Mathematical Modeling of Pancreatic Islet Cell Dynamics: The Power of the δ Cell in Glucagon Control

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Abstract

It is well known that blood sugar is regulated by insulin and glucagon, two hormones produced by pancreatic islet cells. Mathematical modeling of these hormones can be a powerful tool in developing treatments for diseases such as type II diabetes (T2D). This work builds upon the model proposed by Brown and Tzanakakis (2023) [1] by incorporating the effects of a third hormone, somatostatin, an inhibitor of both insulin and glucagon. Our model better predicted glucagon dynamics and showed that somatostatin effectively inhibits glucagon secretion in hyperglycemic conditions, with minimal impacts on insulin. This suggests that somatostatin therapy may be an effective treatment for T2D.

1 Introduction

Diabetes is a chronic condition characterized by high levels of blood glucose due to underproduction of insulin by the pancreas. In 2022, there were 830 million individuals living with diabetes worldwide, with type II diabetes being the most common [8]. Complications from chronic hyperglycemia can include damage to blood vessels, blindness, and increased risk of heart attack, stroke, and kidney failure, making treatment essential to long-term health outcomes.

It is less well-known that in addition to decreased insulin levels, diabetes is also caused by heightened glucagon levels. These hormones have an interdependence: insulin lowers blood sugar and inhibits glucagon secretion, while glucagon raises blood sugar and stimulates insulin secretion. Both hormones, controlled by blood glucose levels, play an important role in maintaining homeostasis of blood glucose, but their interdependence has not been well studied *in vivo*. Less studied is the effect of somatostatin, which inhibits both insulin and glucagon release. Understanding how these hormones interact with each other and affect blood glucose levels could lead to better treatment of T2D.

Brown and Tzanankakis (2023) [1] used mathematical modeling to simulate interactions between insulin and glucagon in both perifusion (dynamic) and batch (static) settings; we expand their model via incorporation of somatostatin and simulate results in a perifusion setting. We begin by providing essential biological background knowledge, proceed with a review of the model in [1] with our modifications, continue by replicating original results and our own simulations, and conclude with a discussion of significance with next steps.

2 Biological Background

The pancreas is responsible for regulating blood glucose levels. Insulin is released when blood sugar is high (hyperglycemia) to move glucose out of the blood and into surrounding tissues, while glucagon is released when blood glucose is low (hypoglycemia) to move glucose out of tissues and into the blood. Pancreatic islets are a collection of tissues around the pancreas that play an important role in secretion and inhibition of insulin and glucagon. This model considers the two most prevalent cell types, β cells and α cells, as well as the mysterious δ cell.

The most common type of cell, β cells compose about 55% of islet cells and are responsible for producing insulin during hyperglycemia, while α cells secrete glucagon at hypoglycemia. Secretion of insulin and glucagon are interdependent: glucagon raises blood glucose levels and triggers insulin release, while insulin lowers blood glucose levels, inhibiting glucagon secretion. Pancreatic δ cells, comprising only 5% of islet cells, produce the hormone somatostatin, which quickly inhibits both insulin and glucagon secretion. Though currently under studied, δ cells play an important role in maintaining blood glucose homeostasis. The interdependence of insulin, glucagon, and somatostatin is shown in Figure 1.

Clearly, the stimulating effects between hormones and of glucose on hormones can only proceed up to a point; it is biologically unfeasible for high levels of glucose to stimulate insulin release infinitely, for example. To control for these types of scenarios, biologists commonly model hormone secretion via a Hill function, a special type of function that incorporates a "saturating," or maximal effect; in the previous example, this would be a maximal effect of glucose levels on insulin release. The generic form of the Hill function is:

$$Y = \frac{mX^n}{X^n + h^n}, \tag{1}$$

where m is a modulating term determining the degree to which stimulant X affects production of Y, h is the concentration of X that leads to half-maximal release of Y, and n is the Hill coefficient, which determines degree of cooperativity in binding (will not be relevant for our purposes). This equation will form the basis for our model. With this prerequisite knowledge, we are prepared to proceed with model development.

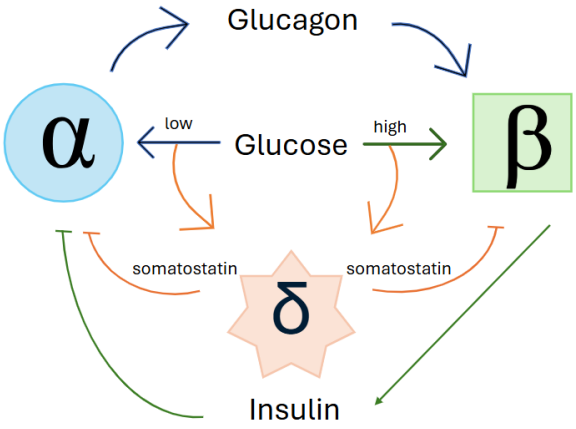

Figure 1: Schematic of Model incorporating α, β, and δ cell activity.

