Modeling Biosystem Controls of Hypoglycemia

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***Abstract*— Effective blood sugar level management is crucial for individuals, as an impaired glucose-glucagon system can possess serious health risks such as diabetes. Diabetes affects around 23.6 million Americans and without proper treatment, diabetes can lead to more severe health conditions. This paper proposes a simplified blood glucose-glucagon model for people experiencing hypoglycemia. This model uses a series of ordinary differential equations to represent the relationship between glucose and glucagon. As glucose levels drop in the bloodstream, the pancreas releases glucagon to increase glucose levels. A control system using PID control was used to stabilize the model and reduce error. The system was modeled using Simulink to verify the feasibility and to achieve the goal of representing physiological changes in the bloodstream. The model is simple in order to gain a better understanding of the complex interactions between glucose and glucagon and how to apply them to people with diabetes, experiencing a hypoglycemic episode.**

***Keywords*— Glucose, Glucogen, Hypoglycemia, PID Control**

I. Introduction

Blood sugar management is a relatively effortless task for anyone with a fully functioning glucose control system in their body, however people with diabetes have an insufficient glucose-insulin regulatory system. Around 23.6 million Americans (7.8% of the population in the United States) have diabetes. If one cannot manage their diabetes, then they are at risk of various health conditions including blindness, heart disease, kidney failure, stroke, and brain death if the condition is not treated [1]. Therefore it is important to design a valid control system that can regulate one's blood glucose levels.

Before designing such a control system, we must determine the scope of the issue. There are two types of diabetes: type 1 and type 2. In a healthy person, beta cells in the pancreas release insulin into the bloodstream when glucose levels increase. The excess glucose is then stored in the liver as glycogen. However, in a diabetic person with type 1 diabetes, their body's immune system destroys the beta cells, preventing them from producing insulin. In a diabetic person with type 2 diabetes, their body develops an insulin resistance [2]. According to the World Health Organization, a normal blood glucose level ranges between 70 mg/dL and 100 mg/dL [3].

Hypoglycemia occurs when the glucose levels in the blood drop below 70 mg/dL while hyperglycemia occurs when the glucose level is higher than 125 mg/dL. In the case of hypoglycemia, the pancreas alpha cells release glucagon which triggers glycogenolysis. In glycogenolysis, glucose is generated from non-carbohydrate sources such as protein and lipids stored as glycogen, and is then released into the bloodstream [4]. We decided to focus on the interactions between glucagon and glucose in hypoglycemia in order to learn how glucagon affects the body and its role in diabetes.

II. Methods

A. Equations and Parameters

To model blood glucose regulation during hypoglycemia, we used differential equations to describe the fluctuations in glucagon and glucose. The mathematical equations to model the dynamics of glucose and glucagon are:

$$\frac{dC}{dt} = \alpha O(t) - \frac{1}{\tau}C(t) \qquad (1)$$

$$\frac{dG}{dt} = kC(t)G(t) \qquad (2)$$

Glucagon is produced when the blood glucose level is decreased. $O(t)$ is the input or impulse for the production of glucagon. The equation for the glucagon concentration is given by $C(t)$. In *equation (1)*, the glucagon concentration is produced at a rate that depends upon the impulse while it is removed from the system as a constant multiple times the concentration of glucagon itself. The α term from *equation (1)* is based on the average total blood volume in the human body [5]. The average person has five liters of blood in their system, so alpha is set to $\frac{1}{5\,L}$ *or* $0.2\,L^{-1}$.The production of glucose is given in *equation (2)*, where the production is dependent upon the concentration of glucagon, the k is the rate at which glucagon stimulates glucose production. the value for k is set to be 0.005 [7]. The τ is the time constant, representing the time it takes for glucagon to settle in the bloodstream after it spikes. In the average human body, it takes anywhere from 180 to 200 minutes for glucagon to settle down, so τ was set to be $\frac{1}{200\,min}$ [7].

