

# Blood Glucose Control in Hypoglycemia

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**Abstract**— Blood glucose control during a hypoglycemic post absorptive state is mainly achieved through the action of glucagon. This project aimed to model the interaction between glucagon secretion and the glucose level as a biosystem controlled through glucagon secretion. The system boundary was defined to be the interaction between the pancreas glucagon release and elimination, the liver glucagon concentration and glucose release, and blood glucose levels. A block diagram was generated through the integration of the relevant processes for blood glucose control. The system was modelled only with a proportional control for glucagon production, and it yielded the expected results. The system seemed stable, but the transfer function of the system showed that there was instability due to the system having two poles. A PD controller was used to stabilize the transfer function of the system. The closed loop transfer function showed a stable system with only one pole at 0.0794 rad/min, and with a phase margin of -90 deg. Upon comparison of the model to actual clinical data, matching waveforms and the amplitude of the waveforms were observed to be similar.

**Clinical Relevance**— This simulation can be adjusted to match other medical conditions such that the behavior of the glucagon glucose relation can be approximated for these individuals. Diseases that have an effect on the rates of production and elimination, the control of glucagon release, and the storage of glycogen can all be correlated with correspondent gains in the block diagram, such that a wide variety of conditions can be simulated.

## I. INTRODUCTION

Blood glucose control during hypoglycemia depends heavily on the action of glycogen to increase blood glucose levels. The main organs at work during the response to correct low glucose levels are the pancreas and the liver; the pancreas works to detect the lowering glucose levels through alpha cells. Alpha cells monitor the fluctuations in the glucose level and depending on the glucose level, they signal a response to start secreting glucagon. Glucagon is taken up by the liver from the bloodstream to activate liver cells into starting glycogenolysis. In this process, glycogen is beaten down into its glucose monomers to then release them into the bloodstream. This increases blood glucose concentrations until they reach basal levels.

The goal of this project is to model the modulation of glucose level control by glycogen. The system and its controller will be modeled through block diagrams, and then further analyzed using Simulink to observe the way the system reacts. A test of stability will be performed to observe whether the system is stable or not, and any instability will be corrected through improvement of the controller system. Finally, results will be compared to physiological observations to understand the utility of our model, propose sources of

error, and gain an understanding of the utility of this model in experimentation.

## II. BACKGROUND

Glucose is an essential fuel for the body, with special interest for the brain. There is very low glycogen storage in the brain, so low that glucose concentrations in the brain are mainly dependent on the glucose that is uptake from the blood [1]. Thus, the regulation of the glucose levels in the blood is of vital importance. In the body, glucose is regulated through two negative feedback responses. If the glucose is too high, the response is the secretion of insulin to store the excess glucose inside of cells. This glucose will be later converted into glycogen(glycogenesis) and lipids(lipogenesis), among other compounds. For glucose levels that are low, the body response will be the secretion of glucagon to stimulate glucose production.

If glucose levels fall too low, the body enters a hypoglycemic state. Hypoglycemia is a condition in which the glucose levels in the blood are lower than the baseline, at an average 4.7 mmol/L (85 mg/dL) [2]. If left untreated, with continually decreasing concentration of glucose, it could lead to coma and further to death. During fasting, the main mechanism by which the body increases the glucose concentration is first through glycogenolysis [3]. Upon depletion of glycogen levels in the body, the mechanism to further maintain glucose levels is gluconeogenesis. The activation of these processes is dependent on the glucose levels. Alpha cells in the pancreas monitor the glucose level through the ratio between ATP produced to glucose absorbed from the blood by the GLUT1 transporter [4]. The response to increase the counterreaction to lowering glucose levels involves a series of steps to affect insulin and glucagon secretion. It starts first with the inhibition of insulin secretion at about 4.4 mmol/dL to stop any storage of glucose [3]. Upon reaching levels of blood sugar of about 3.6 mmol/L, a response to start glycogenolysis is started [3]. First, the pancreas will sense the low sugar levels and it will secrete glucagon, a hormone that oversees the activation of both glycogenolysis and gluconeogenesis to generate glucose. Glycogenolysis happens mainly in the liver, and this process involves the breakdown of glycogen into glucose. The glucose produced is secreted into the bloodstream. There are additional responses, such as cortisol and growth hormone secretion stimulation, but these constitute long term responses with no immediate effect.

