BME331: Physiological Control Systems
Lab 1

Deniz Uzun 1006035005
Shirley Hou 1006208907
Wummy Wen 1006417281
Emily Zhang 1006321473

Part 1

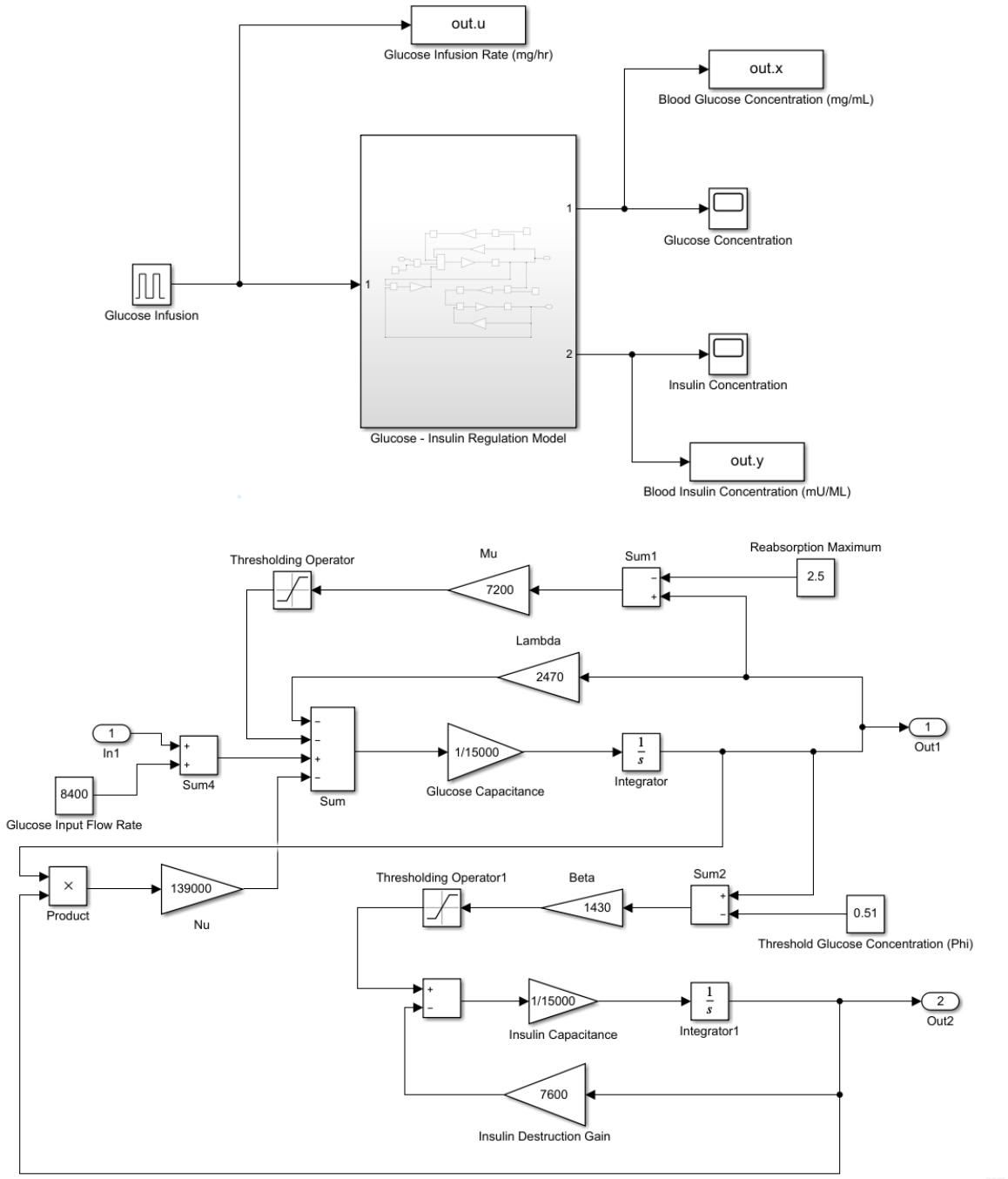

Figure 1:The glucose-insulin SIMULINK model

Part 2

a)

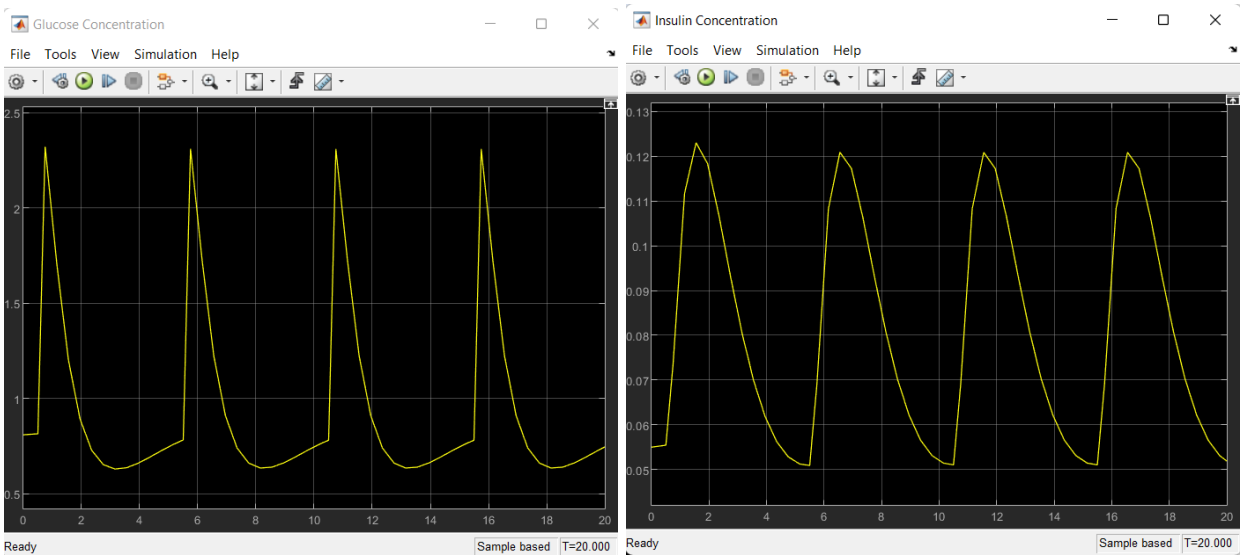

Figure 2a: Glucose and insulin responses for impulse-like glucose infusion every 5 hours. Input period = 5 and Impulse Pulse Width = 5

b)

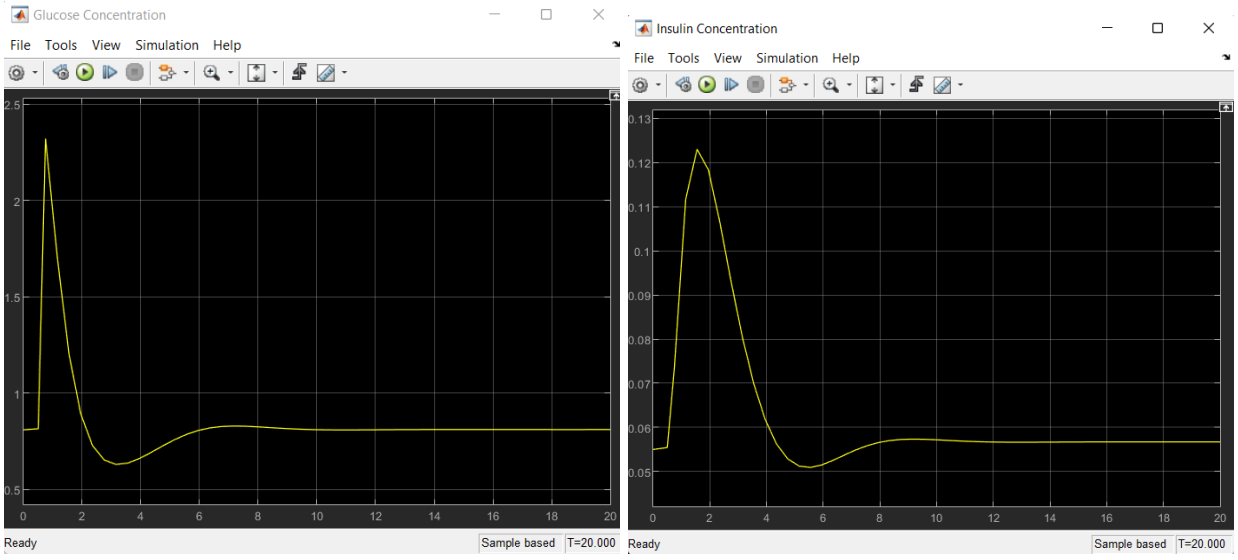

Figure 2b: Glucose and insulin responses for the changed input period and input pulse width. Input period = 100 and Impulse Pulse Width = 0.25

As we increase the input period to 100, we suggest that there will be a glucose infusion every 100 hours. Therefore we are only able to see single impulses within our given time frame, where the glucose levels rise in response to the glucose infusion and return back to normal overtime due to the release of insulin.

Part 3

a) The insulin production rate dependent on the plasma glucose level is given by equation (4). To reduce sensitivity of insulin production to the glucose concentration, we modified β to be 0% (yellow), 20% (dark blue), 40% (orange), 60% (green), 80% (purple) and 100% (light blue) of its default value. In *Figure 3a* we can observe that as we decrease the sensitivity, insulin production decreases due to the model's reduced ability to react to increasing blood glucose levels. Due to the lack of sufficient insulin to promote glucose uptake, blood glucose levels keep increasing.

$$Insulin\ production\ rate = \begin{cases} 0, & x \leq \phi \\ \beta(x - \phi), & x > \phi \end{cases} \qquad (4)$$

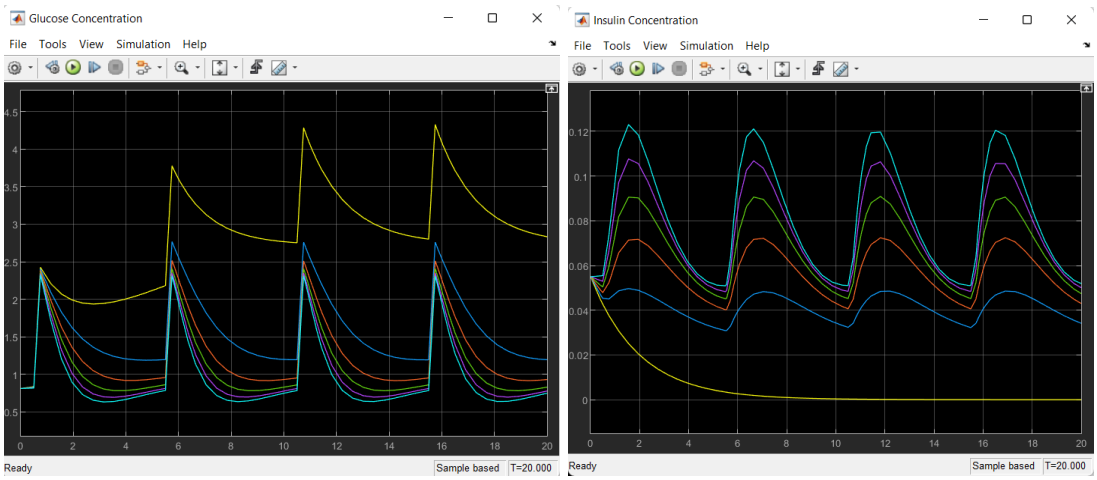

Figure 3a: Glucose and insulin responses for Type I diabetes.