The glucagon production term, O(t), acts as PID feedback control for the glucagon concentration as shown below where K_p represents the proportional control, K_i represents the integral control, and K_d represents the derivative control.

$$O(t) = K_p e(t) + K_i \int_{-inf}^{t} e(t)dt + K_d \frac{d}{dt}e(t) \qquad (3)$$

Using a PID controller is important to maintaining homeostasis in people with type 1 diabetes. The proportional integral derivative controller is used to regulate the glucagon infusion rate when the blood glucose levels fall below the threshold of 70 mg/dL. The controller is also used to successfully maintain the blood glucose and plasma glucagon concentration within a healthy range [4].

Finally, the error term, e(t), is determined as the difference between the target glucose concentration and the measured glucose levels as shown below. The target glucose concentration is based on healthy glucose concentration in the bloodstream for a healthy adult which is above 70 mg/dL [2]. Using a simple conversion, the target was calculated to be equal to 0.388 mmol/L to be consistent with the units.

$$e(t) = T - G_{meas}(t) \qquad (4)$$

System dynamics is modeled for equations 1, 2 and 4. Below is the table summarizing the values we used for our simulations.

Table 1: Coefficient values used in the equations.

$\alpha = 0.2\ [\frac{1}{L}]$	The average total blood volume is 5 liters.
$\tau = \frac{1}{200}\ [\frac{1}{min}]$	Glucagon takes 180-200 min to settle after it spikes in the bloodstream.
$T = 0.388[\frac{mmol}{L}]$	Healthy glucose level in the bloodstream for a healthy adult.
$Kp = 0.006$ [L/min*mmol] $Ki = 0$ [L/min*mmol] $Kd = 1$ [L/min*mmol]	Control parameters for the glucose homeostasis model. Values are found after analyzing the transfer function and Bode Plot.
$k = 0.005\ \frac{L}{t\ mmol}$	Rate constant for glucose production
$G = 0.1\ [\frac{mmol}{L}]$	Initial concentration for glucose
$C = 0.7[\frac{mmol}{L}]$	Initial concentration for glucagon

B. *Assumptions*

In modeling blood glucose management during hypoglycemia, several simplifying assumptions can be made. Factors such as the presence of insulin in the bloodstream, and outside physiological factors such as exercise and metabolic rates were not included. While it is possible to consider all of these factors in our mathematical model, we primarily focused on glucagon feedback for the sake of feasibility, given the amount of time given to work on the model. This way, the model can be modeled using a linear, first-order system of ordinary differential equations. In the model, we used initial concentrations of $0.1\ [\frac{mmol}{L}]$ for glucose and $0.7[\frac{mmol}{L}]$ for glucagon. This was done to match hypoglycemic conditions in the bloodstream.

C. *Simulink*

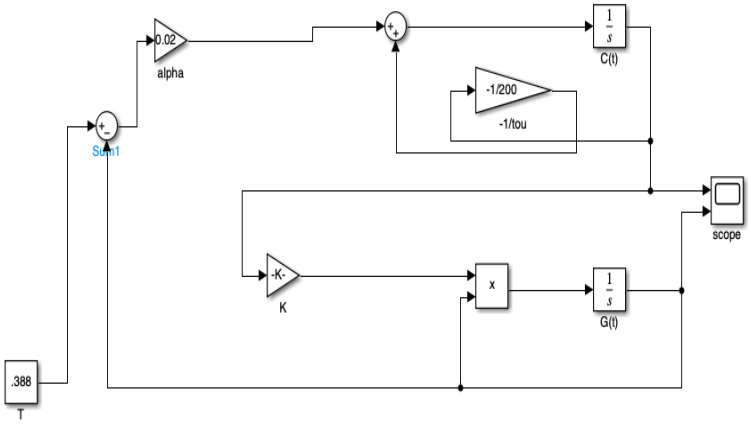

Figure 1: Block diagram for glucose and glucagon dynamics without PID control

The block diagram shows the model for glucose and glucagon dynamics. Each block corresponds to each term in the system. From *Figure 1*, the deduction for equations (1), (2) and (4) are simple. The system response is saved in the scope that can be used to visualize the simulation. The simulation ran for T = 5000 minutes.