A special case that works as a simplification of the double feedback system is the post-absorptive state of the body, in which the glucose produced from a meal has already

been stored in the form of glycogen and other compounds [2]. This state is usually entered 6 hours after a meal, but it is also used to describe the fasted state of the body after a night of sleep. In this state, there is no influence of insulin since there is no consumption of food. Thus, insulin effects can be neglected since they are minimal. This makes glucagon the main mechanism by which blood glucose control is achieved. In this state, the consumption of glucose and the secretion of glucose are in equilibrium so that no net change in glucose is registered [2].

### III. CONTROL SYSTEM MODEL

For the model, the biosystem was defined as the interaction between glucagon, glycogen, and glucose, while the control system is the secretion of glucagon to correct the low glucose levels. The input to the system will be low glucose levels, which will start at 54 mg/dL. This signal is felt by the sensor, which are the alpha cells in the pancreas. The alpha cells compare the glucose levels to the threshold to start the counter response. In the literature, the release of glucagon has been modelled before as a proportional controller, so the starting controller unit was a proportional controller. This release in glucagon increases the glucagon concentration in the liver and triggers glycogenolysis to increase the blood glucose levels. That reaction constitutes the effector of the system. This is summarized in Figure 1, where the overall components of the system are depicted as blocks.

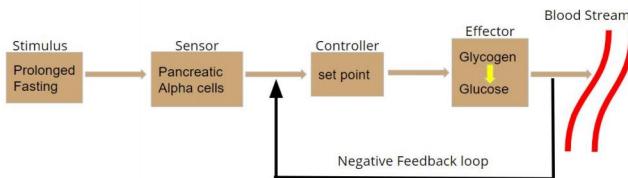


Figure 1. Control system for hypoglycemia featuring a stimulus, sensors, a controller, an effector, and a negative feedback loop

#### A. Assumptions

This is a hypoglycemic model of post-absorptive state. To simplify the model, the following assumption has been made: since there is no insulin secretion, the insulin effects are negligible. There are very low insulin concentrations and they do not play a big role in the balance of glucose during this state. It is assumed that the subject is non-diabetic and in a state of prolonged fasting and minimal physical activity (resting state). Thus, data regarding the average rate of production and consumption of glucose can be used in our model. It is assumed that there is no significant production of glycogen, such that there is a set amount of stored glycogen in the liver decreasing over time as it gets converted to glucose. We assume first order kinetics for the reaction Glycogen  $\rightarrow$  Glucose. It is also assumed that the rates of bodily processes are constants, without taking account for differences between individuals. Lastly, it is assumed that long term response of the body due to hypoglycemia is insignificant and thus it is ignored. This includes conditioning reactions from growth hormone and the effect of cortisol.

#### B. System Boundaries

The system boundaries for our control system model contain the pancreas, the liver, and the bloodstream. Quantities that we are interested in are the concentration of glucagon, glycogen, and glucose.

#### C. Operational Constraints

The limiting factor for the operational time span of the system is either the time it takes for the available stored glycogen in the liver to run out or the time it takes for blood glucose levels to reach the set point value. Whichever happens first is the limiting factor for the system.

#### D. Performance Goals

We are expecting that the overall blood glucose levels will increase and eventually settle at the set point value. We also expect the glycogen concentration to decrease overtime as it gets used up to produce glucose. Lastly, we expect for there to be an initial increase in glucagon concentration that will eventually settle back down to its starting concentration once blood glucose levels reach the set point.