b) The insulin dependent rate of glucose uptake is given by equation (3). To reduce the insulin-dependent tissue utilization rate we modified ν to be 0% (yellow), 20% (dark blue), 40% (orange), 60% (green), 80% (purple) and 100% (light blue) of its default value. In *Figure 3b,* we can observe that as we decrease the tissue utilization rate, blood glucose levels increase as glucose remains in the blood. Due to the increased levels of blood glucose concentration, we can observe that the insulin concentration increases to stimulate tissues and to promote the uptake of the glucose.

$$Tissue\ utilization\ rate\ (insulin - dependent) = vxy \qquad (3)$$

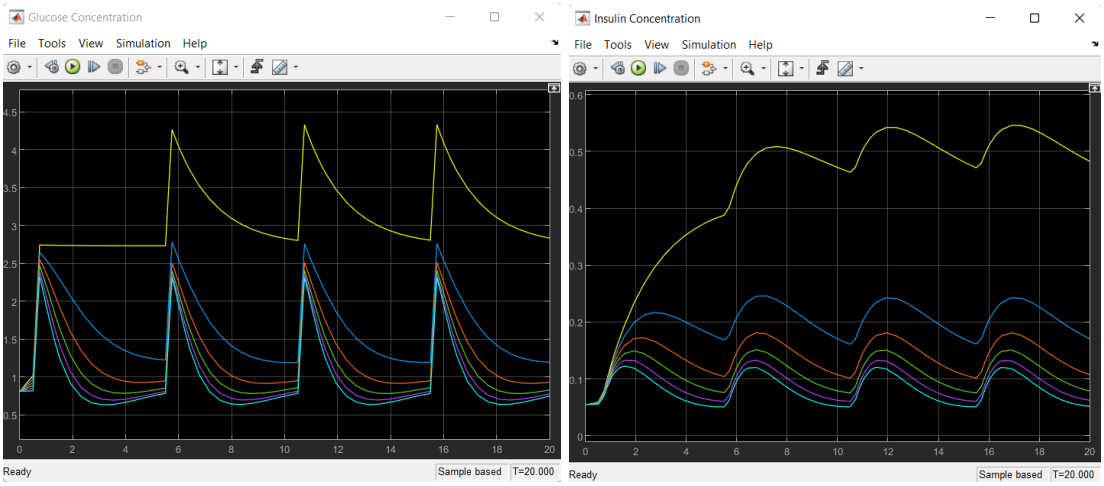

Figure 3b: Glucose and insulin responses for Type II diabetes.

Part 4

a) Managing Diabetes

Type I diabetes

Insulin Injection

Patients with Type I diabetes have an impaired pancreas. Therefore they lack the ability to produce sufficient insulin for themselves. We modified the insulin production rate above the threshold level to be 0 (See *Figure 4a.1.3* or *Figure 3a*, yellow response), impairing ability of Langerhans islets to produce insulin due to lack of sensitivity to glucose concentration by changing the β value from equation (4) to model Type I diabetes of a person with a damaged pancreas. Without any modification, the insulin level would eventually go to zero and the glucose levels would continue to increase with glucose infusion, as the cells will not be simulated to uptake the excessive glucose due to the lack of insulin. In order to achieve the external insulin injection, a new subsystem called "Insulin Injection" is added to the mode (See *Figure 4a.1.1*). This new subsystem is designed to supply the body with sufficient insulin, thus the same multiplier (β value of 1430) of a healthy body is used (See *Figure 4a.1.2*) to achieve a similar rate of insulin secretion. The same threshold operator is used to mimic a healthy body's sensitivity to glucose levels (See *Figure 4a.1.2*). On the simulink model, the subsystem is placed at the same location as the body's internal insulin production route, to represent that it is directly being injected into the bloodstream. Our model is based on the assumption that the blood glucose levels will be monitored constantly, such as a Continuous Glucose Monitor (CGM). As a result of the insulin injection modification, the patients' glucose and insulin levels become stable and healthy (Observe the similarity of *Figure 4a.1.4* and *Figure 4a.1.5*/*Figure 3a*, light blue response). The glucose level is controlled as the insulin gets injected periodically when glucose level is above the threshold.

$$\text{Insulin production rate} = \begin{cases} 0, & x \le \phi \\ \beta(x - \phi), & x > \phi \end{cases} \qquad (4)$$

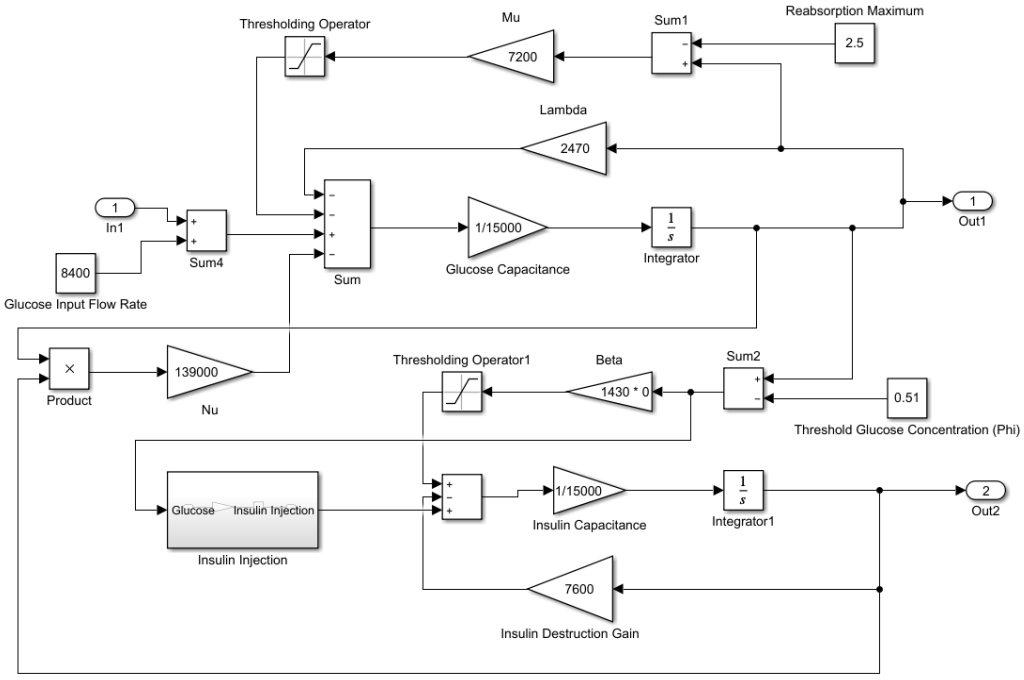

Figure 4a.1.1: Insulin injection model for managing Type I diabetes.

Figure 4a.1.2: Insulin injection block subsystem.

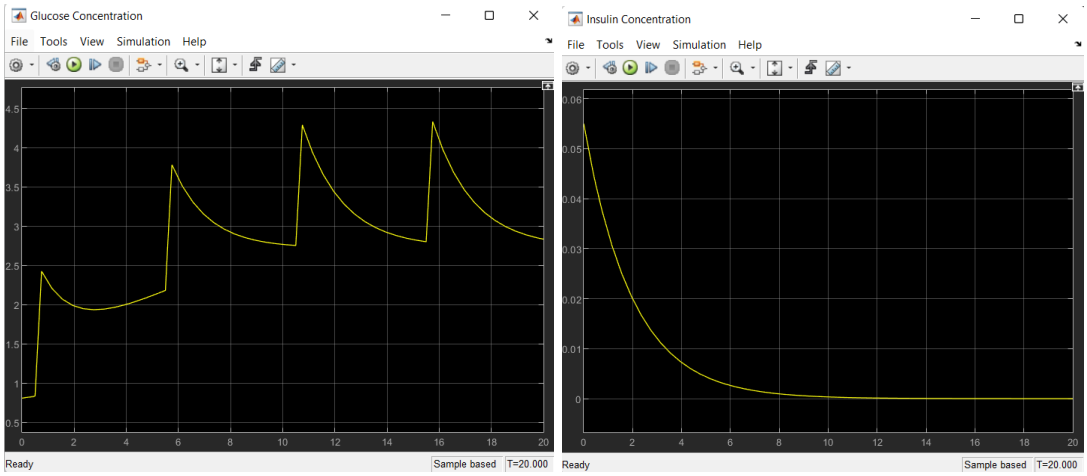

Figure 4a.1.3: Glucose and insulin responses corresponding to Type I diabetes with no insulin production sensitivity to glucose concentration.

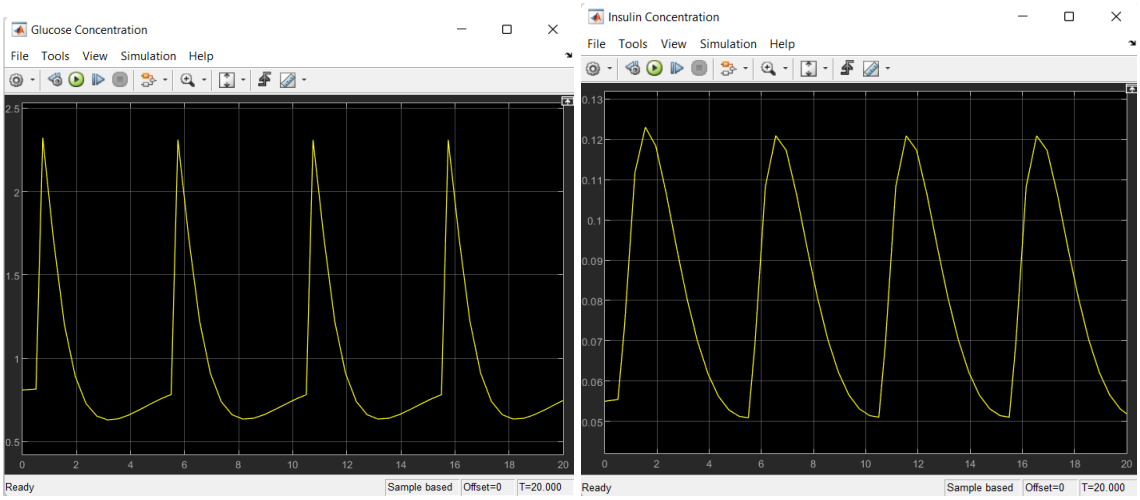

Figure 4a.1.4: Glucose and insulin responses for Type I diabetes management model with insulin injections.

