Mathematical Model of Glucose-dependent Bursting in Pancreatic Beta Cells

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Abstract

Pancreatic beta cells are triggered to release insulin into the bloodstream by fast oscillations ("bursting") of their internal calcium (Ca), which can be mathematically modeled using a system of nonlinear ordinary differential equations. In the original Chay and Keizer model (1983), the dynamics of Ca depend on Ca currents flowing into and out of the cell, which are modified by changes in the cell's electrical potential (itself a function of Ca and potassium in the cell). Keizer and Magnus (1989) and Bertram and Sherman (2004) updated the model to include an ATP-sensitive potassium current as well as an internal Ca compartment (the endoplasmic reticulum).

However, none of these models account for changing levels of blood glucose (which is important, for instance, during a meal). Fridlyand and Philipson (2010) present modeling that connects the ADP/ATP ratio in the beta cells to blood glucose. We integrate their observations into the Bertram and Sherman model via a two-dimensional sigmoid function to establish a relationship between calcium bursting in pancreatic beta cells and glucose concentration. Through computer simulation, we demonstrate a bifurcation to periodic bursting behavior as glucose increases (and ADT/ATP decreases). We also find that there is a linear decreasing relationship between calcium conductance and the critical glucose concentration for the onset of bursting.

Our model can help us to better understand the dynamics of the body's insulin system, particularly in diabetic patients. It allows us to suggest ways to use drugs that alter channel conductance to ensure that beta cells will release enough insulin for a given dose of glucose.

Background

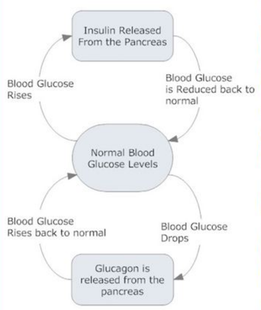


Figure 1: The physiology of glucose and insulin kinetics.

Humans strictly regulate blood sugar concentrations to prevent both hypoglycemia and hyperglycemia (too little or too much blood glucose). Endocrine cells in the pancreas (alpha-cells) release the hormone glucagon when blood glucose drops below normal levels. It stimulates the liver to convert stored glycogen back to glucose, thereby bringing glucose levels back up to normal. When blood glucose levels are high, glucose stimulates the release of insulin from pancreatic beta-cells. Insulin causes muscles to take up glucose and the liver to convert glucose to glycogen, the body's storage form of sugar. As a result, glucose levels are decreased back to normal. These physiological relationships are diagramed in Figure 1.

Here we focus more specifically on what is governing insulin release in the pancreatic beta-cells. A decrease in cytosolic Ca is the primary trigger that causes these cells to release insulin when blood glucose rises. In Figure 2, we see that glucose stimulates Ca to be pumped out of the cell. It also depresses the ADP/ADT ratio, which also modifies the dynamics of the cell through the potassium (K) current.

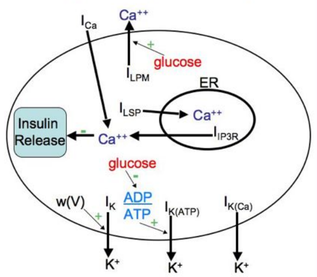


Figure 2: Ca and K currents in the pancreatic beta-cell.

Model Equations

$$\frac{dV}{dt} = \frac{-(I_{Ca} + I_K + I_{K(ATP)} + I_{K(Ca)})}{Cm}$$

$$\frac{dw}{dt} = \phi \frac{w_\infty - w}{\tau_w}$$

$$\frac{dc}{dt} = f \cdot (-\alpha I_{Ca} - I_{LPM}) + \frac{f}{\lambda}[I_{IP3R} - I_{LSP}]$$

$$\frac{dc_{er}}{dt} = \frac{f}{\sigma \cdot \lambda} \cdot [-pIP3R \cdot (c_{er} - c) + v_{LSP} \cdot c]$$

$$\frac{da}{dt} = \frac{a_\infty - a}{\tau_a}$$

Figure 3: The set of coupled ordinary differential equations (ODEs) that comprise our mathematical model.

Current	Function
I_{Ca}	Ca^{++} current (positive)
I_K	K^+ current (w-gate)
$I_{K(ATP)}$	ATP-deactivated K^+ channel
$I_{K(Ca)}$	Ca-activated K^+ channel
I_{LPM}	Linearized plasma membrane Ca-ATPase (pumps Ca^{++} out of cell)
I_{IP3R}	Ca^{++} release channel (allows Ca^{++} out of ER)
I_{LSP}	Linearized SERCA pump (pumps Ca^{++} into ER)

Figure 5: Table of currents and their functions

$$I_{Ca} = g_{Ca} \cdot m_\infty \cdot (V - V_{Ca})$$
$$I_K = g_K \cdot w \cdot (V - V_K)$$
$$I_{K(ATP)} = g_{K(ATP)} \cdot a \cdot (V - V_K)$$
$$I_{K(Ca)} = g_{K(Ca)} \cdot \frac{c}{k_{K(Ca)} + c} \cdot (V - V_K)$$
$$I_{LPM} = v_{LPM} \cdot c$$
$$I_{IP3R} = pIP3R \cdot (c_{er} - c)$$
$$I_{LSP} = v_{LSP} \cdot c$$
$$m_\infty = 0.5 \cdot [1 + \tanh \frac{(V - v_1)}{v_2}]$$
$$w_\infty = 0.5 \cdot [1 + \tanh \frac{(V - v_3)}{v_4}]$$
$$\tau_w = \frac{1}{\cosh \frac{(V - v_3)}{2v_4}}$$
$$a_\infty = \frac{1}{1 + e^{\frac{r_a - c}{S_a} + \frac{g - D}{E}}}$$

Figure 4: Equations for currents (I), gating variables, and the ADP/ATP ratio (a_∞).

