Mathematical Modeling of Hormone Secretion in Pancreatic Islet Cells

Math 308 Final Presentation

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Pancreatic Islet Cells

Cells in tissue surrounding the pancreas are responsible for secretion of essential hormones for regulating blood glucose. The most studied of these are **insulin** and **glucagon**, which are secreted by β and α cells, respectively.

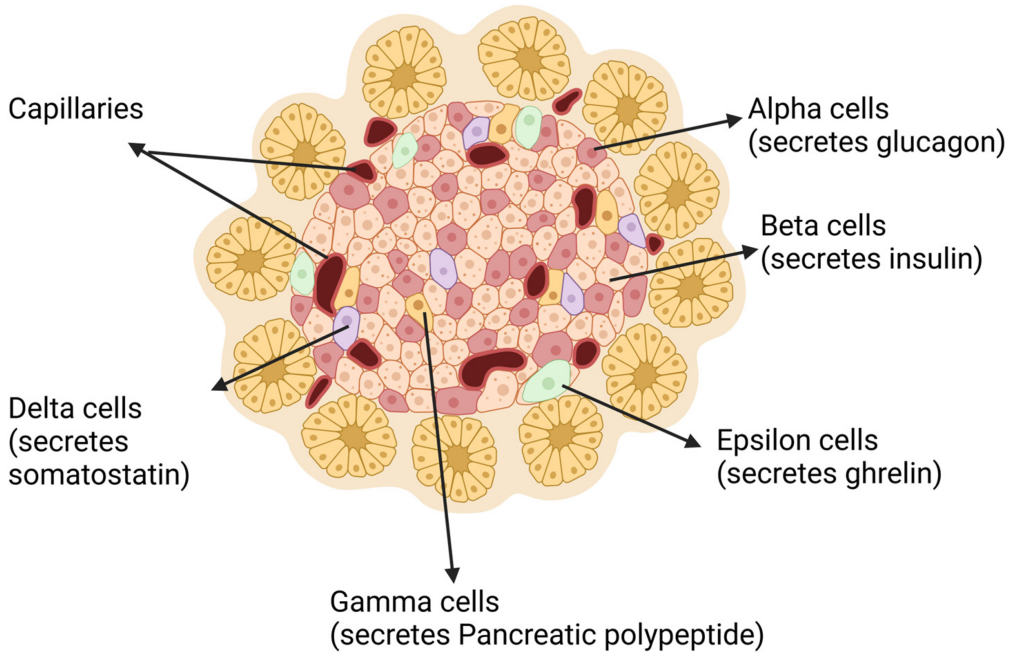

Figure: Image Credit: *https://www.mdpi.com/2073-4409/13/22/1914*

Insulin & Glucagon

- Insulin **lowers** blood glucose levels and is triggered by high blood glucose. Glucagon **raises** blood glucose levels and is triggered by low blood glucose.
- Insulin **inhibits** release of glucagon by α-cells, while glucagon **triggers** release of insulin by β-cells.

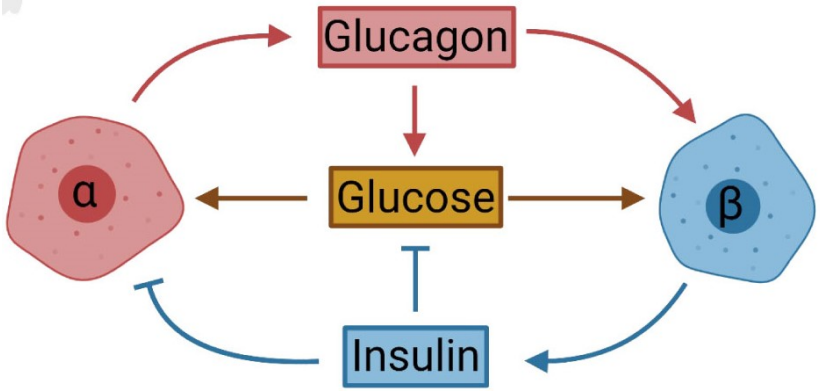

Figure: Interactions between α and β-cells.