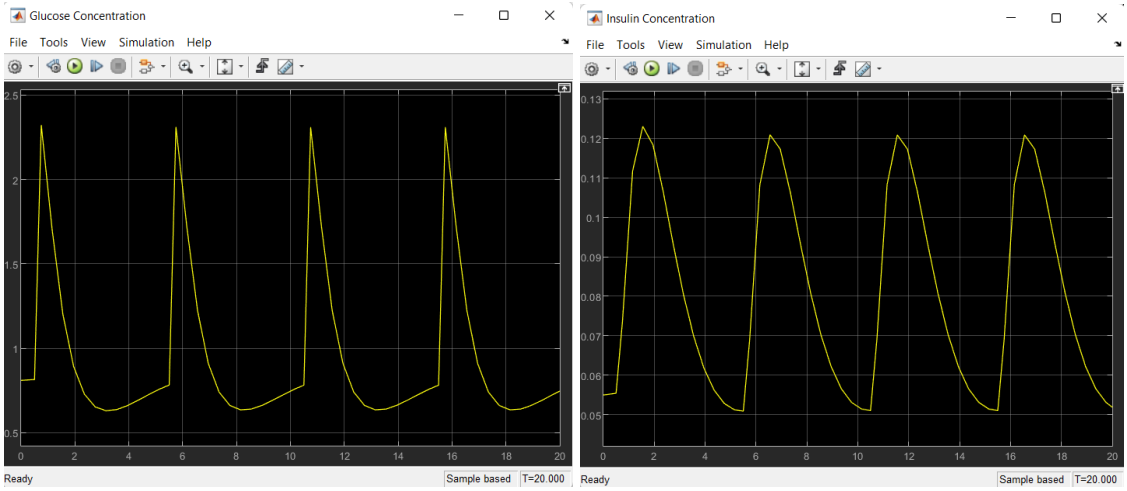

Figure 4a.1.5: Glucose and insulin responses of a healthy person with 100% insulin production sensitivity to glucose concentration.

Diet Management

Limiting glucose intake will not fix the impaired insulin production rate nor it will lead to more insulin secretion. If the pancreas is fully impaired, we wouldn't observe any changes in insulin concentrations with the modification of diet. Therefore, to be able to observe the effects of this modification on insulin levels as well as glucose levels, we assumed that the pancreas will be able to produce some amount of insulin, in response to increasing glucose levels, by setting the β value from equation (4) to 20% of it's default value. To model the limited glucose intake we placed a thresholding operator, limiting the glucose infusion to 70% of its default value (100000), by setting the upper limit to 70000 (See *Figure 4a.2.1*). Without any modifications, glucose levels peak around 2.8 (See *Figure 4a.2.2* or *Figure 3a, dark blue response*), reaching higher levels than a healthy body's blood glucose concentrations (peak ~2.4) (See *Figure 4a.2.4* or *Figure 3a, yellow response)* as the damaged Langerhans islets are unable to produce same levels of insulin like a healthy pancreas to promote the necessary glucose uptake. Limiting the glucose intake by modifying the diet, results in lower levels of blood glucose concentrations, peaking around 2.4 like a healthy response. (Observe the similarity between *Figure 4a.2.3 and Figure 4a.2.4* glucose concentration peaks). However, as we have stated before, diet modifications will not fix the impaired pancreas. Even with the modification, the insulin production will still be insufficient, showing a similar pattern to the non-modified version (Observe the similarity between *Figure 4a.2.2 and Figure 4a.2.3* insulin concentration graphs), with a slight difference of lowered levels of insulin due to less blood glucose. As there will not be sufficient insulin in the blood, glucose levels would remain high for longer periods of time and will not be able to reach levels as low as a healthy response (Observe the difference between *Figure 4a.2.3 and Figure 4a.2.4* glucose concentration change interval lengths and lowest level values).

$$Insulin\ production\ rate = \begin{cases} 0, & x \leq \phi \\ \beta(x - \phi), & x > \phi \end{cases} \qquad (4)$$

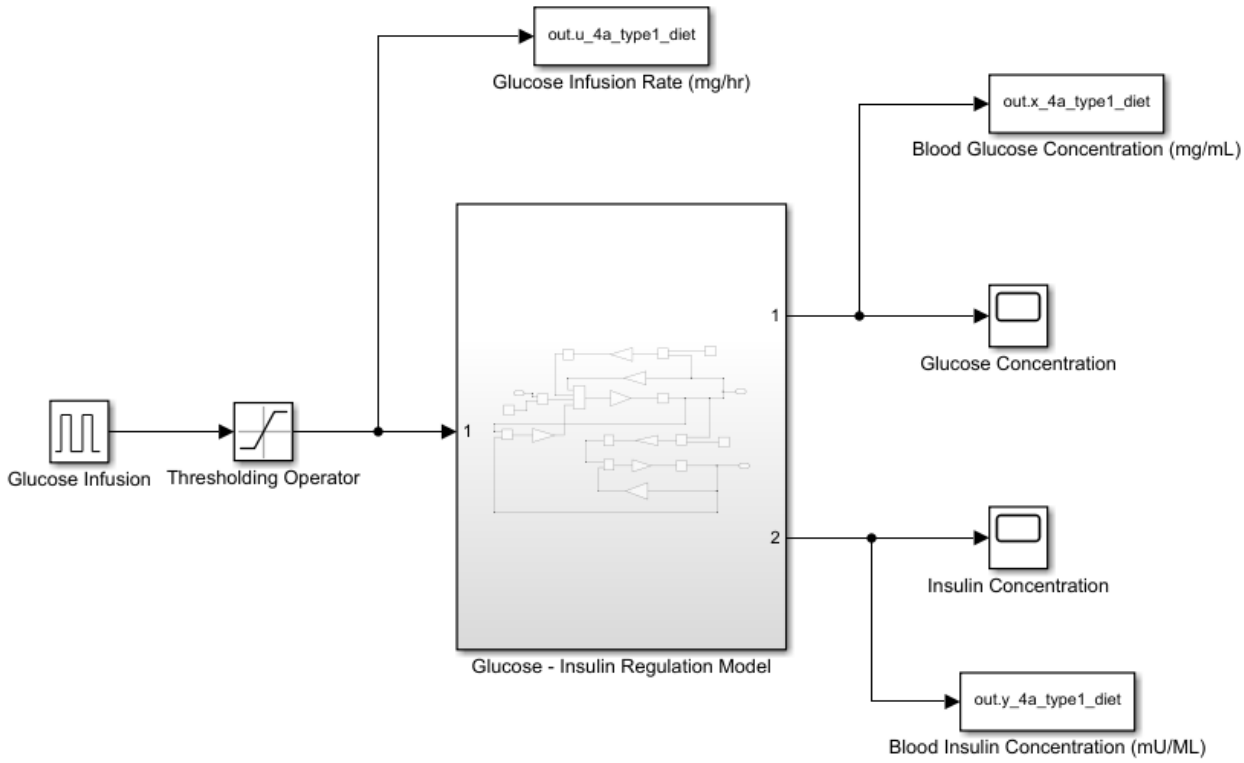

Figure 4a.2.1:Diet management model to limit glucose intake for managing Type I diabetes.

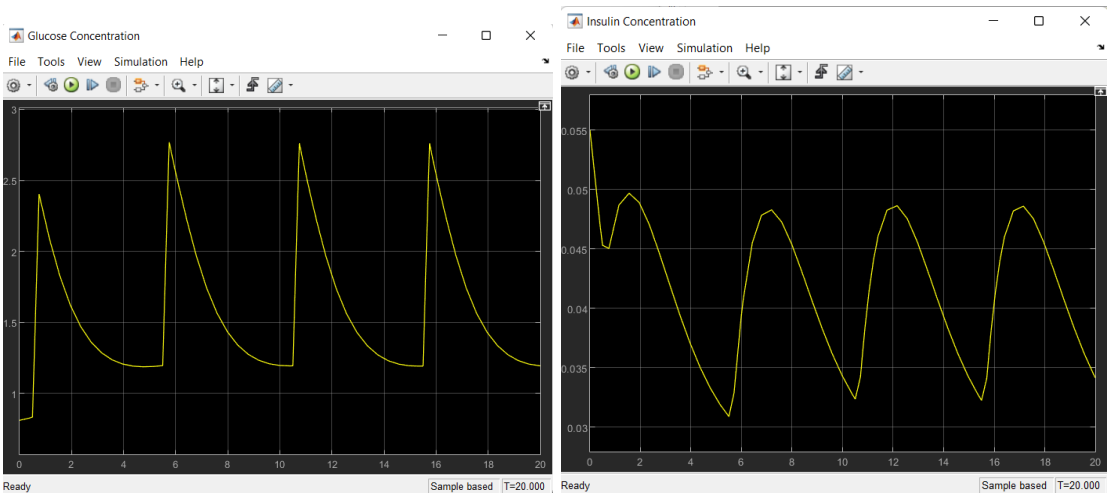

Figure 4a.2.2: Glucose and insulin responses corresponding to Type I diabetes with 20% insulin production sensitivity to glucose concentration.

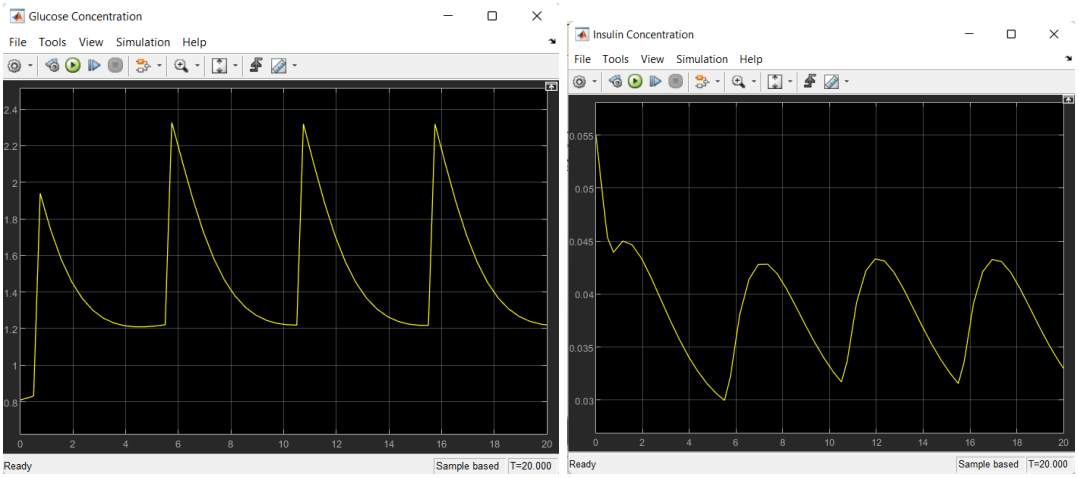

Figure 4a.2.3: Glucose and insulin responses for Type I diabetes management model with limited glucose intake.

