Blood Glucose Control In Hyperglycemia

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***Abstract* - There are more than 422 million people worldwide who are suffering from diabetes/hyperglycemia, so exploration into better glucose-insulin regulation is the main target that we are aiming to solve. One of the theoretical analyses of blood glucose levels control in diabetic individuals is undertaken using a simple mathematical model of the dynamics between glucose and insulin interaction by the Bergman Minimal Model, which effectively describes the glucose-insulin regulatory system in the simplest terms. This project focuses on using this model to control and manage blood glucose and insulin levels in cases of hyperglycemia. We redesigned the model by including a PID controller and a component for externally supplied insulin. This system will act like an artificial pancreas on a daily basis. We strive to develop a closed-loop feedback system using Matlab/Simulink that regulates blood glucose and insulin in hyperglycemic conditions. The results acquired with this redesigned model shows effective control and management of glucose-insulin levels in the blood during hyperglycemic cases. Our plan is to design an improved model to conduct extensive hyperglycemia experiments, which will help prevent possible diabetic situations for patients who would have needed critical medical attention.**

I. INTRODUCTION

Hyperglycemia, also commonly known as high blood sugar/blood glucose, is a disease that usually affects (but is not limited to) individuals with diabetes [1]. This disease occurs from a build up of glucose in the bloodstream and is usually relevant in diabetes because diabates inhibits the production of insulin (type 1 diabetes) and can make the body become insulin resistant (type 2 diabetes) [1]. For people who have hyperglycemia, their blood glucose concentrations usually range above 180 to 200 milligrams per deciliter (mg/dL). Immediate attention to these glucose concentrations is necessary because individuals can develop diabetic ketoacidosis, a condition where ketones/toxic acids aggregate in human bodily fluids (blood and urine) [1]. In substitute for the shortage of blood sugar, the liver breaks down fat and produces ketones so it can be used as fuel for the body. However, according to the CDC, having high amounts of ketones in the body is considered dangerous [2]. Therefore, it would be more desirable to maintain a steady glucose concentration than depending on the production of ketones as fuel for the body.

In the long term, leaving hyperglycemia untreated can harm a person's eyes, heart, nerves, and kidneys, so being able to identify when a person's glucose level is normal and abnormal instantaneously is important to prevent further complications to the individual's health in the future [1]. The improved insulin glucose regulation model explained in this report will describe a strategy that researchers/doctors/scientists can implement into a possible medical device that can function to enhance management of hyperglycemia and diabetes.

II. METHODS

Mathematical Model

The following ordinary differential equations are used to design our glucose insulin regulation model [3]:

$$\frac{dI}{dt} = -\, n(I - I_b) + \gamma(G - h)t + u(t) \qquad (1)$$

$$\frac{dX}{dt} = -\, p_2 X + p_3(I - I_b) \qquad (2)$$

$$\frac{dG}{dt} = -\, p_1(G - G_b) - GX \qquad (3)$$

These equations represent the Bergmann Minimal Model, which is known as a simple model that can describe a person's glucose insulin regulation system [3]. Equation (1) illustrates how insulin concentration dynamics is affected by both insulin and glucose concentration and insulin injection, where n is the disappearance rate of insulin, I is the concentration of insulin over time, I_b is the basal insulin concentration, h is the value of glucose above which the pancreatic β-cells release insulin, and $u(t)$ is the insulin injection rate by the insulin pump. Equation (2) illustrates how much effect that insulin does to the glucose disappearance, where X is the insulin's effect on glucose, p_2 is the spontaneous decreased rate of tissue glucose uptake ability, and p_3 is the increase in tissue glucose uptake ability per unit of insulin concentration increase over the basal insulin.

Equation (3) represents how glucose concentration dynamics is affected by both glucose itself and the effect by insulin, where p_1 is the glucose disappearance rate. The values of the parameters in the equations are shown in Table 1: [4]

Serial Number	Parameters	Values for Normal Patient
1	P_1	0.0317
2	P_2	0.0123
3	P_3	4.92×10^{-6}
4	n	0.2659
5	G_b	70.0
6	I_b	7.0
7	G_0	291.20
8	I_0	364.80
9	γ	0.0039
10	h	79.0353

Table 1: Parameter values for a hyperglycemia patient in the Bergmann Minimal Model [4]. Note that the starting concentration of glucose and insulin, G_0 and I_0, are higher than a normal person.

Assumptions

This is a hyperglycemic model for post absorptive state. In our model there is initial concentration for both blood glucose and insulin secretion with start. To simplify the model, the following assumptions need to made: 1) The insulin input u(t) in the mathematical model is only an experimental manipulation and this value can't be negative (u(t) > 0), this is due to the fact that original insulin input is much higher than the model needed, and as following glucose concentration decreases the insulin injection rate will decrease as glucose level maintain in normal range. To add up to the first assumption, we need an additional assumption that 2) The amount of the insulin input u(t) will not affect the behavior or change the solution of the model, 3) For the accuracy of this model, a time delay of insulin input is considered. This assumption is relatively crucial as the timing of insulin administration relative to food intake and physical activity can significantly impact blood glucose levels. Ignoring this delay can lead to incorrect dosing, either resulting in hyperglycemia if insulin action is delayed more than expected, or hypoglycemia if insulin acts sooner than anticipated. We assume 4) X(0) = 0 because this state represent a healthy sate where there is no insulin-mediated glucose regulation. At last we assume that 5) For our closed loop system, we acknowledge a glucose feedback measurement of G(s) = 1, it implies a direct and proportional relationship between the measured glucose level and its actual value without any delay or distortion. This simplification makes the mathematical modeling and analysis of the system more straightforward and efficient for the whole process.

