in the blood, and result in diabetes mellitus. In order to study the cause of dysfunction of pancreatic islets, a multiple-cell model containing healthy and unhealthy cells is proposed based on an existing single cell model. The β-cells in the model are connected through direct electrical connections between neighboring β-cells. The simulation results show that around 20% unhealthy cells in pancreatic islets will disrupt the insulin secretion. This suggests that a small portion of unhealthy cells may have greater effect in the dysfunction of insulin oscillation than expected.**

I. Introduction

Diabetes Mellitus is one of the leading causes of death in the developed world [1]. There are 23.6 million people in the United States who have diabetes, and these numbers are expected to double within the next two decades. About $25-30$ percent of adults have a high risk of diabetes. Insulin plays a key role in the consumption of glucose. In healthy individuals, insulin is secreted into the bloodstream after a meal as a signal to consume the glucose produced from the digested food. This signaling process helps maintain low blood glucose levels. The disruption of this process may lead to Type II Diabetes [2]. Thus it is important to understand the mechanism of the insulin secretion.

In reality, each cell has different physical properties, leading to different rates of electron transport chain function, Ca^{2+} uptake and release, ATP production, and membrane potential of the cell. These differences finally result in different capability in consuming glucose. Moreover, some β-cells do not behave normally. We call these cells that cannot consume glucose normally unhealthy cells. Because of the electrical connections between cells, unhealthy cells may have a strong effect on healthy cells. Since the overall insulin secretion is determined by the insulin secreted by all the cells in the pancreatic islet, the functionality of the pancreatic islet may get destroyed by a low percentage of unhealthy cells even though most cells are still healthy. Therefore, it is very important to understand how the group of unhealthy cells affect other healthy cells in the insulin secretion process.

In this paper we develop a mathematical model to study the impact of unhealthy cells and scenarios that may lead to insulin oscillation failure. We start with an established mathematical model of insulin secretion from pancreatic β-cells, developed by Bertram et al. [3]–[5]. To include spatial and coupling effects, the original model is modified by incorporating electrical connections between neighboring β-cells. A parameter that represents the function of mitochondrial, the ratio of total mitochondrial volume over cytoplasm volume per β-cell, is modified for unhealthy cells. The effect of unhealthy cells on the overall insulin oscillation is studied by coupling them with healthy cells. From the simulation results of multiple cells, we find that unhealthy cells may cause insulin oscillation malfunction when the portion of unhealthy cells exceeds a certain value (around 20%). To verify this result, simplified coupling topology is used to study the effect of one unhealthy cell on the other healthy cells. The latter study match with the previous discovery.

II. Computational β-cell Modeling

A. Single β-cell Modeling

The mathematical model of a single pancreatic β-cell is based on the deterministic model introduced by Bertram et al. [3]–[5]. The model has four components: a glycolytic component, a mitochondrial metabolism component, cytoplasmic intermediate, and plasma membrane component. Each component of the model is connected by variables interacting between components as illustrated in Figure 1.

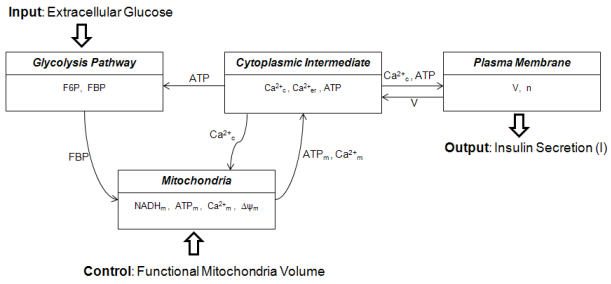

Figure 1. Model components and interconnections.

For more details on these terms in the differential equations of the model, refer to Bertram et al..

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Single cell model is the fundamental structure for multiple cells' simulation. In this model the total amount of ATP and ADP is assumed to obey a conservation law, so only one (ADP) appears in the differential equation (1)

$$\frac{d\ ADP_c}{dt} = J_{hyd} - \kappa J_{ANT}, \tag{1}$$

where J_{ANT} is the flux through the adenine nucleotide translocator which exchanges ADP and ATP molecules between the cytoplasm and the mitochondria, J_{hyd} is the hydrolysis rate of ATP to ADP, and κ is the ratio of the total functional mitochondrial volume to the cytoplasm volume. In the standard model, κ is set as 0.0733. With this parameter value, the cell membrane potential, insulin secretion can both show periodic bursts of rapid oscillation.