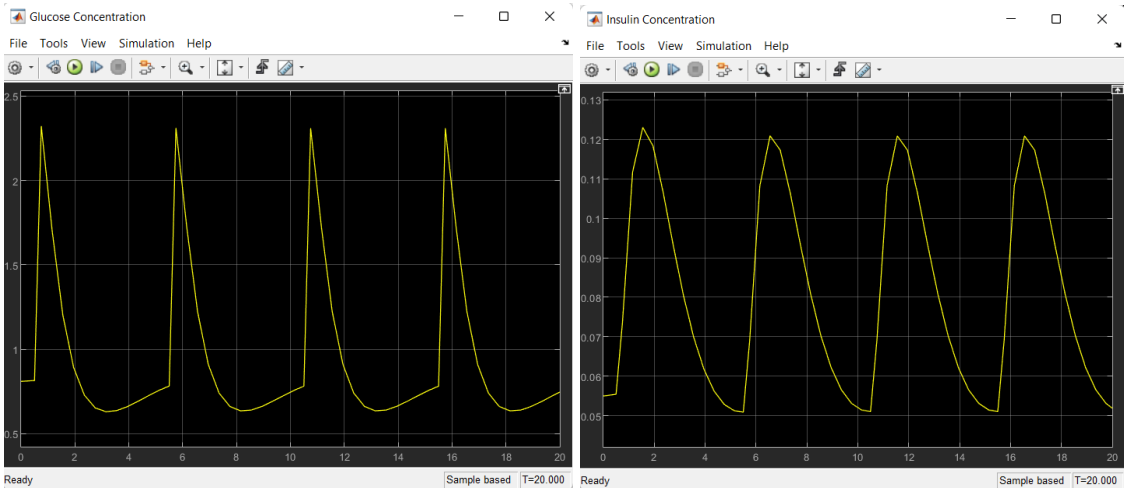

Figure 4a.2.4: Glucose and insulin responses of a healthy person with 100% insulin production sensitivity to glucose concentration.

Physical Exercise

Just as modifying a diet would not repair the impaired insulin production system, physical exercise would not affect the insulin production and we won't be able to observe any changes in the insulin levels when the β value from equation (4) is at zero. Therefore, same as the diet modification example, we will use a Type I diabetes model with 20% insulin production sensitivity to glucose (See *Figure 4a.3.2* or *Figure 3a, dark blue response*), to observe the effect of physical exercise on insulin concentration. Based on the knowledge that physical exercise requires glucose as an energy source, we found it appropriate to modify insulin-independent tissue utilization rates by amplifying the effect of λ in equation (2) by a factor of 3, to simulate the increased glucose uptake demand of the cells during physical exercise (See *Figure 4a.3.1*). By comparing *Figure 4a.3.2* to *Figure 4a.2.2,* we can observe that physical exercise had similar effects on the glucose and insulin concentrations to diet modification. As stated before, physical exercise is unable to fix the impaired pancreas, and doesn't show effects on insulin secretion levels. However it helps the glucose to be maintained in healthy concentrations (See the similarity of glucose concentrations in *Figure 4a.3.3* and *Figure 4a.3.4*).

$$\textit{Tissue utilization rate (insulin} - \textit{independent)} = \lambda x \qquad (2)$$

$$\textit{Insulin production rate} = \begin{cases} 0, & x \le \phi \\ \beta(x - \phi), & x > \phi \end{cases} \qquad (4)$$

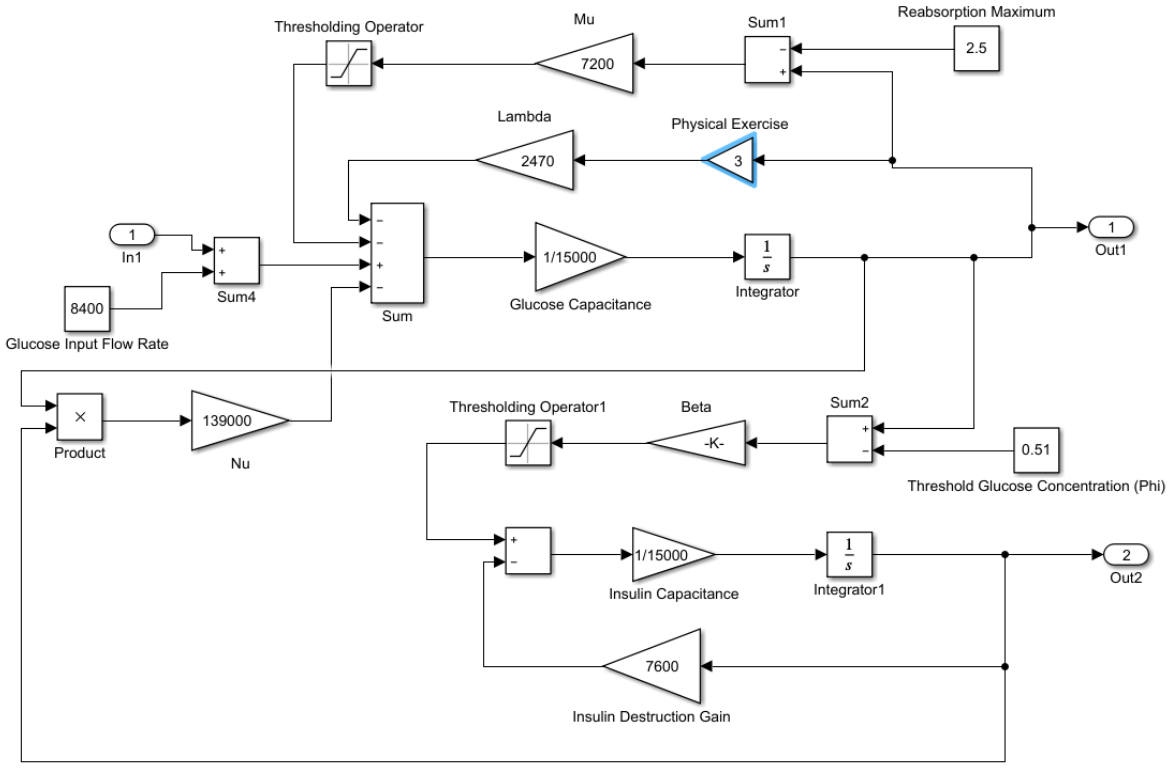

Figure 4a.3.1: Physical exercise model, which requires fuel and promotes the (insulin-independent) uptake of blood glucose to manage Type I diabetes.

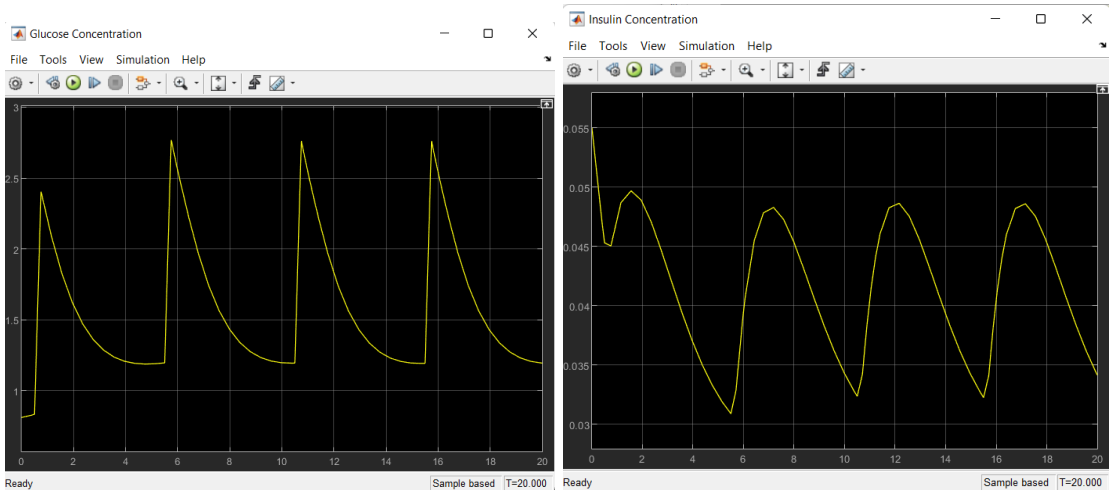

Figure 4a.3.2: Glucose and insulin responses corresponding to Type I diabetes with 20% insulin production sensitivity to glucose concentration.

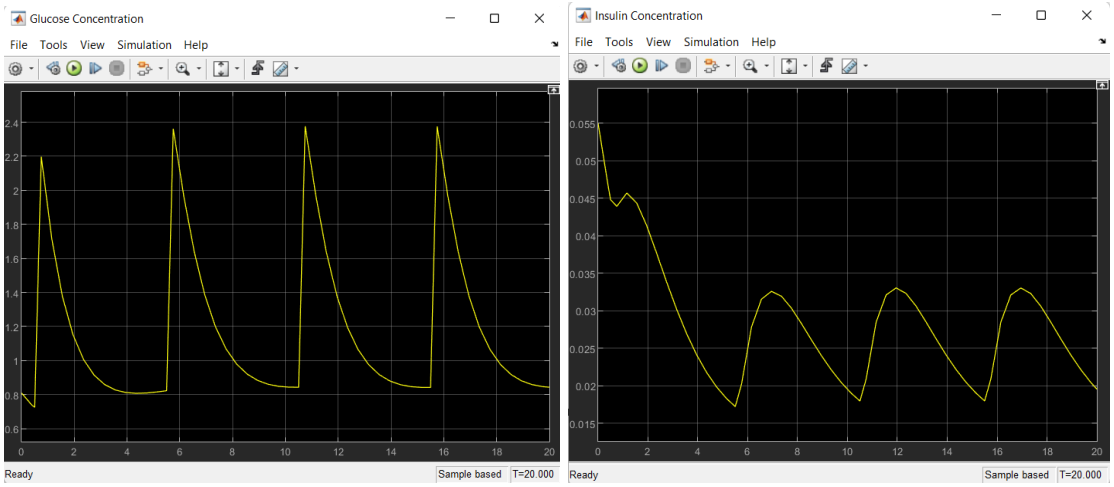

Figure 4a.3.3: Glucose and insulin responses for Type I diabetes management model with physical exercise.