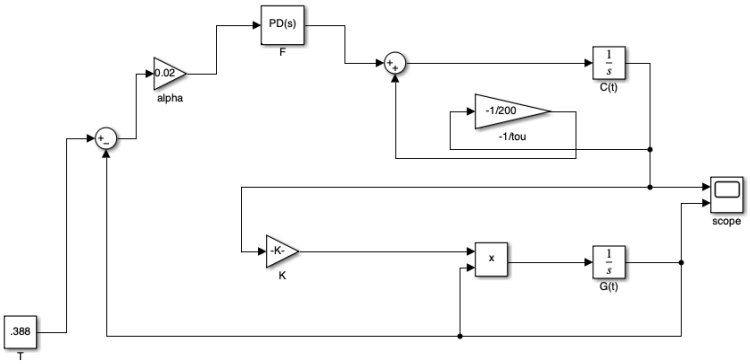

Figure 2: Block diagram for glucose and glycogen dynamics with PID control

The block diagram is the same exact model as *Figure 1*, however the PID control is added.

D. *PID Controller*

A PID controller helps stabilize the system for correcting errors. By adjusting the Kp, we can determine how to correct the system by using the last immediate error. The Kp multiplies the error by its own account and corrects the error according to its magnitude. Kp when correctly applied enhances the way the system responds to changes from the target. By adjusting the Ki, we can correct the system

according to the accumulation of error terms in the past. Lastly, for Kd, the PID controller looks at current trends in the error and tries to predict future errors. By adjusting the Kd, we adjust for this future error [8].

The following values were chosen for the PID controller: Kp = 0.006 [L/min*mmol], Ki = 0 [L/min*mmol], and Kd = 1 [L/min*mmol]. Since Ki is equal to 0 [L/min*mmol], the system does not keep track of previous errors. This means that the system is dependent on current conditions. We designed the system in a way that mimics the state of the pancreas. In a biological setting, we are assuming that the beta cells in the pancreas do not depend on previous conditions to work; for example, if the pancreas had previously encountered fluctuations in blood glucose concentrations, our PID controller assumes that the response of the alpha cells in the pancreas produces glucagon on present conditions and not previous ones.

To get a Kp of 0.006 [L/min*mmol], we increased the gain of Kp until Kp started oscillating. If we made Kp too high, then the system would become unstable [8]. Since Ki is 0 [L/min*mmol], we adjusted Kd to 1 [L/min*mmol] to stop the oscillations. These values are found from the transfer function *equation (5)* and from analyzing the Bode plot, *Figure 5*. In hypoglycemic system a faster response is crucial, so adding a Ki control can lead to overshooting. The primary concern for the system was to correct for the disturbance, and a PD control is sufficient for it. By doing so, we obtained a steady state error and the rate of change for glucagon and glucose settled at their set point. Adjusting values for controller parameters also show stability at the values that was found from the transfer function.

III. Results

A. Simulink

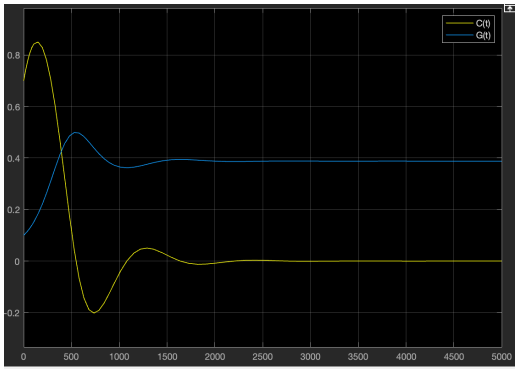

Figure 3: System response for glucose (blue) and glucagon (yellow) without PID control

From *Figure 3* the system response of glucose (blue) and glucagon (yellow) is shown . While the response is stable we see oscillations in the response. In a biosystem the concentrations cannot be negative and given enough time the concentrations will set at a steady state. In hypoglycemia the low concentration of glucose will trigger the response of glucagon to increase the concentration of glucose. From the Bode diagram, we can tune the controller to get a better phase margin and signal amplification by adding the Kp and Kd. The result for the system response is given below.