3 Model Development

3.1 α and β Cell Model

We separated the model into steady-state and kinetic behavior in order to understand both baseline behavior and how the system maintains homeostasis. We begin with replicating the model in [1] and consider somatostatin involvement in Section 3.2. In Section 3.1.1, we describe equations for the mass secretion rates of insulin R_I and glucagon R_G as functions of net signals in β-cells X_B and α-cells X_A, then define equations for these signals. Then, Section 3.1.2 introduces a compartmental model to describe the movement of insulin and glucagon between cells. Finally, we describe changes in signal intensity in Section 3.1.3 using concentrations of glucose, insulin, and glucagon.

3.1.1 Steady-State Behavior

We assume that the mass secretion rates of insulin R_I and glucagon R_G are functions of net cell signals X_B for β cells and X_A for α cells; we will construct these net signals X_B and X_A later. A Hill function was used to model the saturating effect of signal strength on mass secretion; that is, the secretion of both insulin and glucagon takes the shape of a sigmoid function, with a half maximal secretion rate h_I for insulin and h_G for glucagon. Constants m_I and m_G are modulating terms for the percentage of the secretion governed by the net signal and n_G and n_I are the Hill coefficients of glucagon and insulin, respectively, representing the cooperative effect of signal concentration on hormone secretion. Hence,

$$R_I(X_B) = \frac{m_I X_B^{n_I}}{X_B^{n_I} + h_I^{n_I}},$$
$$R_G(X_A) = \frac{m_G X_A^{n_G}}{X_A^{n_G} + h_G^{n_G}}.$$

Next, we construct the net signals for α and β cells. The net signal dominating insulin secretion, X_B, was constructed based on the assumption that insulin secretion is based on the additive effects of glucose signal concentration (in beta cells) X_{gB}, glucagon signal concentration X_G, and a base signal intensity X_{B0}, which was added to model experimental data where insulin was secreted even in the absence of glucose. A normalized signal was used to scale units. The direct relationship between glucose levels and insulin fueled the assumption that X_B would be linear in X_{gB}. This means that

$$X_B = X_{gB} + f(X_G) + X_{B0},$$

where $f(X_G)$ is a function of glucagon signal concentration. Glucagon requires glucose to stimulate insulin secretion, with glucose acting as a switch for glucagon-stimulated insulin secretion. Letting $m(X_G)$ be a function of glucagon signal concentration and using a Hill function to model the glucose "on-off" switch, we assume $f(X_G) = m(X_G)\frac{X_{gB}^{n_{gB}}}{X_{gB}^{n_{gB}}+h_{gB}^{n_{gB}}}$. Again, a Hill function was used to model the saturating effect of glucagon on insulin secretion; specifically, higher concentrations of glucagon signal will stimulate insulin secretion in a sigmoidal pattern. With this assumption, $m(X_G) = \frac{m_{GB}X_G^{n_{GB}}}{X_G^{n_{GB}}+h_{GB}^{n_{GB}}}$; note that the subscript GB denotes glucagon in β cells, while X_G is the net glucagon signal.

Similarly, the net signal for α cells X_A was assumed to be a function of glucose concentration (in α cells) X_{gA}, insulin concentration X_I, and a basal secretion term X_{A0}. The dependence of glucagon on glucose and insulin levels has been observed *in vitro*, but basal levels of glucagon signal have not been yet observed *in vivo*; the basal signal term X_{B0} was added based on the assumption that glucagon and insulin have similar signaling dynamics. Assuming that glucose concentration has a linear effect on glucagon secretion and that insulin has an inhibitory effect means that $X_A = f(X_{gA}) - f(X_I) + X_{A0}$. We assumed that

(1) Insulin acts in a saturating manner on X_A, with a maximal impact of insulin concentration on glucagon signal.