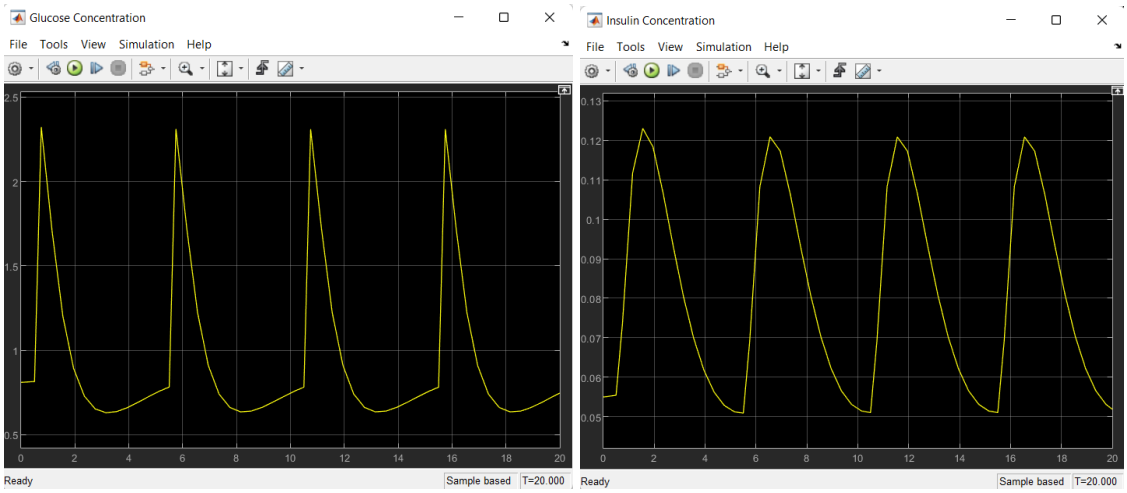

Figure 4a.3.4: Glucose and insulin responses of a healthy person with 100% insulin production sensitivity to glucose concentration.

Type II diabetes

Insulin Injection

For the Type II diabetes model, we reduce the insulin-dependent tissue utilization rate we modified ν from equation (3) to be 20% of its default value. The insulin injection subsystem for Type II diabetes model is the same as the model used for Type I diabetes (See *Figure 4a.4.1* and *Figure 4a.4.2*). From *Figure 4a.4.3* we can observe that the body will produce more insulin compared to a healthy body (*Figure 4a.4.5*), to initiate a similar response to regulate glucose levels. However with lower sensitivity of cells, blood glucose levels remain higher. With the insulin injection modification (See *Figure 4a.4.4*), the insulin concentration becomes much higher (peak ~0.35) compared to the level of insulin for the unmodified system (peak ~ 0.25). The increased levels of insulin helps promote the glucose intake, therefore we can observe that the modification helps glucose levels to be closer to a healthier level, compared to the unmodified version. By having more insulin in their body, the likelihood of the cells to utilize insulin increases.

$$\textit{Tissue utilization rate (insulin} - \textit{dependent)} = \textit{vxy} \qquad (3)$$

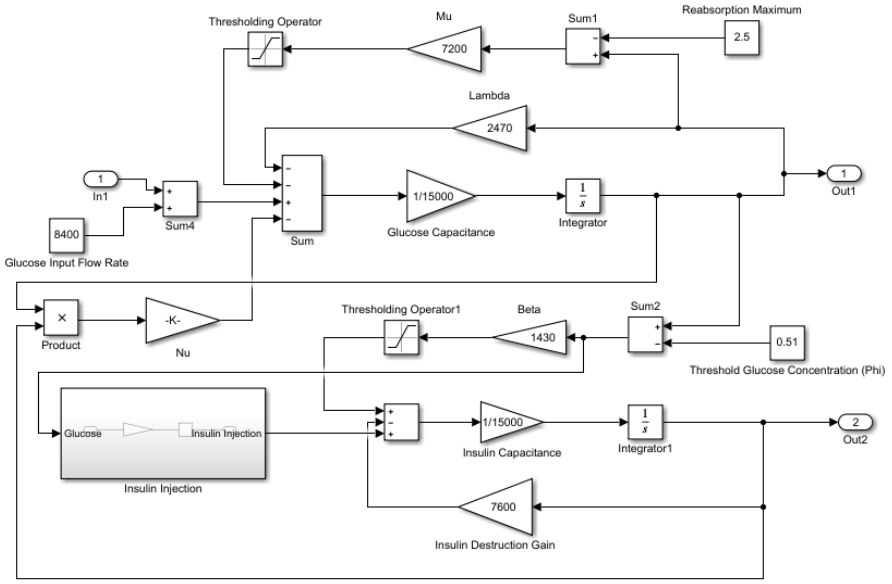

Figure 4a.4.1: Insulin injection model for managing Type II diabetes.

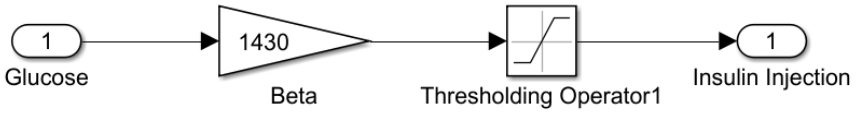

Figure 4a.4.2: Insulin injection block subsystem.

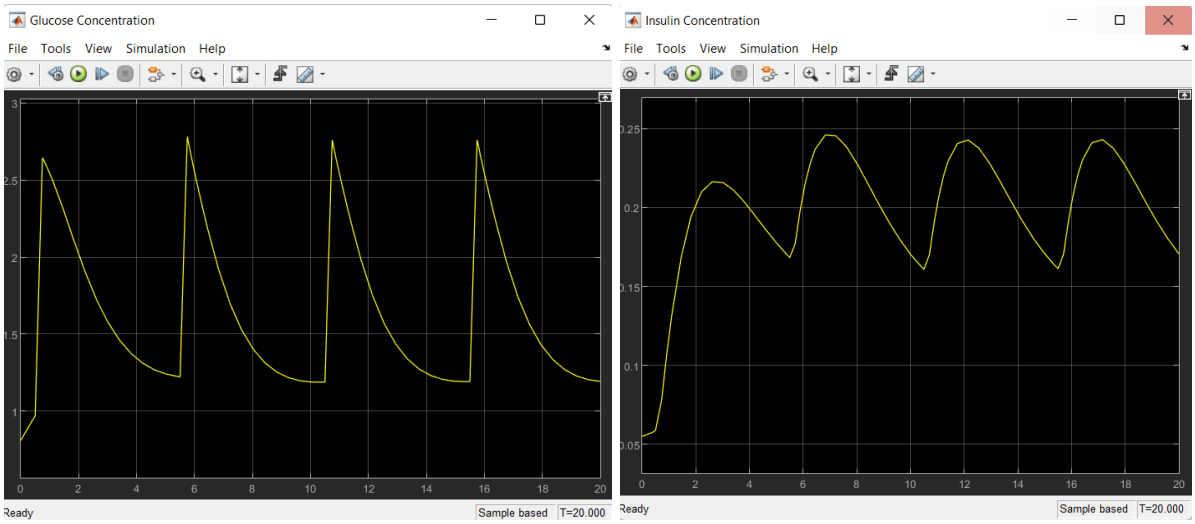

Figure 4a.4.3: Figure 4a.4.5: Glucose and insulin responses of a person with 20% tissue utilization rate.

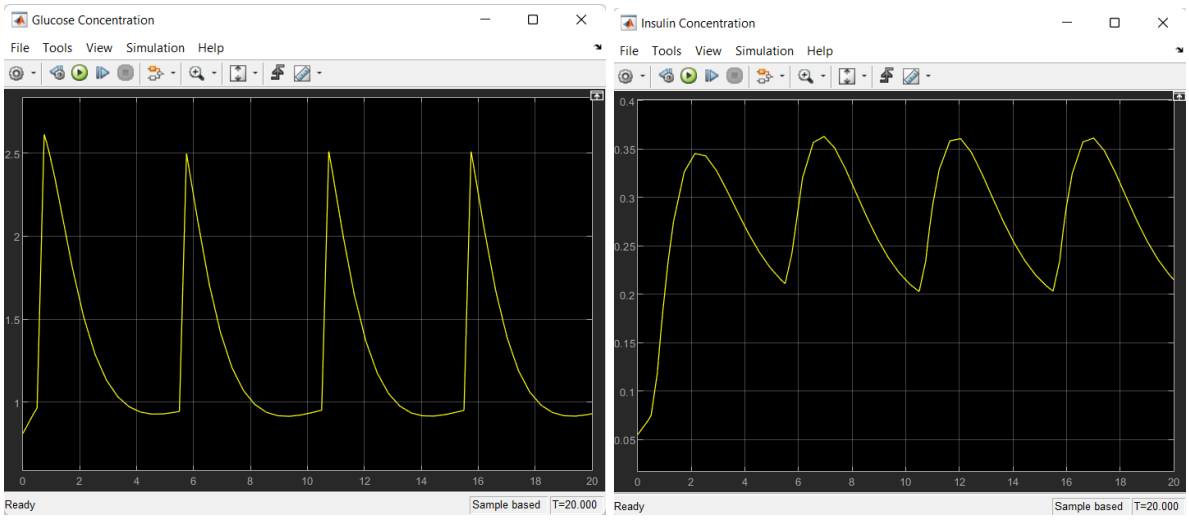

Figure 4a.4.4: Glucose and insulin responses for Type II diabetes management model with insulin injections.

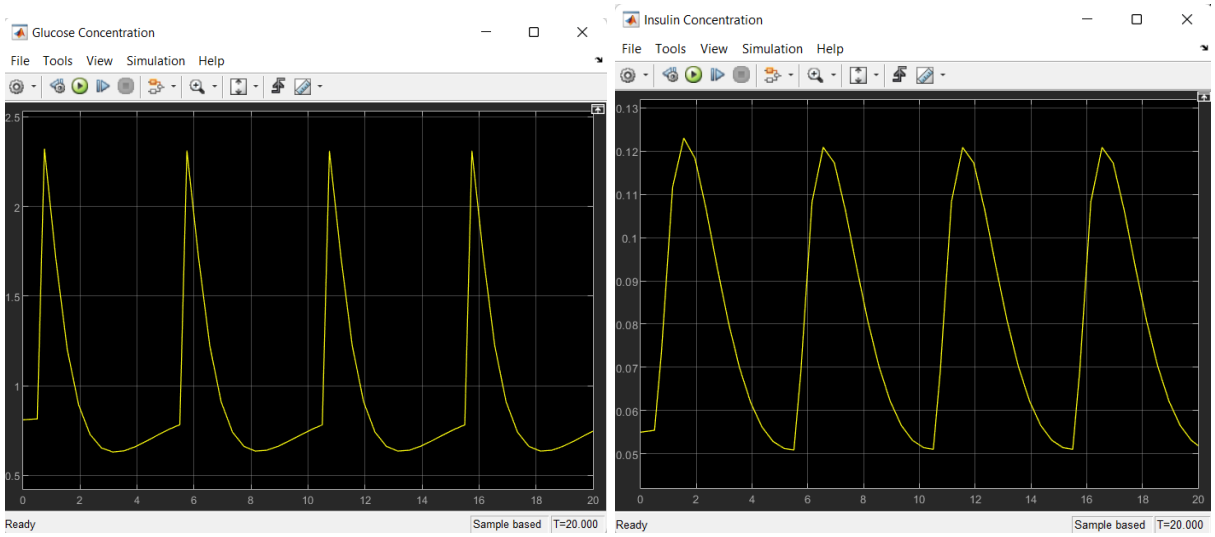

Figure 4a.4.5: Glucose and insulin responses of a healthy person with 100% tissue utilization rate.