### IV. MATHEMATICAL MODEL

The mathematical model for blood glucose control in hypoglycemia based on assumptions mentioned in sections III part A can be broken down into four parts: The secretion of glucagon by pancreatic alpha cells, glucagon concentration, glycogen concentration, and glucose concentration.

#### A. Equations with constants

The secretion of glucagon by pancreatic alpha cells  $M(t)$  is modeled as:

$$M(t) = K(T - G(t)) \quad (1)$$

In which  $K$  is the rate at which pancreatic alpha cells release glucagon.  $T$  is the target blood glucose levels and  $G$  is the current blood glucose concentration.

Glucagon concentration  $N(t)$  is dependent on glucagon secretion from the pancreas and glucagon disappearance due to the liver and is modeled as:

$$\frac{dN(t)}{dt} = aM(t) - bN(t) \quad (2)$$

The constant  $a$  represents the rate of excess plasma glucagon stimulated glucagon activity and constant  $b$  represents the rate of glucagon disappearance from plasma.

Glycogen concentration  $Y(t)$  in the liver decreases at a rate that is proportional to the rate of glucagon effectiveness  $j$  times the current glucagon concentration and is modeled as:

$$\frac{dY(t)}{dt} = - jN(t) \quad (3)$$

Finally, glucose concentration  $G(t)$  is modeled as:

$$\frac{dG(t)}{dt} = cY(t)N(t) - d(G(t) - T) \quad (4)$$

Where  $c$  is the rate of excess plasma glucagon stimulated glucose activity and  $d$  is the glucose effectiveness. The first half of the equation is the production rate of glucose into the bloodstream based on the glucagon and glycogen

concentrations. The second half of the equation is the rate at which glucose is being used up by the body.

### B. Parameter values

Parameter values used in the example for investigating blood glucose levels control via. glucagon secretion.

Parameter	Value	Unit
K	0.1	L/min
T	85	mg/dl
G(0)	54	mg/dl
N(0)	$1.26 \times 10^{-7}$	mg/dl
Y(0)	5490	mg/dl
a	$1 \times 10^{-4}$	$ng/l \min^{-2} (mg/dl)^{-1}$
b	0.055	1/min
j	0.01	$mg/dl \min^{-1} (ng/l)^{-1}$
c	$5 \times 10^{-3}$	$\min^{-1} (ng/l)^{-1}$
d	0.01	1/min

Figure 2. Values are based on data from sources [5] and [6]. The initial concentration of glycogen is based on source [7].

For a non-diabetic subject, the normal fasting blood glucose level is around 70 mg/dl to 100 mg/dl [2]. Anything under 70 mg/dl is considered hypoglycemia. Therefore, we decided to pick 85 mg/dl as our target set point to bring blood glucose levels up to the middle range of the safe zone. We also decided to set the initial glucose concentration as 54 mg/dl which is the glucose level that would require immediate medical attention.

### C. Simulink Model

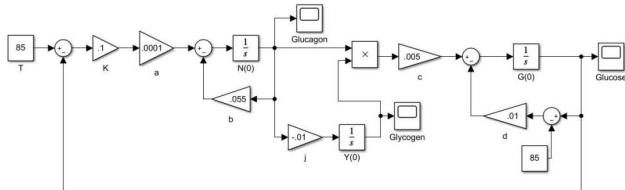


Figure 3. Simulink model for our control system based on the four equations listed part A.

The input for the system is the secretion of glucagon by pancreatic alpha cells as represented on the far left. This process is controlled by the feedback loop and the target set point value. The summation of this process and the glucagon disappearance due to the liver made up the glucagon concentration  $N(t)$ . Glycogen concentration  $Y(t)$  is controlled by the glucagon concentration and the rate of glucagon

effectiveness. These processes along with the uptake of glucose by the body made up the glucose concentration.