(2) Insulin can fully inhibit glucagon secretion, meaning the effects of the basal secretion term X_{A0} can be fully "switched off" by high enough concentration of insulin,

making the steady-state equations for the net signal X_A

$$X_A = X_{gA} - \frac{(m_g X_{gA} + X_{A0})X_I^{n_{IA}}}{X_I^{n_{IA}} + h_{IA}^{n_{IA}}} + X_{A0}.$$

Therefore, the net signals for α and β cells are given by

$$\begin{aligned} X_A &= X_{gA} - \frac{(m_g X_{gA} + X_{A0})X_I^{n_{IA}}}{X_I^{n_{IA}} + h_{IA}^{n_{IA}}} + X_{A0}, \\ X_B &= X_{gB} + \left(\frac{m_{GB}X_G^{n_{GB}}}{X_G^{n_{GB}} + h_{GB}^{n_{GB}}}\right)\left(\frac{X_{gB}^{n_{gB}}}{X_{gB}^{n_{gB}} + h_{gB}^{n_{gB}}}\right) + X_{B0}, \end{aligned}$$

meaning that we are now prepared to develop the dynamic secretion model.

3.1.2 Dynamic Secretion Model

A compartmental model was used to describe hormone movement between cell membranes and out of the cell. Both insulin and glucagon were modeled using a reserve pool, a docked pool (for storage after synthesis) and a readily releasable pool (for immediate release/secretion); see Figure 2 for a visualization. It was assumed that the reserve pool is large enough that the in/outflow rates are near constant, so the movement rate from the reserve to the docked pool can be the mass secretion rates R_I and R_G, developed in Section 3.1.1. We assume that rates of movement between pools are functions of net cell signaling hormone (X_A for α cells and X_B for β cells) because the signaling hormone triggers the cascade of hormone release, including movement between and out of the pools. For insulin secretion, the docked pool I_1 and the readily releasable pool I_2 can be modeled by equations

$$\begin{aligned} \frac{dI_1}{dt} &= R_I(X_B) - k_1(X_B)I_1, \\ \frac{dI_2}{dt} &= k_1(X_B)I_1 - k_2(X_B)I_2, \end{aligned}$$

where $k_1(X_B)$ and $k_2(X_B)$ are Hill functions to reflect the saturating effect of insulin signaling hormone on kinetic response; that is, high levels of glucose trigger insulin signaling hormone, which can only increase

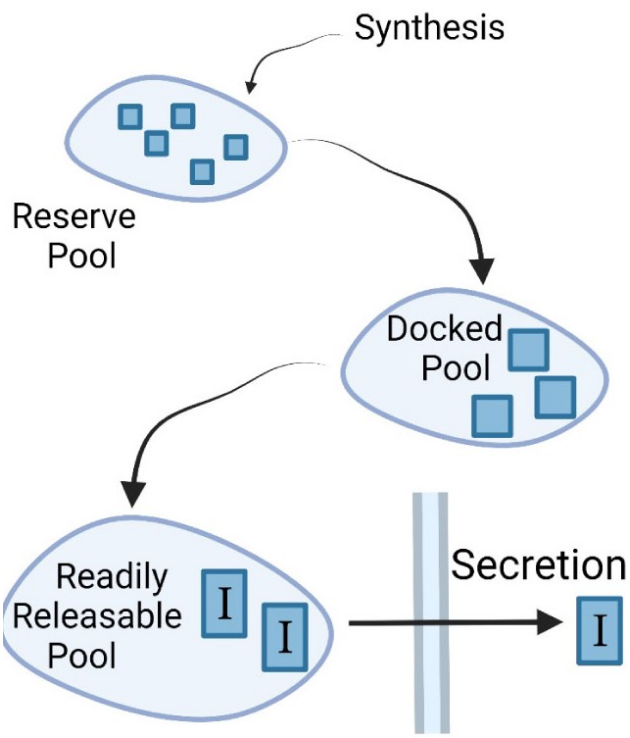

Figure 2: Schematic of the three pools used to develop the dynamic secretion model. This model was chosen by Brown and Tzazakis [1] due to its relative simplicity and biological accuracy.

movement of insulin from the docked to releasable pools to a maximal level. Therefore, we let $k_1 = \frac{m_{I1} X_B^{n_{I1}}}{h_{I1}^{n_{I1}} + X_B^{n_{I1}}}$ and $k_2 = \frac{m_{I2} X_B^{n_{I2}}}{h_{I2}^{n_{I2}} + X_B^{n_{I2}}}$, where m_{I1} is the modulating term of saturation, n_{I1} is the Hill coefficient, and h_{I1} is the half maximal level of secretion (without loss of generality for the readily-releasable pool, I_2).