However, in reality κ varies. Particularly for cells with some weakened mitochondria due to aging, κ will be smaller than the default value. Thus it is important to study how sensitive the pattern of the cell membrane potential V and the insulin secretion I to the change of parameter κ. In our study, the original single cell model is modified by varying the parameter κ representing different levels of functional mitochondria within the cell. Based on the changes in the pattern of V, Ca^{2+}, and I, the bursting behavior of the model can be divided into four domains depending on the volume of functioning mitochondria in the β-cell: burst formation, periodic burst, burst loss, and decoupling.

To quantify the bursting behavior and to trace its development and eventual loss, we define the "bursting fraction" as the fraction of the total time taken up by the bursts with the burst duration measured from the first to the last peak in each burst. The original model has a bursting fraction of approximately 55% (meaning that a burst in the oscillations of the model variables is ongoing for 55% of the time). However, if we either reduce or increase the mitochondrial volume fraction of the cell, this bursting fraction rapidly changes (Figure 2), and the pattern of the cell membrane potential V, the calcium ion concentration Ca^{2+}, and the insulin secretion rate I all alter significantly. The ranges of mitochondrial volumes corresponding to the four behaviors we have defined (burst formation, periodic bursts, burst loss and decoupling) are denoted on Figure 2. Since these descriptions are qualitative, there are no sharp divisions between the behaviors and the ranges are drawn overlapping. For the first three stages (formation, periodic busts, and loss), the membrane voltage, calcium ion concentration, and insulin release all have nearly identical bursting fractions. In the decoupling stage the bursting fraction in the calcium ion concentration and in the insulin release rapidly drop to zero, while the voltage bursting fraction remains relatively constant. The normal bursting behavior of the β-cell model only occurs within a highly constrained range of mitochondrial volumes ranging from approximately 7% to 8% of the cellular volume.

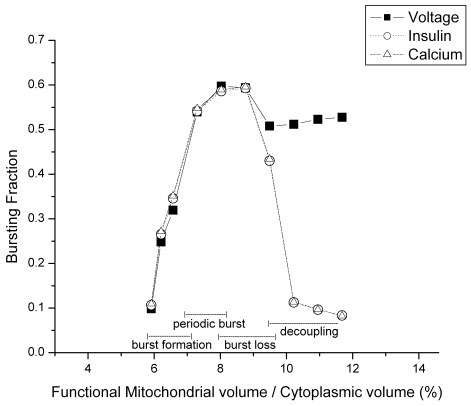

Figure 2. Bursting fraction of the cell membrane potential V, the calcium ion concentration Ca^{2+}, and the insulin secretion rate I.

Because when the volume fraction of the mitochondria is either lower than 6% or higher than 9.5%, the insulin bursts can totally be destroyed, this feature gives us an easy way to define "healthy cell" and "unhealthy cell". We define that a cell is a *healthy cell* when its volume fraction of the mitochondria κ is between 6% and 9.5%, a cell is an *unhealthy cell* when κ is out of this range. Realistically it is more possible that some mitochondria lose their function resulting a smaller κ. In the following numerical experiments, we take $\kappa = 5\%$ for unhealthy cells and $\kappa = 0.0733$ (the standard value) for healthy cells.

B. Multiple β-cells Modeling

There are about one thousand β-cells in each pancreatic islet. The interactions among them are through direct electrical connections between neighboring β-cells in the pancreatic islets. This interaction effect can be included in the single-cell model by making a single change for the plasma membrane potential V_j of cell j:

$$\begin{aligned} \frac{dV_j}{dt} &= -(I_K + I_{Ca} + I_{K(Ca)} + I_{K(ATP)} + I_j)/C, \\ I_j &= gc \sum_{i \in N(j)} (V_j - V_i), \end{aligned} \tag{2}$$

where $N(j)$ is the set of indices of the neighbor cells of cell j, I_j is the whole-cell coupling current for cell j, gc is the electrical coupling conductance between cell j and each of its neighbors i. The number of neighbors surrounding cell j depends upon the position of cell j within a 3-D hexagonal lattice. Figure 3 shows three layers in the 3-D hexagonal lattice. Each internal cell is connected with six cells in the same layer, three cells in the upper layer and three other cells in the lower layer.

Besides the spatial differences among cells in pancreatic islet, each cell has its own parameter values. Among all the parameters of the single cell model, κ, the ratio of

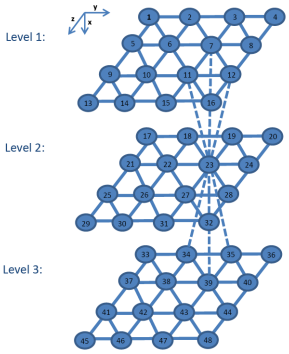

Figure 3. Three layers in 3-D hexagonal lattice.