Performance Goals

Creating a hyperglycemia model with a PID controller, a type of automated system, is mainly about helping manage diabetes better. This system helps keep blood sugar levels in check by adjusting insulin delivery according to real-time blood sugar readings. It's especially useful in making devices like artificial pancreases, which can automatically give insulin to people with diabetes. The system can be customized for each person's unique insulin needs, reducing the risk of both high and low blood sugar. The model is also valuable for research, helping more researchers to understand how various factors affect blood sugar levels. The model is great for testing and training, allowing doctors and patients to learn more about diabetes and its treatment. Ultimately, this model aims to make life better for those with hyperglycemia by ensuring more consistent control of their blood sugar levels.

Analysis

A. Linearization

Linearizing equation (1), (2), and (3) respectively:

$$\frac{d\hat{I}}{dt} = -n\hat{I} + \hat{u} \tag{4}$$

$$\frac{d\hat{X}}{dt} = -p_2\hat{X} + p_3\hat{I} \tag{5}$$

$$\frac{d\hat{G}}{dt} = -p_1\hat{G} - (\overline{G}\,\hat{X} + \overline{X}\,\hat{G}) \tag{6}$$

B. Transfer Function

After linearization, the next step is to convert Equation (4), (5), and (6) from time domain to s domain by Laplace Transformation.

Convert Equation (4):

$$sI(s) - I(0) = -nI(s) + u(s)$$

$$sI(s) = -nI(s) + u(s)$$

$$I(s) = \frac{1}{s+n}u(s) \tag{7}$$

Convert Equation (5):

$$sX(s) - X(0) = -p_2X(s) + p_3I(s)$$

$$sX(s) = -p_2X(s) + p_3I(s)$$

$$X(s) = \frac{p_3}{(s+p_2)} I(s) \quad (8)$$

Plugging (7) into (8):

$$X(s) = \frac{p_3}{(s+p_2)(s+n)} u(s) \quad (9)$$

Convert Equation (6):

$$sG(s) + G(0) = -p_1 G(s) - (\bar{G}\, X(s) + \bar{X}\, G(s))$$

$$sG(s) = -p_1 G(s) - (\bar{G}\, X(s) + \bar{X}\, G(s))$$

$$G(s) = \frac{-\bar{G}}{s+p_1+\bar{X}} X(s) \quad (10)$$

Plugging (9) into (10):

$$G(s) = \frac{-\bar{G}\, p_3}{(s+p_1+\bar{X})(s+n)(s+p_2)} X(s)$$

Therefore, the transfer function for this model is:

$$H(s) = \frac{-\bar{G}\, p_3}{(s+p_1+\bar{X})(s+n)(s+p_2)}, \quad (11)$$

where $\bar{G}$ and $\bar{X}$ are the stable values of glucose concentration and insulin effect. The transfer function has three negative poles, which involves oscillations in the system. In order to improve the system response, we decided to add a PID controller along with our system to eliminate one of the poles in the transfer function denominator.

Block Diagram

Figure 1 is the general closed loop design for our glucose insulin regulation system for patients who have hyperglycemia or diabetes. When glucose levels spike above the desired glucose range, a glucose sensor will detect the current concentration and alert the PID controller to measure the necessary amount of insulin for the patient. Then, a medical device that serves to deliver insulin (such as an insulin infusion device) can be utilized to release the appropriate dosage of insulin into the patient's bloodstream so their glucose concentrations revert back into the desired range [5].

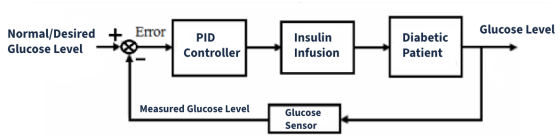

Figure 1: The general system block diagram for blood glucose control.

The block diagram in figure 2 shows the Simulink simulation of the integrated PID controller for insulin glucose regulation. The following values shown in figure 2 are taken from the parameter values in table 2. The PID control parameters were chosen to be K_p = 0.01 mL/min, K_d = 0.1 mL, and K_i = 0. These chosen PID parameters assisted in reducing the oscillations in the insulin and glucose concentration graphs to obtain the desired system response.

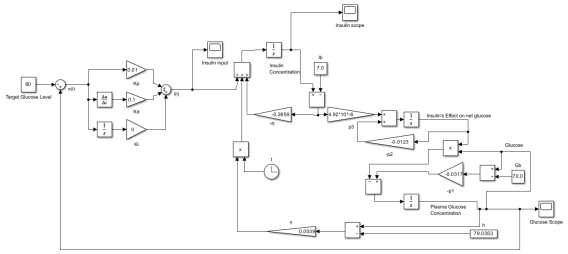

Figure 2: The designed PID controlled insulin glucose regulation system using Simulink.(Bigger block diagram image on last page so zoom in wouldn't be needed).