Though there has been less research on α-cell secretion dynamics, we assume a similar scheme for glucagon movement. Letting G_1 be the docked pool of glucagon and G_2 be the readily releasable pool of glucagon in α-cells, we have that

$$\begin{aligned} \frac{dG_1}{dt} &= R_G(X_A) - k_3(X_A)G_1 \\ \frac{dG_2}{dt} &= k_3(X_A)G_1 - k_4(X_A)G_2, \end{aligned}$$

with k_3 and k_4 similarly defined as Hill functions $k_3 = \frac{m_{G1} X_A^{n_{G1}}}{h_{G1}^{n_{G1}} + X_A^{n_{G1}}}$ and $k_4 = \frac{m_{G2} X_A^{n_{G2}}}{h_{G2}^{n_{G2}} + X_A^{n_{G2}}}$. With the dynamic secretion model complete, we proceed with the signal transduction model to understand how changes in signal intensity affect hormone secretion.

3.1.3 Signal Transduction Model

Understanding the signal transduction dynamics is essential to understanding interdependence of insulin and glucagon secretion. While the physiology-based model originally relied on ATP, ADP, K^+, and Ca^{2+} dynamics to describe the signal transduction network, we use the simplified model which depends only on concentrations of glucose and hormones. See Appendix in [1] for the full derivation.

$$\frac{dX_{gB}}{dt} = k_{gB}(\frac{[g]}{[g]_{ba}} - X_{gB})$$
$$\frac{dX_G}{dt} = k_G(\frac{[G]}{[G]_{ba}} - X_G)$$
$$\frac{dX_{gA}}{dt} = k_{gA}(\frac{[g]}{[g]_{ba}} - X_{gA})$$
$$\frac{dX_I}{dt} = k_I(\frac{[I]}{[I]_{ba}} - X_I)$$

The signal transduction equations describe the signal propogation of intracellular glucose, glucagon, and insulin based on extracellular concentration of glucose ($[g]$), insulin ($[I]$) and glucagon ($[G]$). The constants k_{gB}, k_G, k_{gA}, and k_I represent the transduction rates of intracellular glucose in β cells, glucagon in β-cells, glucose in α-cells, and insulin in α-cells, respectively. Note that the square brackets are common notation for concentration, while the ba subscript denotes the basal concentration. The dynamics involving δ cells and somatostatin will be considered next.

3.2 Incorporating δ-cells

Delta cells release somatostatin, a powerful hormone that quickly inhibits both insulin and glucagon secretion in order to maintain blood sugar homeostasis. There is evidence that somatostatin impacts blood sugar in type II diabetes patients, with hyperglycemia exacerbated by low δ-cell activity [5], so understanding how somatostatin contributes to blood sugar homeostasis could inform future treatments.

We assume similar dynamics for somatostatin as insulin and glucagon; we will proceed by developing equations for steady-state and kinetic behaviors.

3.2.1 Steady-State Behavior

Let X_D be the net signal determining secretion of somatostatin by δ-cells. Despite a lack of research in this area, we assume that the mass secretion rate of somatostatin, R_S, will take the shape of a Hill function to reflect a maximal effect of signaling hormone on secretion rate. Therefore, we let

$$R_S(X_D) = \frac{m_S X_D^{n_S}}{X_D^{n_S} + h_S^{n_S}}.$$

where n_S is the Hill coefficient of somatostatin, h_S is the half-maximal secretion rate, and m_S is a scaling factor. Next, we develop the equation for X_D, the net signal of somatostatin secretion from δ cells, dictated by the following assumptions:

(1) δ cell net signal secretion is dependent on insulin signaling hormone X_I, glucagon signaling hormone X_G, and glucose concentration in δ cells X_{gD}, based on consensus on δ-cell function [4].

(2) Both low and high blood sugar trigger somatostatin release while also triggering glucagon/insulin release (respectively). Since glucose signals insulin and glucagon which, in turn, signals somatostatin, incorporating glucose signaling is redundant. To simplify the model, we will assume that only glucagon and insulin signals impact X_D (i.e., we are removing the impact of glucose levels on somatostatin signaling).

(3) X_D will be an additive function of form $X_D = f(X_I) + f(X_G)$ since high levels of insulin or glucagon, or both, will trigger release.

(4) Both $f(X_I)$ and $f(X_G)$ will be linear functions, with the amount of somatostatin signal proportional to amounts of insulin and glucagon signal. This assumption is justified since we use normalized signals, controlling for units.

Hence, we let $X_D = X_G + X_I$. Unlike X_G and X_I, we do not assume any basal signal due to a lack of experimental evidence. We also do not include a maximal secretion rate via a Hill function since we will incorporate an inhibitory effect of somatostatin on insulin and glucagon secretion via new equations for X_A and X_B, controlling for spikes in somatostatin release.