Diet Modification

For the Type II diabetes model, we reduce the insulin-dependent tissue utilization rate we modified v from equation (3) to be 20% of its default value. The same modification is applied to the model to achieve the effect of diet for Type II diabetes as for Type I diabetes. Compared to the unmodified system (See *Figure 4a.5.2*), the modified glucose level is brought down to the healthier level of upper bound of 2.3 and lower bound of 1.2 (See *Figure 4a.5.3* and compare to *Figure 4a.5.4*). As the glucose levels are lower, the insulin required to maintain these levels would be less. Therefore we can observe that diet modification will result in less insulin production compared to the unmodified system.

$$Tissue\ utilization\ rate\ (insulin-dependent) = vxy \qquad (3)$$

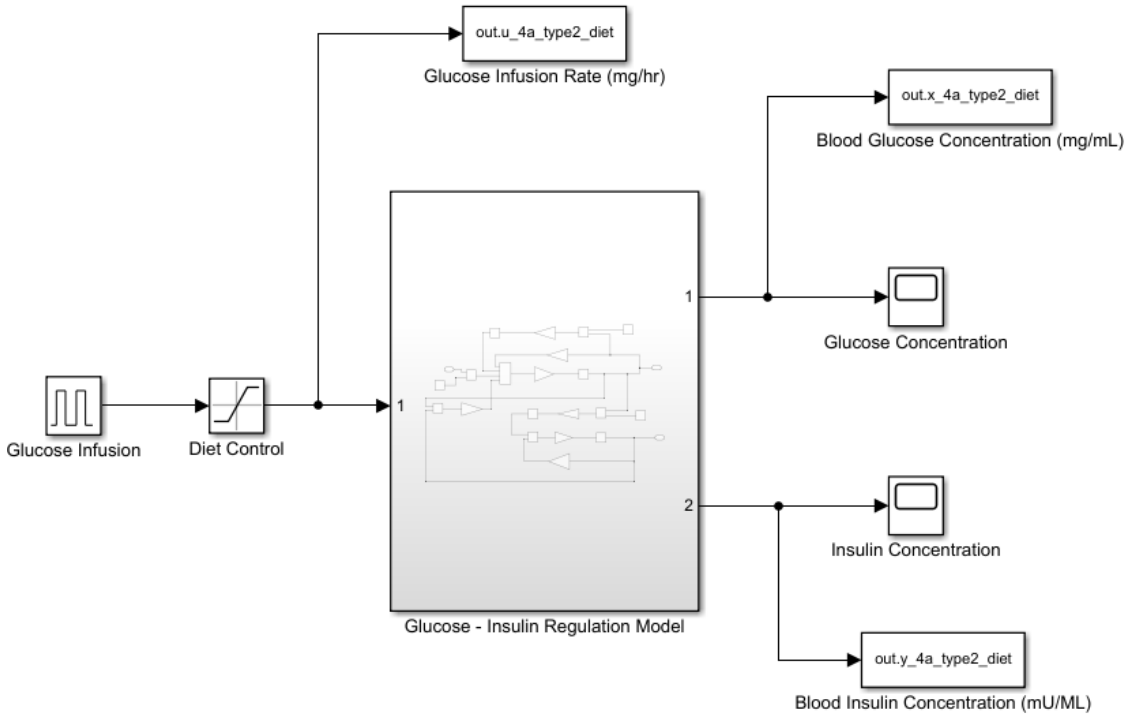

Figure 4a.5.1:Diet management model to limit glucose intake for managing Type II diabetes.

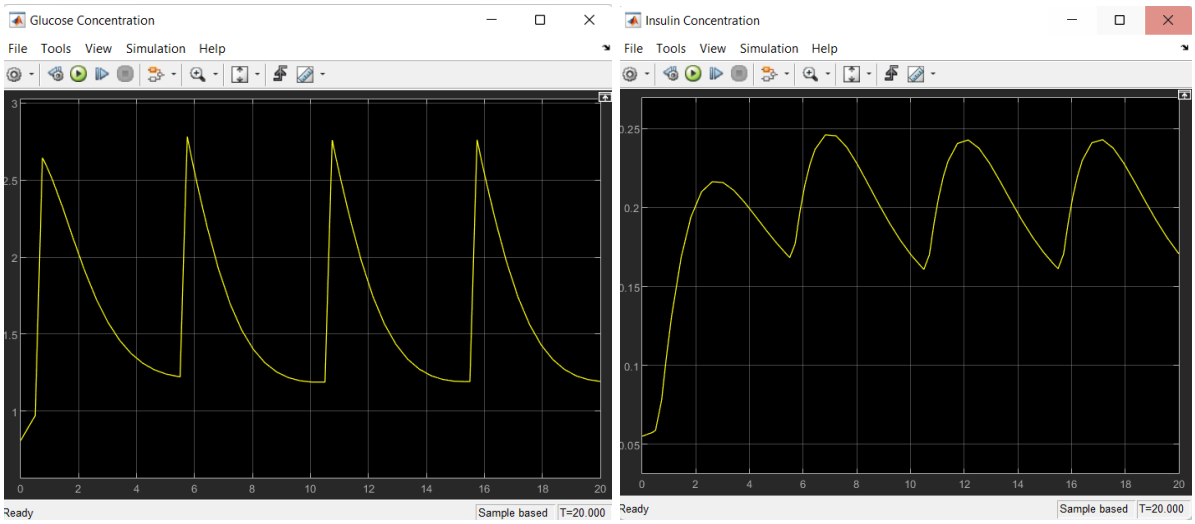

Figure 4a.5.2: Figure 4a.4.5: Glucose and insulin responses of a person with 20% tissue utilization rate.

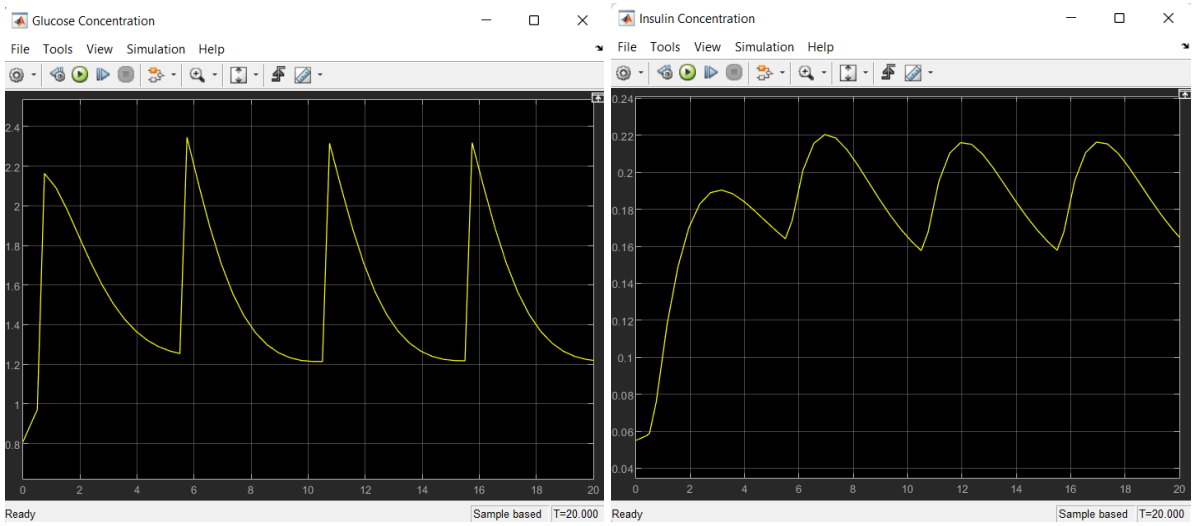

Figure 4a.5.3: Glucose and insulin responses for Type II diabetes management model with limited glucose intake.

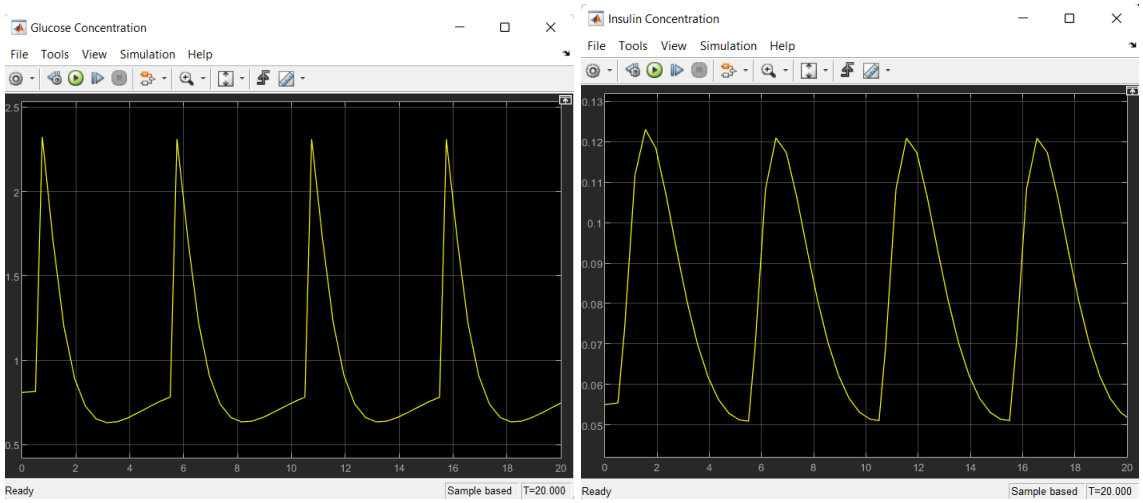

Figure 4a.5.4: Glucose and insulin responses of a healthy person with 100% tissue utilization rate.