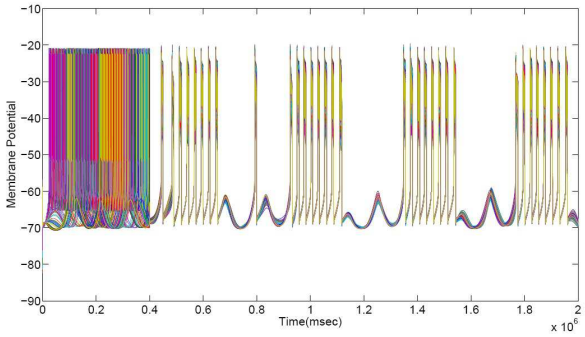

Figure 4. Membrane potential of 125 healthy cells.

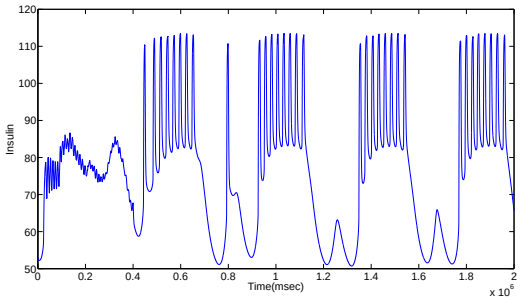

Figure 5. Insulin secretion of 125 healthy cells.

mitochondria volume over cytosol volume, corresponds to the amount of functional mitochondria in the cell and thus represents the function of mitochondria. In our single cell study, we have found that the oscillation behavior of a cell is very sensitive to κ. Thus we select κ to highlight the cell differences in parameters: The value of κ is different for each cell in the 3-D structure, while all other cell parameters are set the same.

In the multiple β-cells simulations, we first study the case with 125 cells coupled together in the 3-D hexagonal lattice. In reality there are about 1,000 cells in each pancreatic islet. The main reason for us to study 125 cells first is that the CPU time for simulating 1,000 cells is excessively long. In the model to represent 1,000 heterogeneous cells, each single cell keeps a copy of the single cell model with different parameters. Thus there will be more than 10,000 state variables, forming a quite large ODE system. It took 26 hours to run from Time 0 to Time 2×10^6. Such high computational burden makes both simulation and analysis quite difficult. On the other hand, the oscillation patterns we observed from 125 cells are no much different from the pattern observed from 1,000 cells. Thus we believe it is fine to focus on the model with 125 cells.

If there is no unhealthy cell, the membrane potentials of all the cells are synchronized after the coupling is turned on, which is done by changing gc from 0 to 150, at Time 400,000 milliseconds(msec). Figure 4 and 5 show the membrane potential and total insulin secretion respectively of 125 cells without unhealthy cells. The curves in the membrane potential plot are out of phase at the beginning, but soon after 400,000 msec, these curves coalesce as shown in Figure 4. The total insulin is relatively flat before synchronization because the insulin levels of some cells are high while others are low. After the coupling is turned on, the total insulin secretion immediately shows bursts and its value is magnified by a hundred of times than that of a single cell. That's because there are more than one hundred cells working together and releasing insulin at the same phase.

In order to see how unhealthy cells, through the coupling in the 3-D structure, affect the total insulin secretion, we focus our study on total insulin secretion. The coupling is turned on at the beginning of the simulations to save CPU time. Figure 6 shows the total insulin behavior with 10% unhealthy cells. These unhealthy cells spread uniformly in the 3-D structure. The total insulin does show periodic oscillations as in the case of 100% healthy cells and maintains a reasonable level. When the fraction of unhealthy cells increases to 15%, the oscillations of total insulin still look normal. But some bursts have fewer spikes. When the percentage of unhealthy cells increase to 20% and 30%, the spikes in each burst become much fewer than the ones in 10% and 15% unhealthy cells (Figure 7 and 8). The bursts are much more irregular. What makes it even worse is that the bursts will finally disappear as shown in Figure 8 after Time 225,000 msec. It suggests that the group of unhealthy cells dominate the global behavior. The level of total insulin becomes too low to maintain proper pancreatic islet function. Thus the simulations suggest that if there is more than 20% unhealthy cells, the function of the pancreatic islet will be severely affected.