δ-Cells and Somatostatin

- Somatostatin is a hormone secreted by δ-cells. It **lowers** both glucagon and insulin levels.
- Diabetic patients have been observed to have high levels of glucagon, meaning that somatostatin may be an effective treatment.

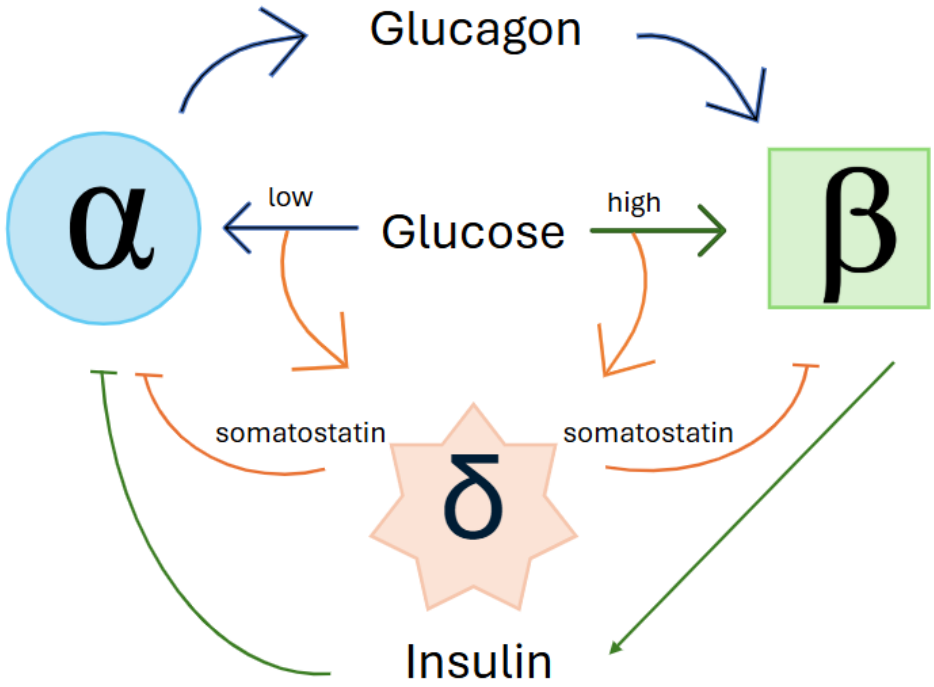

Figure: Model schematic when incorporating δ cells.

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The Hill Function

Similar to Michealis-Menten Kinetics, the Hill equation models a "saturating" effect of hormone secretion. The generic form is:

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

where m is a modulating term, h is the half-maximal concentration of X, and n is the Hill coefficient (determines degree of cooperativity in binding).

Takeaway

High concentrations of X increase concentration of Y, to a maximal level.

Steady-State Behavior

Mass secretion rates of insulin (R_I), glucagon (R_G) and somatostatin (R_S) are functions of the net cell signals of β, α, and δ cells, respectively.

$$R_I(X_B) = \frac{m_I X_B^{n_I}}{X_B^{n_I} + h_I^{n_I}}$$

$$R_G(X_A) = \frac{m_G X_A^{n_G}}{X_A^{n_G} + h_G^{n_G}}$$

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

Net Signal Equations

$$X_A = X_{gA} - \frac{(m_g X_{gA} + X_{A0}) X_I^{n_{IA}}}{X_I^{n_{IA}} + h_{IA}^{n_{IA}}} + X_{A0} - c_1(X_S)$$

$$X_B = X_{gB} + \left(\frac{m_{GB} X_G^{n_{GB}}}{X_G^{n_{GB}} + h_{GB}^{n_{GB}}}\right)\left(\frac{X_{gB}^{n_{gB}}}{X_{gB}^{n_{gB}} + h_{gB}^{n_{gB}}}\right) + X_{B0} - c_2(X_S)$$

$$X_D = X_G + X_I$$

Dynamic Secretion Model

Assume hormones are stored in a **reserve pool** after synthesis, moved to a **docked pool** for storage, and travel through a **readily releasable pool** before secretion.