To incorporate this effect, we further assume that somatostatin signal X_S proportionally decreases both insulin and glucagon signaling, which decreases net signals of α and β cells in agreement with all previous assumptions about X_A and X_B. We moderate the effects of somatostatin on α and β cell activity with a simple Hill Function. We assume that there is the same amount of somatostatin signal in both α and β cells, since δ cells make up a small proportion of pancreatic islet cells and are located between α and β cells [4]. Therefore the new equations for net signals of glucagon, insulin, and somatostatin release, respectively, are

$$
\begin{aligned}
X_A &= X_{gA} - \frac{(m_g X_{gA} + X_{A0}) X_I^{n_{IA}}}{X_I^{n_{IA}} + h_{IA}^{n_{IA}}} + X_{A0} - \left(\frac{X_S^{n_{SA}}}{X_S^{n_{SA}} + h_{SA}^{n_{SA}}}\right) X_S, \\
X_B &= X_{gB} + \left(\frac{m_{GB} X_G^{n_{GB}}}{X_G^{n_{GB}} + h_{GB}^{n_{GB}}}\right)\left(\frac{X_{gB}^{n_{gB}}}{X_{gB}^{n_{gB}} + h_{gB}^{n_{gB}}}\right) + X_{B0} - \left(\frac{X_S^{n_{SB}}}{X_S^{n_{SB}} + h_{SB}^{n_{SB}}}\right) X_S, \\
X_D &= X_G + X_I,
\end{aligned}
$$

where the subscript SA relates to somatostatin in α cells and SB relates to somatostatin in β cells; in simulations, we will assume these values are equal. For simplicity, we assume somatostatin will not inhibit basal secretions of insulin and glucagon, though the model may easily be adjusted to include this effect.

3.2.2 Dynamic Secretion Model

Following the assumptions of the two-pool model for δ cells, we let S_1 be the docked pool for somatostatin secretion and S_2 be the readily-releasable pool. The dynamic secretion equations for somatostatin are thus

$$
\begin{aligned}
\frac{dS_1}{dt} &= R_S(X_D) - k_5(X_D) S_1 \\
\frac{dS_2}{dt} &= k_5(X_D) S_1 - k_6(X_D) S_2,
\end{aligned}
$$

where $R_S(X_D)$ is as defined in section 3.2.1. We also define a Hill function for $k_5(X_D)$ and $k_6(X_D)$ to reflect a maximal kinetic rate between the docked and releasable pools based on net signaling hormone from δ cells. Therefore, we let $k_5 = \frac{m_{S1} X_D^{n_{S1}}}{h_{S1}^{n_{S1}} + X_D^{n_{S1}}}$ and $k_6 = \frac{m_{S2} X_D^{n_{S2}}}{h_{S2}^{n_{S2}} + X_D^{n_{S2}}}$.

3.2.3 Signal Transduction Model

In a similar fashion to glucagon and insulin, we let the change in somatostatin signal, X_S be defined based on somatostatin concentration and signal concentration:

$$
\frac{dX_S}{dt} = k_S\left(\frac{[S]}{[S]_{ba}} - X_S\right).
$$

Notably, as we did not define X_D with a reliance on intracellular glucose levels, we do not have a corresponding equation for $\frac{dX_{gD}}{dt}$ to represent the concentration of glucose in δ cells. With our model complete, we continue with parameter fitting and numerical simulations in MATLAB.

4 Results

4.1 Parameter Estimation

We use the same parameters in the α-β cell model as estimated by Brown and Tzanakakis [1], provided in Table 1. Basal levels of insulin and glucagon were taken directly from literature, while steady-state and

Model Parameters			
Kinetic Parameters	Values	Steady-State Parameters	Values
k_{gB}, k_G (1/min)	0.554	m_{GB}	1.11
k_{gA} (1/min)	0.022	h_{GB}	502
k_I (1/min)	2.77	n_{GB}	0.63
m_{I1}, m_{G1}, m_{S1} (1/min)	0.336	h_{GB}	1.07
h_{I1}, h_{S1}	3.75	h_{IA}	10.0
n_{I1}, n_{G1}, n_{S1}	9.97	n_{IA}	1.17
m_{I2}, m_{S2} (1/min)	0.360	m_g	0.60
h_{I2}, h_{G2}, h_{S2}	0.968	m_I (pg/min/15 islets)	103
n_{I2}, n_{G2}, n_{S2}	6.68	m_S (pg/min/15 islets)	103
h_{G1}	3.75	h_I	3.97
m_{G2} (1/min)	0.360	h_S	3.97
h_G	1.06	n_I	4.84
n_G	3.5	n_S	4.84
X_{B0}	2.60	m_G (pg/min/15 islets)	2.24
X_{A0}	4.40	n_{gB}	0.35