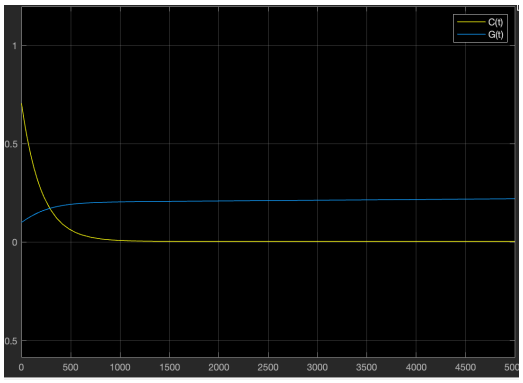

Figure 4: System response for glucose (blue) and glucagon (yellow) with PID control

The proportional control added a gain in the system and the derivative control gave a better damping and removed the initial rise of the response. There are no more oscillations in the system because of this controller. The system stabilizes at the steady state more rapidly as needed in the hypoglycemic system. There is a rise in the glucose concentration as the system starts at a hypoglycemic initial condition. The increase in glucose concentration is in response to the decrease in glucagon concentration that exponentially decreases to the steady state.

B. Transfer Functions

$$H(s) = \frac{G(s)}{O(s)} = \frac{k\,\alpha}{s + \frac{1}{\tau} + k\,\alpha} \qquad (5)$$

Equation 5 represents the closed loop transfer function. The overall function gives no zeros and a pole at $p_1 = -(\frac{1}{\tau} + k\alpha)$. The pole is negative so the system is stable. There is damping and the system will settle in its equilibrium state in response to time, which is confirmed from the system response.

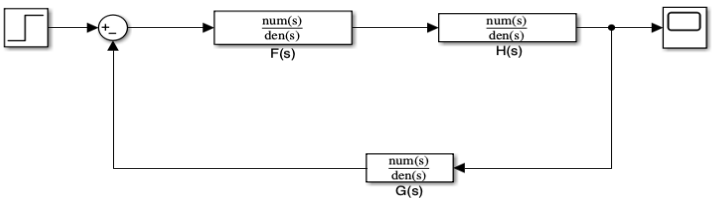

Figure 5: Closed loop simplest block diagram

This block diagram is a version for our simulink model reduced to a closed loop feedback system. Closed loops transfer function is given by:

$$CL(s) = \frac{F(s)H(s)}{1 + F(s)G(s)H(s)} = \frac{(Kp + Kd\,s)k\,\alpha}{s + \frac{1}{\tau} + k\,\alpha} \qquad (6)$$

$$F(s) = Kp + Kds;\quad Kp = 0.006\,;\ Kd = 1 \qquad (7)$$

$$H(s) = \frac{k\,\alpha}{s + \frac{1}{\tau} + k\,\alpha};\quad G(s) = 1$$

C. *Bode Plots*

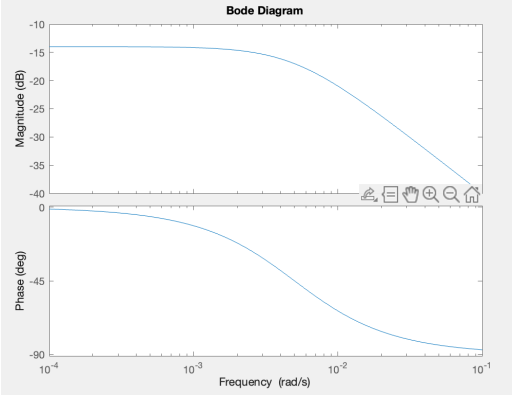

Figure 6: Open loop transfer function Bode plot without PID control

The negative dB values at lower frequencies implies that the corresponding components of the signal at those frequencies are reduced. This reduction could be due to factors like damping, filtering, or regulatory mechanisms in the physiological system. Also since the dB values are negative, this implies that the system is stable. The PID control helped to stabilize the system and reduce oscillations.