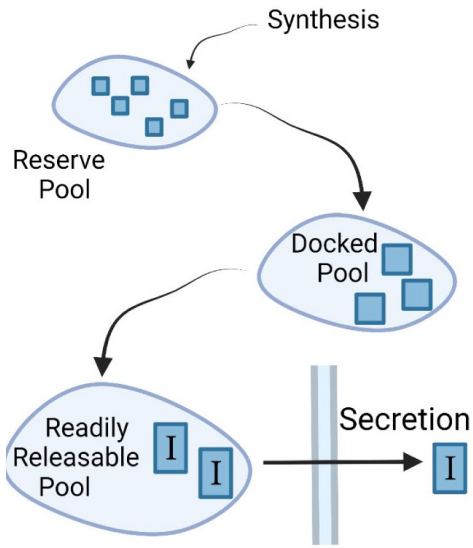

Figure: Movement of hormone through pools.

Dynamic Secretion Equations

For insulin (I_1 = docked, I_2 = readily releasable)

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

For glucagon (G_1 = docked, G_2 = readily releasable)

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

For somatostatin (S_1 = docked, S_2 = readily releasable)

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

$k_1 - k_6$ are Hill equations and functions of net cell signal.

Signal Transduction

Derived from K^+, Ca^{2+}, and ATP dynamics, the change in net signal depends on hormone (glucose) concentration, basal hormone (glucose) concentration, and net signal concentration.

$$\frac{dX_{gB}}{dt} = k_{gB}\left(\frac{[g]}{[g]_{ba}} - X_{gB}\right)$$

$$\frac{dX_G}{dt} = k_G\left(\frac{[G]}{[G]_{ba}} - X_G\right)$$

$$\frac{dX_{gA}}{dt} = k_{gA}\left(\frac{[g]}{[g]_{ba}} - X_{gA}\right)$$

$$\frac{dX_I}{dt} = k_I\left(\frac{[I]}{[I]_{ba}} - X_I\right)$$

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

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α and β Cells

As expected, insulin secretion **increases** with glucose levels. Higher amounts of insulin correspond to lower amounts of glucagon.

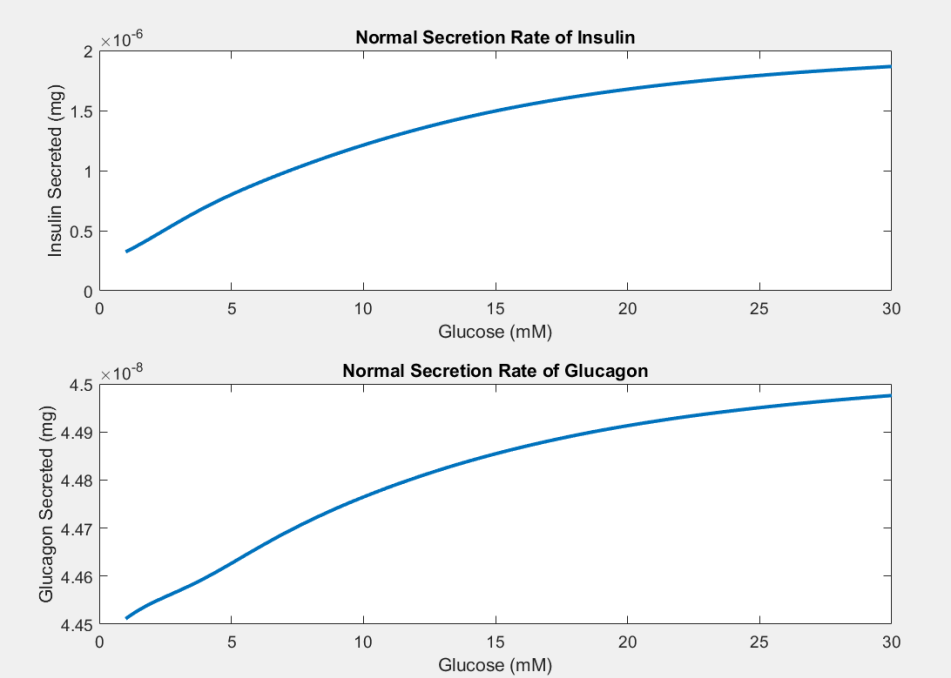

Figure: Insulin and Glucagon Secretion as a function of glucose concentration.

