A Model of Glucose, Insulin and β-Cell Mass Kinetics with Stochastic Noise and Varying Glucose Input

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ABSTRACT

We have adapted a mathematical model proposed by Topp, et al. to describe the kinetics of β-cell mass, insulin, and glucose in functional and diabetic biological pathways to account for periodic glucose intake. Our model accounts for a multitude of parameters including sensitivity of glucose to insulin, rate of insulin secretion by β-cells, and natural death rate of β-cell populations. We developed a multi-time-scale reduction algorithm to decrease the computational complexity of the model and to separate “fast” and “slow” dynamics of the β-cells/insulin/glucose system. The reduced system yielded solutions that allowed glucose and insulin to oscillate with period corresponding to a small time scale while letting β-cells vary slowly over a longer time interval. The model was further enhanced via the introduction of stochastic noise (Gaussian form scaled according to modifying parameter) to two separate parameters that have empirically been shown to be noisy. The first was in the periodic intake term of the glucose equation and the other was in the Hill function corresponding to insulin production. Model simulations suggest that noise has limited effects when propagated via the glucose equation, but significantly affects the system when enacted upon insulin production. This model can be further studied to determine appropriate parameter values in the context of stochastic noise that cause the system to enter a diabetic state.

INTRODUCTION

In a fully functional glucose pathway, pancreatic β-cells produced in the islets of Langerhans secrete insulin in response to the presence of glucose in the bloodstream. An excess of glucose can be toxic—insulin must be released to convert glucose to glycogen, a safer and more easily storable form.

Diabetes mellitus is a disease characterized by the surplus of glucose in the blood, which can be caused by either a decrease in β-cells in the pancreas or an inability of β-cells to secrete appropriate amounts of insulin. Various factors can contribute to the transition of a normal glucose/insulin/β-cell system into the diabetic state, namely regulated hyperglycemia and dynamical hyperglycaemia as reported by Topp, et al. It is necessary, however, to adapt the Topp model to account for fluctuating glucose input (which more accurately represents human eating patterns) and the noisy nature of individual parameters in the system. As it currently stands, the model is neither fully robust nor entirely relevant from a biological perspective—it assumes, for instance, that glucose input is constant and that parameters are fixed over time and unaffected by surrounding biological systems.

Our new model can be characterized to determine the new equilibrium concentrations of the three species as well as the appropriate combination of parameters under which diabetes is induced. We report here the derivation of this model and various simulations used to test its efficacy.

MATHEMATICAL MODEL

The Topp model was first used as a reference point to capture the fundamental dynamics of the system. Glucose (G), insulin (I), and β-cell mass (β) were calculated using basic accounting principles; their respective equations were of the form “quantity produced” minus “quantity uptaken”. Below are the equations:

\[
\frac{dG}{dt} = R_G - \left( \frac{G}{EC_0 + G} \right) \beta I
\]  
(1)

\[
\frac{dI}{dt} = \frac{\beta G}{\alpha G + I} - k I
\]  
(2)

\[
\frac{d\beta}{dt} = \left( -d_\beta + r_\beta G - r_\beta G^2 \right) \beta
\]  
(3)

R_G represents the input of glucose into the system, while the second term corresponds to the uptake of glucose by the bloodstream. This uptake is dependent on both the natural uptake factor (EC_0) and the sensitivity of insulin to breaking down glucose (\( \beta \)).

In equation (2), insulin is produced proportionally to the mass of β-cells in the system; these cells are presumed to produce insulin at a constant rate. Insulin is released in response to the concentration of glucose in the bloodstream and is bound when glucose is large, thereby necessitating the use of a Hill function (with the function reaching 0.5 at G = 10^\alpha) with respect to glucose. Finally, insulin is uptaken at rate k.

In equation (3), \( d_\beta \) is the natural decay rate for the β-cells, while \( r_\beta G \) is the replication rate. All of these parameters are multiple orders of magnitude smaller than the ones in the prior equations. This is reflective of the fact that β-cell mass varies slowly compared to glucose and insulin from a biological perspective.

In order to allow our model to more accurately reflect the true nature of the biological pathway, we made two significant changes to the Topp equations. First, we adapted \( R_G \) in equation (1) to be a periodic function whose amplitude was given in Bergman et al. in order to simulate the cyclic nature of normal glucose ingestion. This change adds an additional degree of realism to the glucose equation.

Secondly, Gaussian noise (appropriately scaled) was added in a stochastic manner to the system on two separate occasions. It was appended to the input of the glucose equation in order to reflect the randomness associated with the digestive system’s absorption of glucose into the bloodstream. Noise was also added to the α of the insulin equation’s Hill function, since α has empirically been proven to be noisy, as shown by Fimage et al.

VIABILITY OF REDUCTION ALGORITHM

The first simulation was a test of the efficacy of our reduction algorithm, which was developed to decrease the computational complexity of solving the system. We applied both an explicit numerical solver method and the reduction algorithm to the same set of initial data: G_0 = 100, I_0 = 10, and B_0 = 300. This initial condition corresponds to equilibrium concentrations of the three species as stated by Topp et al. The following plots reveal the results of the explicit solver and the reduction method, respectively:

Summary

We have successfully developed a reduction algorithm to determine solutions to the Topp system of equations. Additionally, we have adapted the model to account for periodic glucose input and have obtained validated solutions that are in accordance with biological findings. We have incorporated Gaussian, stochastic noise to two of the empirically noisiest parameters of the system (i.e. glucose input and insulin production parameter α) and have determined that the system remains resistant to glucose noise but loses its periodicity upon application of large noise.

REFERENCES