In order to make the simulation more realistic and also verify the results of totally 125 cells, we performed simulations for the model with 1,000 cells. The 1,000 cells are coupled together at the beginning of each simulation. For this much larger model, we cannot run it as long as in

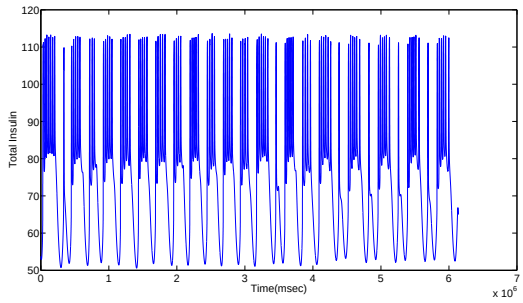

Figure 6. Insulin secretion of 125 total cells with 10% unhealthy cells.

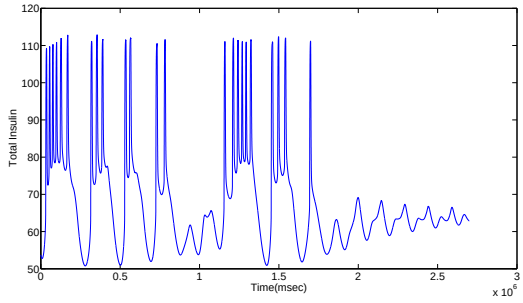

Figure 7. Insulin secretion of 125 total Cells with 20% unhealthy cells.

the case of 125 cells. But note that in reality, when insulin secretion cannot generate enough spikes for a certain time, the pancreatic islet is defined as malfunction. Thus in our simulation, we keep tracking the numbers of spikes of the last five bursts. If the average number of spikes is below 3, we assume that the overall system malfunctions and the simulation is stopped. Figure 9 shows the simulations of totally 1,000 cells with 20% unhealthy cells. It is viewed as malfunction based on the aforementioned "malfunction criteria". Besides these simulations, we also did the simulation for only 10% unhealthy cells. No malfunction is found in an extremely long time. Comparing these results with the

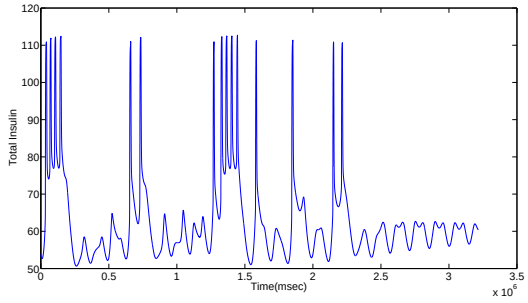

Figure 8. Insulin secretion of 125 total Cells with 30% unhealthy cells.

Table I
COMPARISON OF TWO DIFFERENT RATIOS

Ratio of Links	Ratio of Quantities
9.45%	10%
14.77%	15%
19.63%	20%
29.94%	30%

ones of 125 cells simulations, we can see that they are quite similar. If the percentage of unhealthy cells is larger than 20%, the system will malfunction. Between 10% and 20%, the system still works fine but is close to malfunction. Below 10%, the system definitely can work very well. Therefore we believe the model with 125 cells is sufficient for our study of the impact of unhealthy cells.

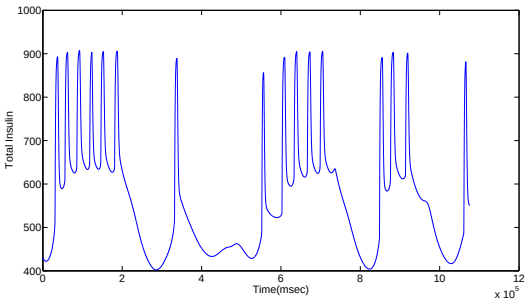

Figure 9. One thousand cells with 20% unhealthy cells.

In conclusion, the insulin secretion of pancreatic islets usually will be destroyed when there are more than 20% unhealthy cells among all the cells. The more unhealthy cells, the insulin secretion will be more irregular.

REFERENCES

[1] E.S.Ford, W.H.Giles, A.H.Mokdad. "Increasing prevalence of the metabolic syndrome among us adults," *Diabetes Care*, 27:2444-2449, 2004.

[2] Nesher R. "Modeling phasic insulin release: immediate and time-dependent effects of glucose", *Diabetes*, 51: S53-S59, 2002.

[3] Richard Bertram, Leslie S. Satin, et al. *Interaction of glycolysis and mitochondrial respiration in metabolic oscillations of pancreatic islets*, Biophysical Journal, Vol 92:1544-1555, 2007.

[4] Richard Bertram, Rudy C. Arceo II. "A mathematical study of the differential effects of two SERCA isoforms on Ca^{2+} oscillations in pancreatic islets," *Bulletin of Mathematical Biology*, 70:1251-1271, 2008.

[5] Bertram R, Gram Pedersen M, Luciani DS, Sherman A. "A simplified model for mitochondrial ATP production", *Journal of Theoretical Biology*, 243: 575-586, 2006.