Physical Exercise

For the Type II diabetes model, we reduce the insulin-dependent tissue utilization rate we modified ν to be 20% of its default value. The same modification is used on Type II diabetes models as Type I diabetes models to simulate the effect of physical exercise. (See *Figure 4a.6.1*) Based on the knowledge that physical exercise requires glucose as an energy source, we found it appropriate to modify insulin-independent tissue utilization rates by amplifying the effect of λ in equation (2) by a factor of 3, to simulate the increased glucose uptake demand of the cells during physical exercise (See *Figure 4a.6.1*). As a result, the glucose level is maintained at a healthy level and the overall insulin concentration decreased (See *Figure 4a.6.3*). This is because with the help of a higher insulin independent glucose utilization rate, the impaired system is able to respond to the increase in glucose concentration like a normal body (See *Figure 4a.6.2*). Less insulin is required compared to the unmodified system (See *Figure 4a.6.4*) since with this physical exercise most of the glucose is removed through facilitated diffusion.

$$Tissue\ utilization\ rate\ (insulin-independent) = \lambda x \qquad (2)$$

$$Tissue\ utilization\ rate\ (insulin-dependent) = vxy \qquad (3)$$

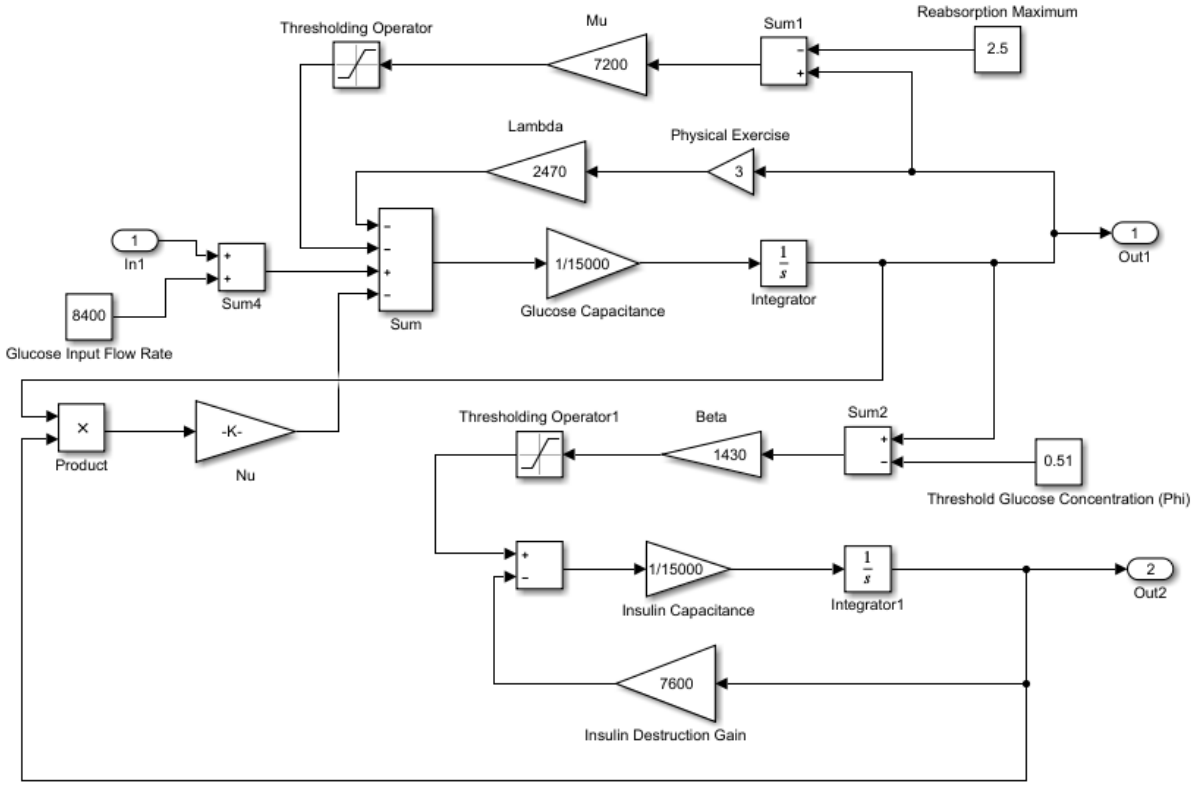

Figure 4a.6.1: Physical exercise model, which requires fuel and promotes the (insulin-independent) uptake of blood glucose to manage Type II diabetes.

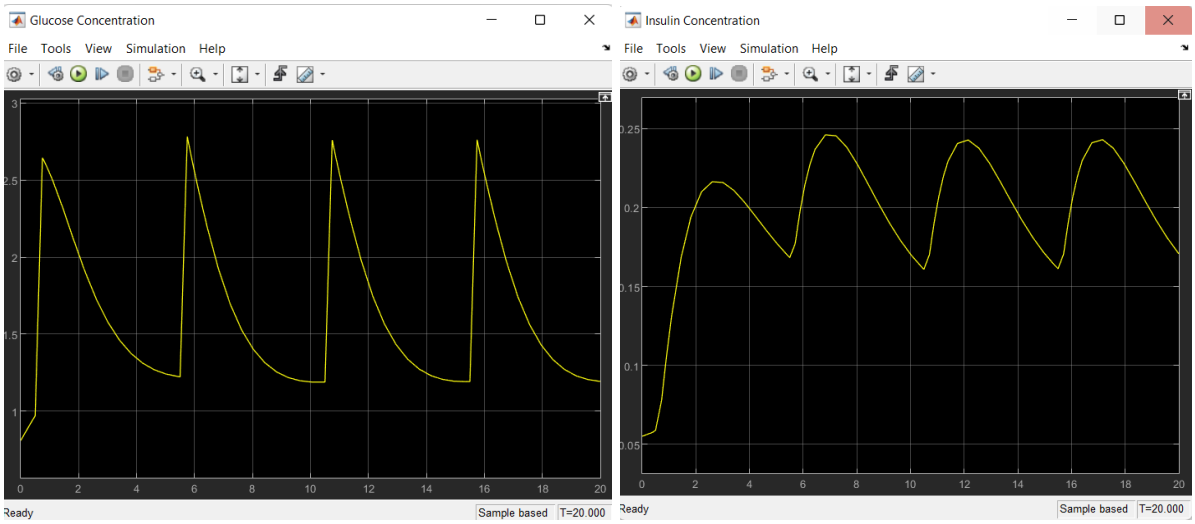

Figure 4a.6.2: Figure 4a.4.5: Glucose and insulin responses of a person with 20% tissue utilization rate.

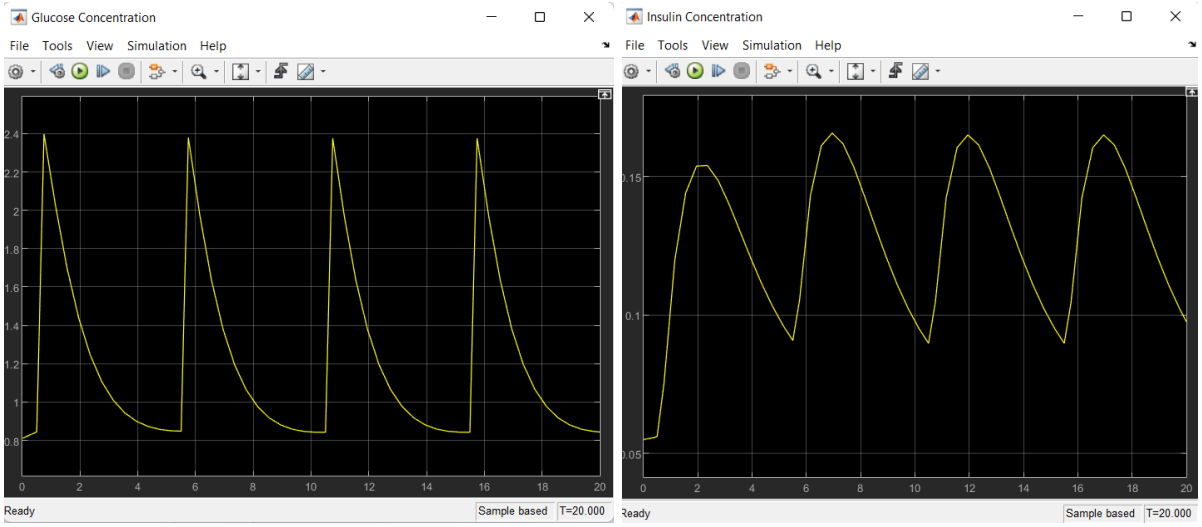

Figure 4a.6.3: Glucose and insulin responses for Type II diabetes management model with physical exercise.

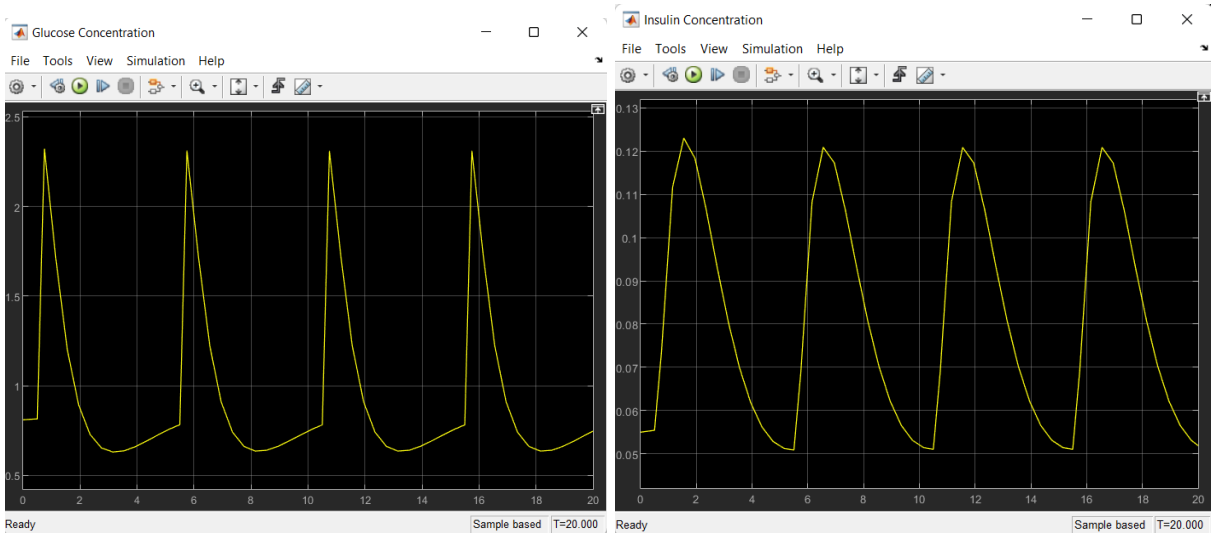

Figure 4a.6.4: Glucose and insulin responses of a healthy person with 100% tissue utilization rate.

b) Impairment of Glucose Removing Pathways

Renal Loss of Glucose

Since the renal loss of glucose pathway is imparied, the μ value from equation (1) is modified to zero (see *Figure 4b.1.1*). This means the kidney no longer excretes glucose even when the plasma glucose concentration exceeds the threshold. The resulting glucose and insulin level was almost not at all affected (Compare *Figure 4b.1.2* to *Figure 4b.1.3*). This could be a result of renal loss having a low contribution to overall glucose elimination in the body.

$$Renal\ loss\ rate = \begin{cases} \mu(x - \theta), & x > \theta \\ 0, & x \leq \theta \end{cases} \quad (1)$$