The glucagon and glucose concentration over time based on the simulink model above are the following:

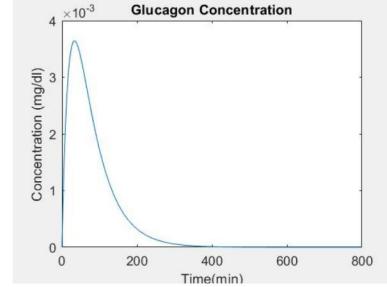


Figure 4. Glucagon concentration over time in unit of mg/dl

The glucagon concentration displayed an initial increase due to the initial low blood glucose level. As the glucose concentration slowly rises over time, the feedback loop reduces glucagon secretion and decreases glucagon concentration. Once blood glucose levels reached the intended set point value, the feedback loop no longer triggers glucagon secretion from the pancreas. Therefore, glucagon returned to its initial concentration of around 7 pmol/L.

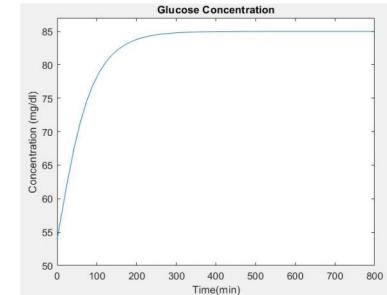


Figure 5. Glucose concentration over time in unit of mg/dl

The glucose concentration shows an overall increase in concentration over time as more glucagon is being secreted from the pancreas to bring the blood glucose level up to the set point. Once the glucose concentration reached the set point value of 85 mg/dl, it maintained around that concentration unless some external stimulus like insulin was introduced into the system which then the glucose level would decrease again.

## V. ANALYSIS

### A. Linearization

When linearizing the  $G(t)$  equation (4), we get:

$$\begin{aligned} \frac{dG(t)}{dt} &= cj(N(t))^2 - d(G(t) - T) \\ \frac{d}{dt} G(t) &= \{2cj\bar{N}, -d\} \\ \frac{dG(t)}{dt} &= 2cj\bar{N}N(t) - dG(t) + dT \end{aligned}$$

Then we should get two equations:

$$\frac{dN(t)}{dt} = aM(t) - bN(t) \quad (2)$$

$$\frac{dG(t)}{dt} = \gamma N(t) - dG(t) + d * T \quad (5)$$

$$\text{Assuming } \gamma = 2cj\bar{N}$$

## B. Transfer Function

To find the transfer function of our system, we first took the laplace using the two linearized equations above.

$$\begin{aligned} sN(s) - N(0) &= aM(s) - bN(s) \\ N(s) &= \frac{aM(s)}{(s+b)} \\ sG(s) - G(0) &= \gamma N(s) - dG(s) + \frac{dT}{s} \\ sG(s) + dG(s) &= \gamma N(s) + G(0) \\ G(s) &= \frac{\gamma N(s) + G(0)}{(s+d)} \end{aligned}$$

Giving us the transfer function:

$$H(s) = \frac{\gamma a}{(s+b)(s+d)} \quad (6)$$

However, if we were to just use the transfer function in simulink, we would get a lot of oscillations in our system. To improve the system response, we decided to add a PD controller along with the transfer function for our simplified block diagram.

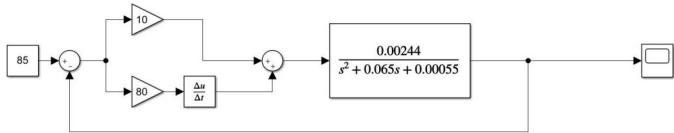


Figure 6. Reduced simulink model using the PD controller and the transfer function.

This system has two real negative poles located at 0.01 rad/min and 0.055 rad/min. To stabilize the system, it was only necessary to eliminate one of the poles in the denominator. This was achieved through the use of a proportional and derivative control, and the values seen in Figure 6 for the constants make the system stable. A plot of the glucose concentration as given by the PD controller is shown in Figure 7.