δ cells

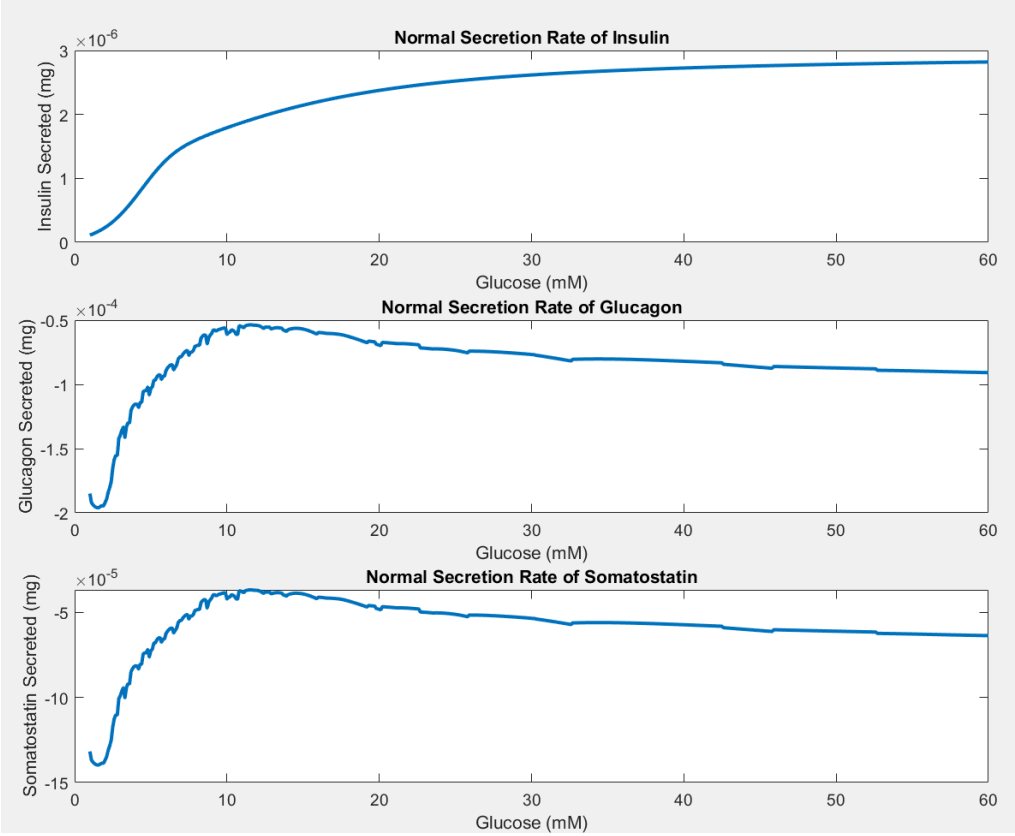

Figure: Higher glucose levels increase insulin, as expected. Insulin and glucagon trigger somatostatin release, which **lowers** glucagon secretion.

Discussion

Significance

Incorporating somatostatin showed a **inhibitory** effect on glucagon secretion. Since T2D patients show heightened levels of glucagon secretion, somatostatin treatment could be effective. These results align with literature!

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Next Steps

- There are many ways to model inhibition of hormone secretion - trying out different functions for somatostatin inhibition of α and β cell activity.
- Choosing better parameters: the values here led to some unrealistic behavior (negative y-axis values??). And units: somatostatin is usually measured in pg/L and insulin/glucagon are measured in mg/L. 1 pg $= 1 \times 10^{-9}$ mg.
- What about the side effects of somatostatin treatment (digestive issues, diabetes mellitus)? Can we find a "sweet spot" for somatostatin dosing?

Questions?

Figure: Me simulating my results in MATLAB