III. RESULTS

When the PID control was implemented into the system, there was a noticeable difference in the concentration of glucose over time and insulin over time. Looking at figure 3 for glucose concentrations, the drop in glucose that was present for the model without the PID controller is not as dramatic as it was in the model with the PID controller. Also missing in the model with the controller is a rebound spike that the model without the controller had

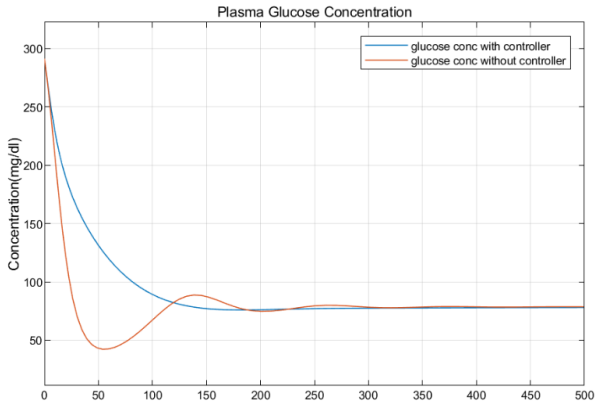

Figure 3: The graph showing glucose concentration over time (minutes) for the simulated model without the PID controller (orange) and the simulated model with the PID controller (blue).

When looking at the graph for insulin concentrations in figure 4, there was a big difference instantly as the simulation without the PID had an insulin spike starting at t=0 while the model with the PID controller had a large drop starting at t=0. After

its spike model without PID controller had a drop that exceeded the other model's drop as it struggled to reach steady state. After its initial drop, the model with a PID controller rises to steady state.

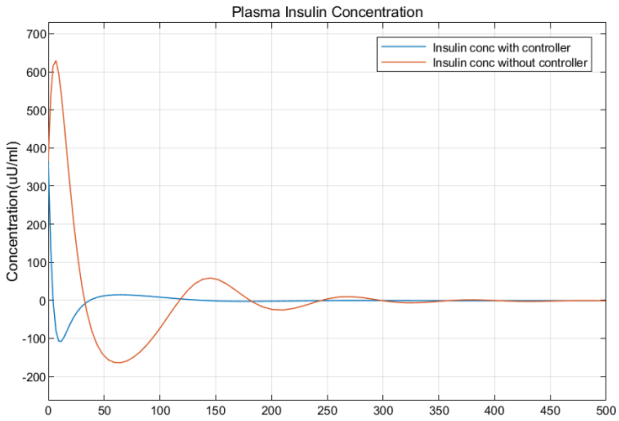

Figure 4: The graph showing insulin concentration over time (minutes) for a simulated model without a PID controller (orange) and one with a PID controller (blue).

IV. DISCUSSION

The biggest features our PID controller showcased is that the concentration of glucose or insulin did not spike or drop as much the model without it while also going into steady state sooner than the other model.

One component missing from the model was the delay. Two reasons to impose delay would be 1) after an increase in glucose, there is a delay in the production of insulin, and 2) the effect of insulin on glucose is naturally delayed[6]. Knowing that the model initial values of insulin, I_0, and the effect of insulin, X_0, makes sense as at time=0, I_0 is high at 364 μU/ml and X_0 is 0, so our model assumes both of these delays and the simulations starts after both these delays end at t=0. At t=0, X is 0 so there is no effect of insulin on glucose at the time, which is a healthy state, so there is still a 1 minute delay in the system. Overall, except for the lack of the time delay, the PID controller can effectively control the injection of the insulin pump and can reduce the glucose and insulin concentration to the target value faster than the insulin pump without PID control. Also, with fitted values of parameters, the PID controller can eliminate the oscillations of the whole system and reduce glucose concentration to the target value in a critically damping behavior. Missing the time delay function is the major limitation of the model since in reality, there should be a time delay for the sensors to detect the change in blood glucose concentration, and there is also a delay for the insulin to take the effect of consuming glucose. The future work is mainly about adding the time delay function between the measured value of glucose concentration and target value of glucose concentration and between the insulin effect function, X, and the glucose concentration function G, and analyzing the effect of PID control and explore how PID controller can optimize the response of the system with time delay.

Our model succeeds as a simple simulation of the glucose-insulin interaction in a hyperglycemic subject. As insulin concentration in the simulation went negative, this shows our model is missing a component that stops depletion of insulin. Since our glucose dips below the target glucose level even when the controller is present, we could add something to prevent the dip, but that is not necessary as our model shows that the glucose concentration rises naturally without a compensation mechanic.

Our model supports the work of Gallardo-Hernández et al. and the model they worked on. The parameter of insulin effectiveness on glucose is a mechanic that needs more exploration as it wasn't properly experimented with in this project, but is interesting as it has a delay that could be implemented and in a variable that is naturally at zero at homeostasis. .

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