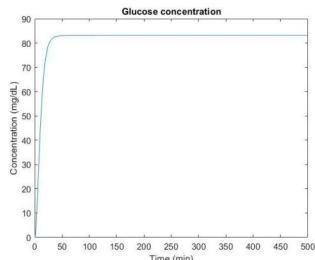


Figure 7. Reduced simulink model using the PD controller and the transfer function.

The glucose concentration plot for the reduced simulink model displayed a similar behavior as that of our original system. Glucose gradually increases over time to eventually reach the set point value. However, we saw that in this plot, the glucose level did not reach 85 mg/dL exactly but it is very close. The response also happened much quicker. This could be due to the PD controller parameter K being much larger than in the original system.

## C. Bode Plot

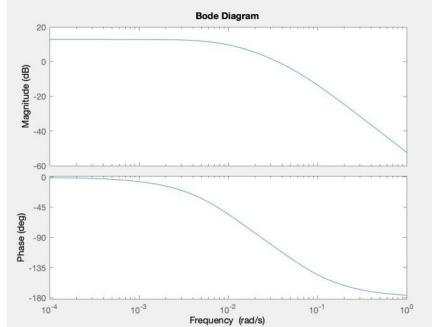


Figure 8. Bode analysis for the transfer function of the system. Note how the system itself is unstable because of the two poles.

The biosystem itself is unstable as shown in the bode plot from Figure 8. Based on the transfer function, two poles were identified at 0.01 and 0.055 rad/min. The two poles would bring the phase margin of the system passed -90 deg, which is why the use of a PD controller was necessary to make the system stable. The pole at 0.01 rad/min was neutralized with the zero placement of the PD controller, and the plot of Figure 10 was the resulting bode plot of the closed loop transfer function. It added a factor of ten to the numerator, and it placed a zero at 0.0794 rad/min.

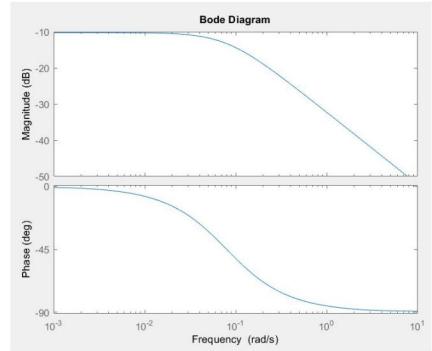


Figure 9. Stable system upon the integration of a PD controller for the secretion of glucagon.

## D. Compare simulation results with physiological observations

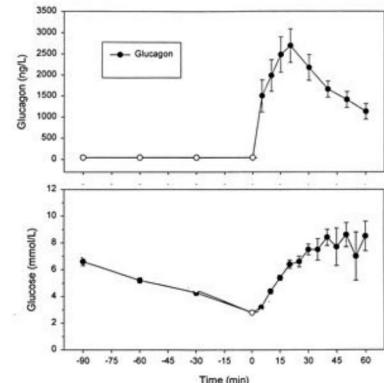


Figure 10. The glucagon and glucose concentration plots after administration of glucagon from source [8]

Based on the research paper “Epipen as an Alternative to Glucagon in the Treatment of Hypoglycemia in Children With Diabetes” by Teresa Monsod<sup>5</sup>, we see that the glucagon and glucose concentration plots after the administration of glucagon are very similar to our own plots in Figure 4 and 5. Glucagon concentration displayed an increase in concentration after its administration, reached a peak value, and gradually decreased overtime as glucose concentration increased, similar to how our simulation for glucagon behaved. Similarly, glucose displayed an overall increase in concentration after glucagon is administered and eventually reached a steady state just like our simulation.