Table 1: Parameter values used in numerical simulations. Methods of estimation and sources for insulin and glucagon related parameters described in [1], while somatostatin related parameters assumed to be the same as those for insulin. Basal somatostatin levels from [6]. All parameters non-dimensionalized as they relate to normalized signals, unless otherwise noted.

kinetic parameters for insulin were estimated by minimizing sum of squared errors of model prediction compared to experimental data. Kinetic and steady-state parameters for glucagon were assumed to be the same and with k_{gA} and k_I varied to better reflect the expected qualitative responses.

Our model incorporating δ cells assumes the same parameters as [1]. Parameters for steady-state behavior, kinetic behavior, and basal levels of somatostatin were assumed to be the same as those for insulin due to data availability constraints. Future work may adjust these parameters based on new experimental data or to better match observed qualitative behavior. Additionally, this paper focuses on dynamic conditions rather than static since these results may be better generalized in vivo and in vitro; therefore, the parameters used in this portion are from perifusion experiments; see [1] for more details. All simulations were performed with 5 islet cells. Basal somatostatin levels of $1.3 \times 10^{-6} mg/dL$ were taken from [6]; due to the significant unit differences between normal insulin/glucagon levels and somatostatin levels (mg vs. pg), ensuring that basal levels of somatostatin were realistic was imperative to the validity of results, reported in Sections 4.2 and 4.3.

4.2 α and β Cell Model

Figure 3 shows the mass secretion rates of insulin and glucagon, R_I and R_G, respectively, as a function of glucose concentration. As expected, insulin is secreted at a higher rate as glucose volume increases, up to a maximal level, while glucagon remains relatively constant.

Varying basal levels of insulin changes glucagon concentration independent of glucose level. As seen in Figure 4, lower basal insulin levels correspond to higher mass secretion rates of glucagon. For abnormal basal insulin levels, like those seen in Type 2 Diabetes, the secretion rate of glucagon remains relatively constant, near its maximal level. This reveals that glucagon secretion is highly sensitive to insulin levels and confirms that Type 2 diabetes is characterized by both low insulin and hyperglucagonemia. Additionally, glucagon secretion was modeled for higher glucose levels to better simulate the higher blood glucose typically associated with Type 2 Diabetes (0-60 mM glucose rather than 0-30 mM glucose). Even with insulin injection (5x basal levels), glucagon levels are elevated above baseline until a critical glucose threshold is crossed, where the insulin

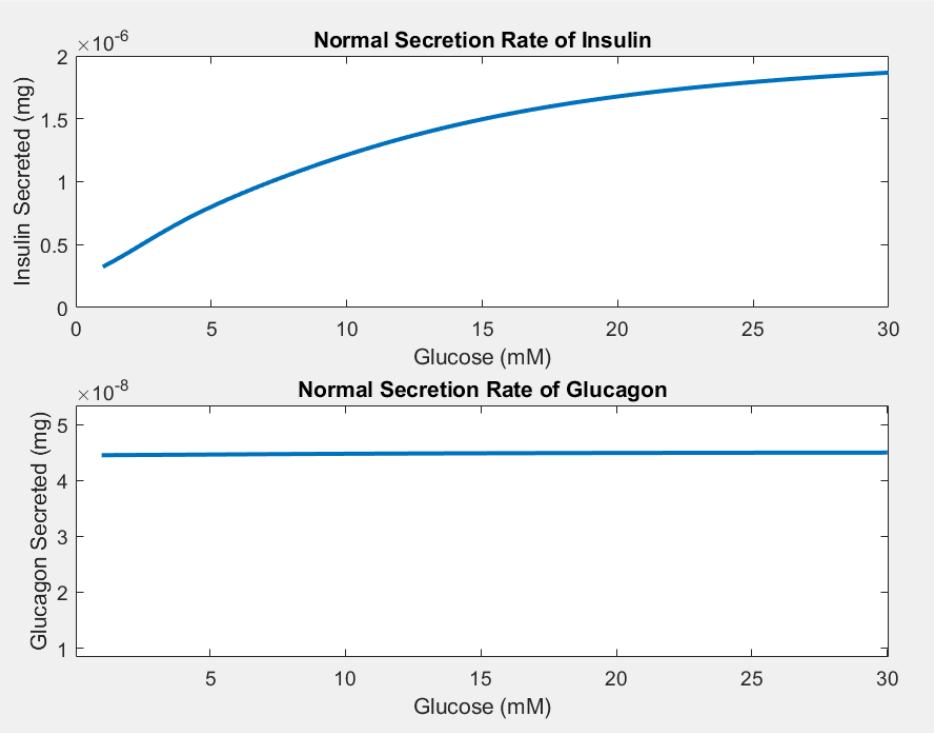

Figure 3: Mass Secretion Rates of Insulin and Glucagon as a function of Glucose volume