IV. Conclusion

A. *Discussion*

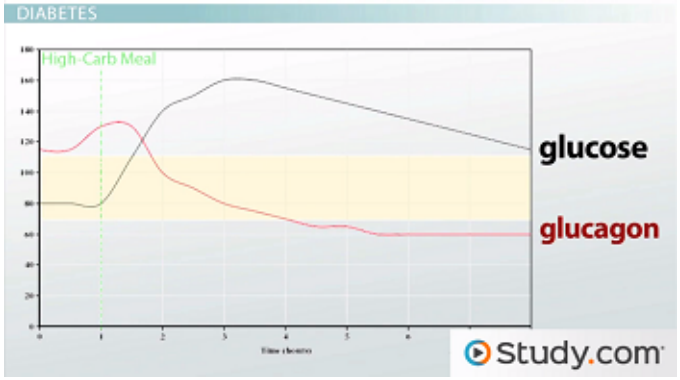

Figure 7: Glucose and Glucagon dynamics in diabetes [9]

Assessing the graphical depictions of our glucose and glucagon concentrations over time, we can immediately see the inverse relationship between glucose and glucagon concentration. This response is in correlation with biology seen in *Figure 7*, because glucose concentration increases as a result of an increase in glucagon concentration. Once the glucose is nearly done increasing, glucagon has already begun to decrease. Then glucose and glucagon experience a leveling concentration, with glucose having increased and glucagon having decreased. If glucose dips passed the 70 mg/dl threshold, the concentration of glucagon gradually increases to raise glucose concentration accordingly. *Figure 3* representing a run without the PID controller shows that glucose and glucagon concentrations are varied at high frequencies. There is also a glucose concentration error with the system we built, which also causes some glucagon concentration errors. The PID controller tames these oscillations and changes due to error.

B. *Future Improvements*

Something we would improve on for future models would be to add a differential equation that further describes the relationship between glucagon and glucagon. While obtaining our results it became evident that our observed discrepancies were due to the oversight of this relationship. While glucose downregulation is driven by a direct interaction between insulin and glucose, glucose upregulation is a direct interaction between glucagon and glucagon, and not glucagon and glucose as we initially modeled. This realization suggests that the discrepancy observed in our data can be attributed to the absence of this omitted relationship between glucagon and glucagon. We expected that our data will show that glucose rises and settles into the target, from a blood sugar deficit in the blood instead of dropping down to the target we chose.

The dynamics of glucose and glucagon are not only dependent upon each other but are highly complex and depend on various other factors such as insulin, hormones, food intake, etc. The model in this paper talks about constants that do not change over time. But in reality, the constants can vary depending on the environment. The analysis of glucose and glucagon dynamics can be studied further by sliding the constants to see the change in system behavior. This bifurcation analysis can tell us about the environmental conditions where the concentrations behave differently.

C. *Advantages and Disadvantages*

One advantage of our simulation to an actual physiological experiment is the fact that our simulation obtains results much faster. Instead of having to run an experiment that measures the responses of glucagon production in a patient and their glucose concentration, we can observe glucagon's response to glucose concentration with our own set of parameters in a hypoglycemic environment. We can see the changes in concentrations of glucose and glucagon from when glucose is below its threshold to when it goes back up above it. A disadvantage of our simulation to a physiological experiment is that our simulation includes glucose concentration error and, as a result, glucagon concentration error. Also the simulation does not contain possible factors such as food intake which produces a simplified model. The simulation uses the same parameters, however each person has their own different parameters. For example, the liters of blood in one's body varies between each person which will affect the glucagon response rate.

D. *Conclusion*

In conclusion, while the identification of our missing equation highlighted the need for ongoing refinement, our research yielded valuable insights into the intricacies of the blood glucose control system that operates inside the human body. The late discovery emphasized that any simplification of a model should ensure that all relevant equations and variables are included. Moving forward a thorough pathophysiological

analysis which includes obtaining a larger amount of relationships and variables than are needed for a simplified model be considered so that our simplified model can be validated.

V. Acknowledgments

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VI. References

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