## VI. ERROR

For our model, we are not taking into account small perturbations in rates and baseline values which might be different depending on the subject gender, age and weight. Here, we are assuming that the effect of gluconeogenesis is very minimal, almost negligible which might also be very different depending on each subject. Similarly, one of the other sources of error might be not including the rate at which glycogen, glucose, fats and other sources of energy are consumed by organs other than pancreas and liver. For example, muscle also stores glycogen just like liver in our body and the breakdown of glycogen depends on how much energy our body needs depending on the specific state our body is in. Moreover, there was much conflicting information about the specific number of stored glycogen in the liver that gets broken down into glucose which might have also affected our plots for glycogen. Lastly, since we are also assuming negligible concentration of insulin in our system when glucagon is released from pancreas, simply the math might have greatly affected our plots. Because in our body Insulin and glucagon work together as Glucagon interacts with the liver to increase blood sugar while insulin reduces blood sugar by helping the cells use glucose, completely ignoring the insulin concentration would not be a good idea overall.

## VII. CLINICAL SYNDROMES AND MODIFIED SYSTEM

Some of the clinical syndromes of hypoglycemia are:

- i) Glycogen synthase deficiency
- ii) Liver Phosphorylase deficiency
- iii) Glucagon deficiency

Glycogen synthase deficiency is the deficiency in the enzyme named glycogen synthase which is needed for the body to make glycogen [9]. The amount of glycogen that the body can store in the liver is very low. Liver Phosphorylase deficiency is the deficiency when the liver cannot break down glycogen properly and the excess amount accumulates in the liver causing a buildup also known as Hers disease [10]. Similarly, the deficiency of glucagon secretion resulting in severely low blood glucose level which cannot be controlled without administering glucagon is known as Glucagon deficiency also known as Hypoglycemia syndrome. [11]

We then took glucagon deficiency clinical syndrome and modified our system by adding a step function input into

our glucagon model which represents a glucagon input in our body via injection to restore the blood glucose level. Glucagon in this scenario is slowly being released into the bloodstream at a constant rate.

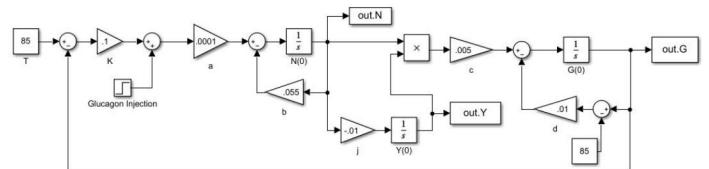


Figure 11. Modified simulink model for glucagon deficiency clinical syndrome via glucagon injection.

As the glucagon gets injected into the body its concentration spikes up and then gradually decreases reaching the steady state value but not zero because of the constant input of glucagon through a step function input. The glucose concentration also increases, reaching the steady state value which is slightly higher than the setpoint value as can be clearly seen on the plots below:

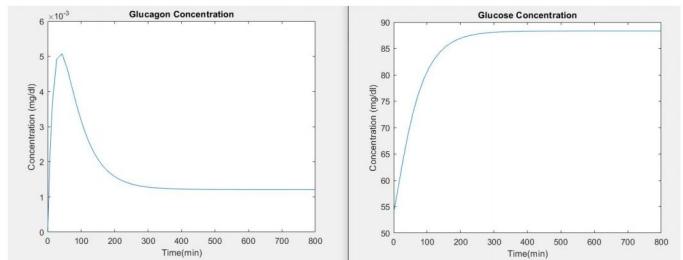


Figure 12. Glucagon and Glucose concentrations for the modified simulink model

## VIII. CONCLUSION

It is very important to understand how our body controls the blood glucose level in our body through the secretion of glucagon and the breakdown of glycogen in the liver. Glucagon is a hormone that has a very important role in the body to prevent blood glucose levels dropping too low and Glucagon works along with the hormone insulin to control blood sugar levels and keep them within the set levels. The release of glucagon is prevented by raised blood glucose and carbohydrate in meals, detected by cells in the pancreas. In the longer-term glucagon is crucial to the body's response to lack of food. For example, it encourages the use of stored fat for energy in order to preserve the limited supply of glucose. Therefore, a physical model that shows how the glucose level is maintained in our body is important to treat many different clinical syndromes such as deficiency of glucagon secretion mostly in babies.

## IX. ACKNOWLEDGMENT

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