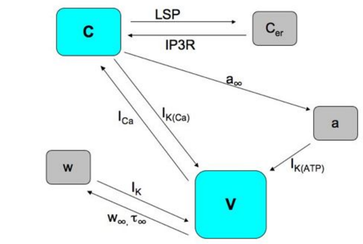


Figure 6: Relationship diagram between the five state variables. Note that cytosolic Ca (c) and cell voltage (V) are central.

The set of differential equations shown in Figures 3 and 4 model the dynamics of cytoplasmic calcium (c), ER calcium (c_{er}), voltage (V), and ADP/ATP ratio (a) in pancreatic beta cells, with (w) as a dynamic gating variable controlling the potassium current with time constant τ_w. (m_∞) is a gating variable controlling the Ca current. Each current in Figure 2 is also represented by an equation. Glucose modifies both the LPM current and the steady-state ADP/ATP ratio (a_∞).

A New Equation for ADP/ATP Ratio (a_∞)

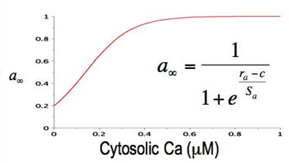


Figure 7: Experimental data shows that for a fixed glucose concentration, the steady-state ADP/ATP ratio (a_∞) increases as cytosolic [Ca] increases [1] . The relationship is described by the sigmoid equation above, where r_a is the "half-max" [Ca] corresponding to an ADP/ATP ratio of 50%, and s_a is the steepness of the curve.

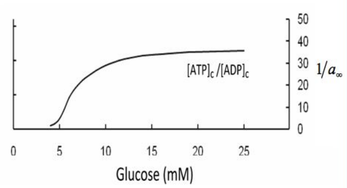
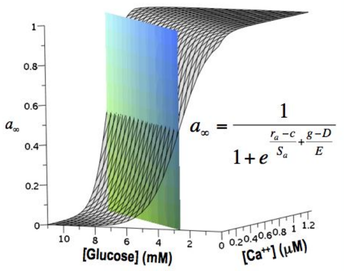


Figure 8: Modeling studies [4] suggest that the *inverse* of the steady-state ADP/ATP ratio ($1/a_\infty$) increases as extracellular glucose increases. This relationship can also be described by a sigmoid equation similar to that used in Fig. 7

Figure 9: We constructed a two-dimensional sigmoid function that models the simultaneous dependence of the ADP/ATP ratio on both [glucose] and [Ca]. The half-max (c, D) and slope parameters (s_a, E) are chosen to be consistent with data referenced in Figs. 7 and 8.



Results

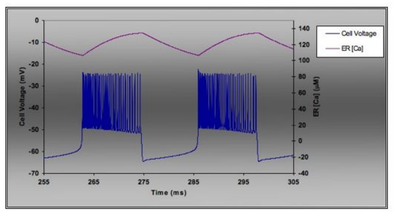
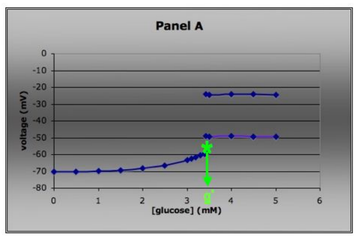
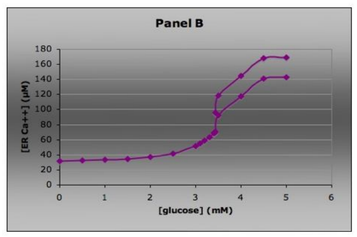


Figure 10: The cell voltage oscillates sharply in bursts lasting about 10 sec, for appropriate values of [glucose]. We obtain this solution to our system of ODEs using the numerical differential equation solver "Berkeley Madonna" (with step size of 1μs). The ER [Ca] reaches a critically low value, at which point bursting begins. Then, as ER [Ca] rises to a high enough level, bursting terminates.

Figure 11: By plotting steady-state cell voltage (Panel A) and ER [Ca] (Panel B) versus [glucose], we observed a critical glucose value (labeled g^*) that corresponds to the onset of bursting (periodic behavior). At this onset, both cell voltage and [ER Ca] oscillate between maximum and minimum values, seen here as the two forks of the bifurcation plots. (Simulations are for fixed calcium conductance, g_{Ca} = 1000 pS)





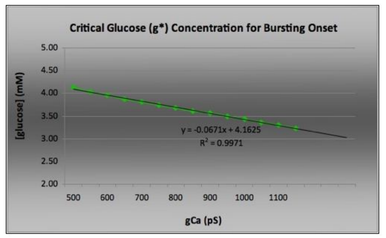


Figure 12: Now we observe how the critical glucose concentration (g^*) required for the onset of bursting changes as the conductance of the calcium channel (g_{Ca}) is modified. As calcium conductance increases, less glucose is required to initiate bursting (and cause insulin release). This linear decreasing relationship is of interest because we have calcium channel blocker drugs that can be used to alter this conductance. As such, we can predict what dose of glucose will ensure that pancreatic beta cells burst to release insulin for a given calcium conductance.

Ca Channel Blockers

- Allosterically bind to Ca channels that transverse the cell membrane
- Alter calcium conductance through the channels
- Traditionally used to treat conditions such as hypertension and angina because they can alter the electrical activity of smooth muscle cells in the heart and blood vessels
- Examples of Ca channel blockers approved for use in the US include diltiazem (Cardizem), nifedipine (Procardia, Adalat), and nicardipinie (Cardene)

- **Significance to our research:** Modelling the action of Ca channel blockers via altered calcium conductance (g_{Ca}) allows us to predict the ability of these blockers to modify insulin release in pancreatic beta cells.

References

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