treatment become more effective at inhibiting glucagon. Hence, insulin treatments are only effective at reducing glucagon secretion for patients with high blood glucose levels, which is to be expected.

4.3 α, β, and δ Cell Model

Normal secretion rates of insulin, glucagon, and somatostatin at varying levels of glucose are shown in Figure 5. Insulin still behaves as expected, with higher secretion at higher levels of glucose, to a maximal level. Insulin is therefore largely unaffected by somatostatin secretion, despite the negative effect of somatostatin signal X_S on insulin signaling hormone X_I. Conversely, glucagon secretion shows qualitatively different behavior than the somatostatin-free case: rather than remaining relatively constant (with very small increases to maximal levels as glucose increases), glucagon secretion soars for the first 10 mM of blood glucose and actually decreases afterwards as glucose concentrations increase. Somatostatin secretion follows a similar pattern as glucagon.

5 Discussion

While many models have been proposed to model pancreatic hormone release, this model incorporates the often overlooked δ cell, which we have shown has powerful effects on insulin and glucagon secretion. Our model incorporating somatostatin shows qualitative behavior aligning more with the inhibitory effect of insulin on glucagon observed in literature, since glucagon secretion decreases at higher levels of glucose. When only modeling α and β cell activity, we observed a constant flow rate of glucagon at varying glucose levels, instead of a decrease. Hence, this model improves qualitative behavior of glucagon secretion.

Somatostatin secretion notably had a greater impact on glucagon than insulin, despite its inhibitory effect on both hormones. Indeed, the qualitative and quantitative behavior of insulin remained largely unchanged, suggesting that insulin has a lower sensitivity to somatostatin than glucagon. These results suggest that somatostatin therapy could be a viable treatment option for patients with T2D, as it has been shown to

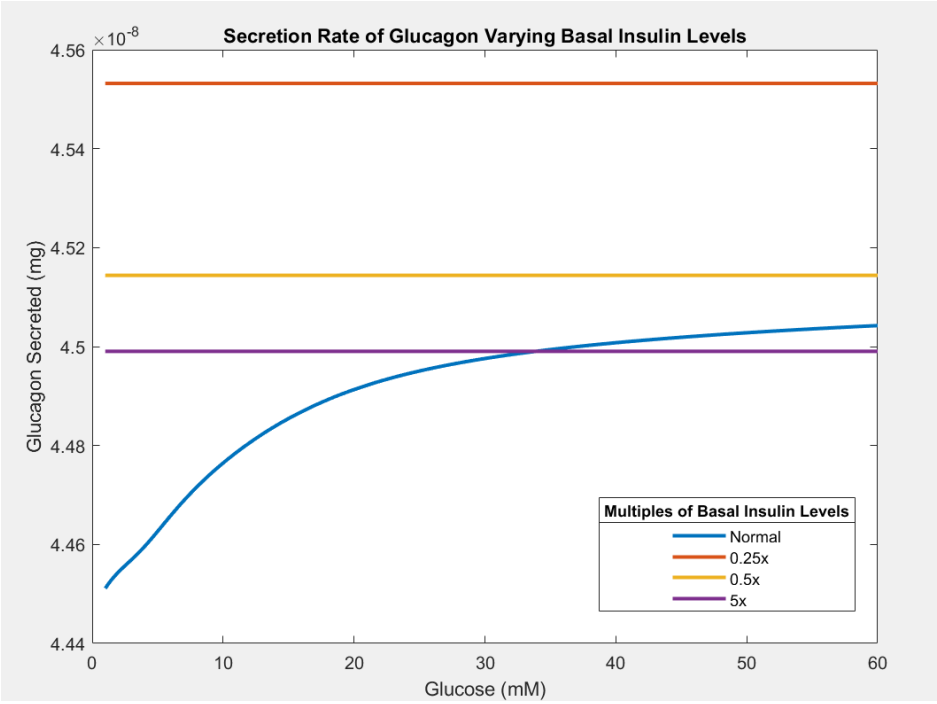

Figure 4: Mass Secretion Rate of Glucagon Varying Basal Insulin Levels

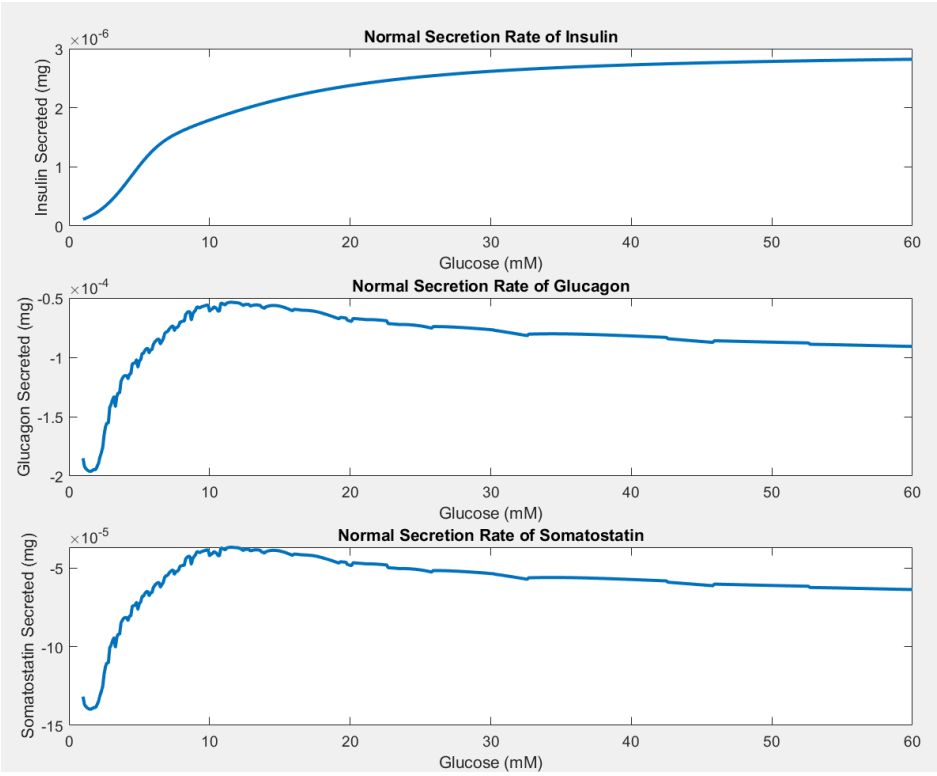

Figure 5: Mass Secretion Rates of Insulin, Glucagon, and Somatostatin as functions of Glucose Volume.

lower glucagon secretion without affecting insulin. However, these trends have not been observed *in vivo*; somatostatin is well-known to have an inhibitory effect on insulin secretion. Tumors in the δ cells, called somatostatinomas, are known to cause mild diabetes due to the inhibition of insulin secretion via overproduction of somatostatin [7]. Therefore, the model must be adjusted to better model the inhibitory role of somatostatin on insulin production. Model behavior might be exacerbated by the dual inhibition of glucagon by both insulin and somatostatin, making the effects of somatostatin on glucagon more pronounced than its effects on insulin.

This model did not include the dependence of somatostatin secretion on blood glucose levels, but this assumption may have contributed to some of the unexpected behavior. Somatostatin can be triggered by both low and high glucose levels, in different forms, to inhibit either glucagon or insulin, and this behavior might be essential to inter-islet dynamics. Future work might consider incorporating other triggers for somatostatin release, such as blood glucose, stomach acidity, and some nutritional signals, to improve predictive accuracy of the model.

Due to the unrealistic parameter values for somatostatin secretion, our model shows unrealistic quantitative behavior, with glucagon and somatostatin secretion being negative. Here, we only interpreted qualitative behavior to avoid misrepresenting our results. Although we used a realistic value for basal somatostatin levels and scaled to the appropriate units, kinetic and steady-state parameters for δ-cells were assumed to be the same as insulin. This issue could easily be resolved by fine-tuning parameters to fit with observed data and should certainly be considered in the future.

Overall, our augmented model forms a sound basis for further work analyzing inter-islet dynamics by improving the qualitative behavior of glucagon via incorporation of somatostatin. Parameter-fitting and adjustment of hormone signaling equation X_D may be further steps for improvement, and future work may also consider δ cell behavior in other scenarios (batch, different numbers of islets, etc.) This model paves early steps in somatostatin control as a form of treatment for T2D.

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