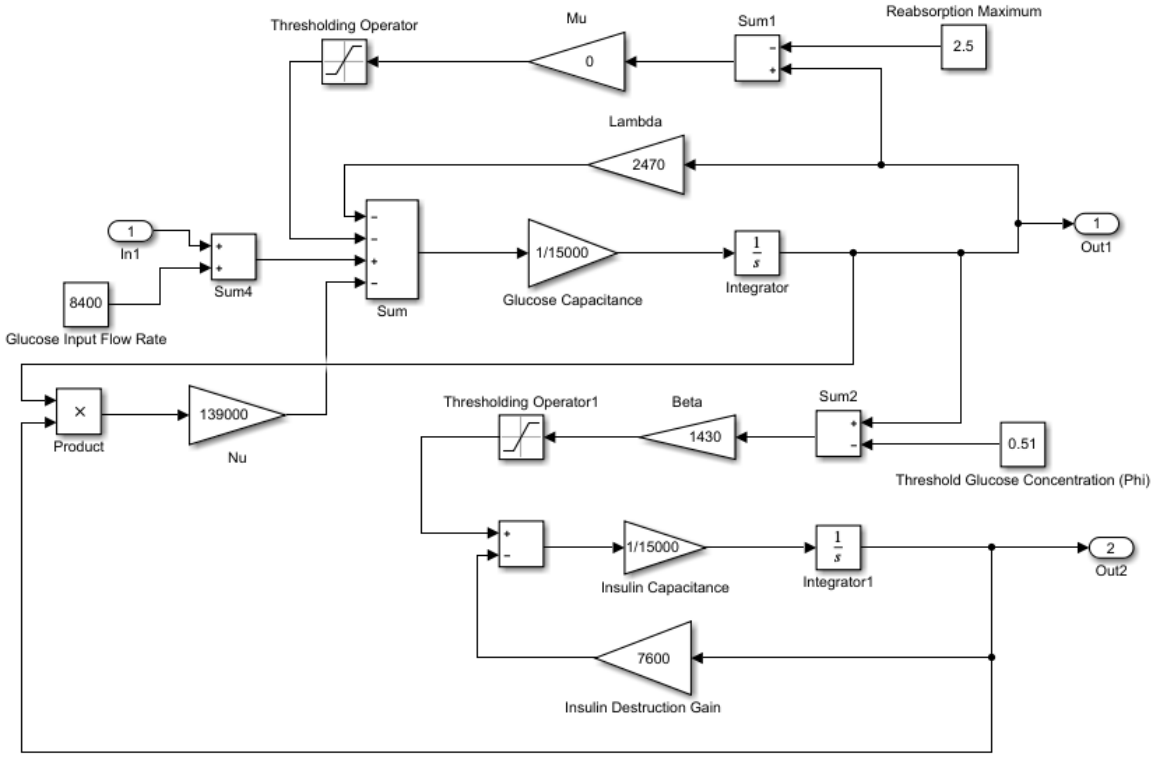

Figure 4b.1.1: Impaired renal loss pathway model.

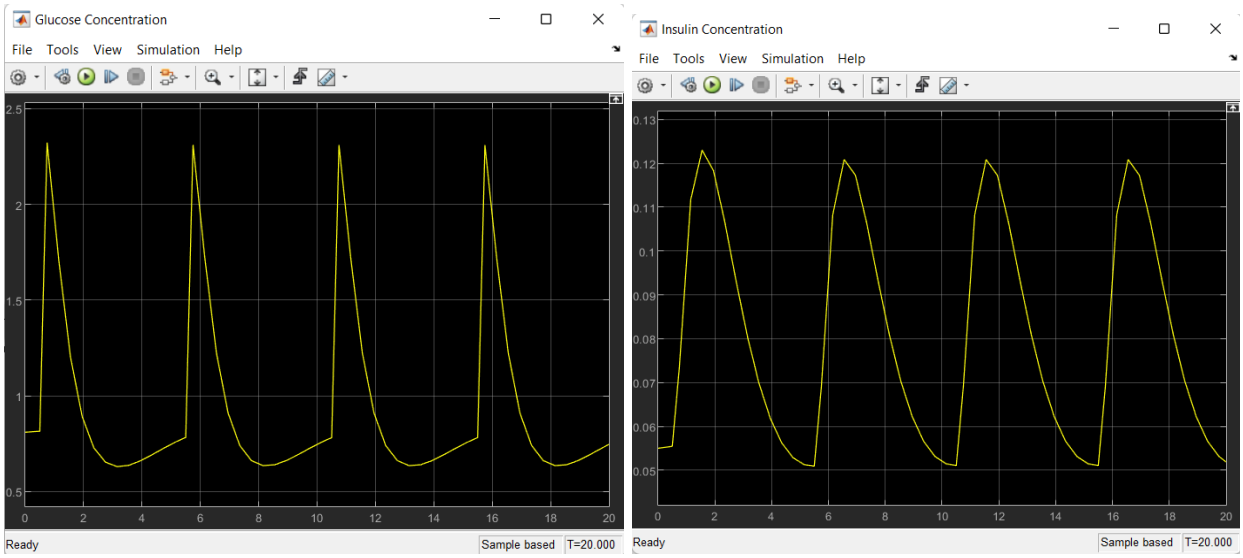

Figure 4b.1.2: Glucose and insulin concentrations corresponding to the impaired renal loss pathway model.

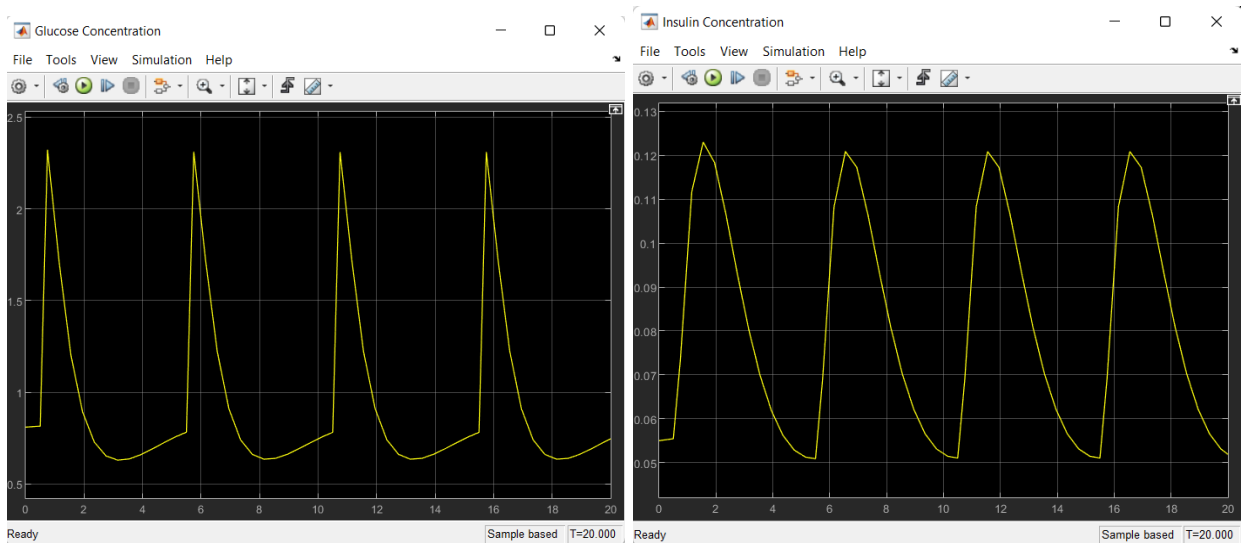

Figure 4b.1.3: Glucose and insulin responses of a healthy person.

Insulin Dependent Tissue Utilization Rates

The impaired insulin dependent tissue utilization rate pathway simulates the same condition as the type II diabetes when the insulin-dependent tissue utilization rate is 0% (See *Figure 3b, yellow response*). Therefore the value of v from equation (3) is modified to zero (See *Figure 4b.2.1*). The modified glucose concentration could only stabilize at a much higher level compared to a healthy body (Compare *Figure 4b.2.2* to *Figure 4b.2.3*), since the main source of glucose elimination from blood is imparied. The insulin level increases gradually, in an attempt to respond to the high glucose concentration, but the body could not utilize those insulin effectively.

$$Tissue\ utilization\ rate\ (insulin-dependent) = vxy \qquad (3)$$

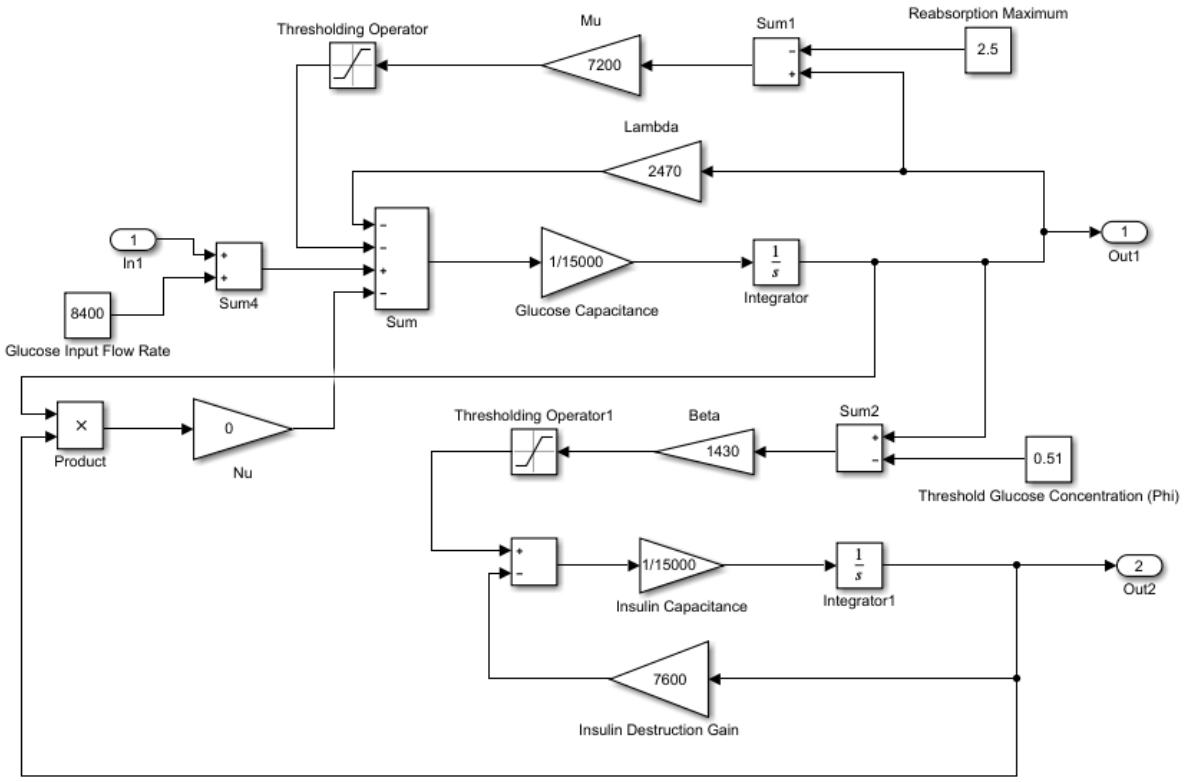

Figure 4b.2.1: Impaired insulin-dependent tissue utilization pathway model.

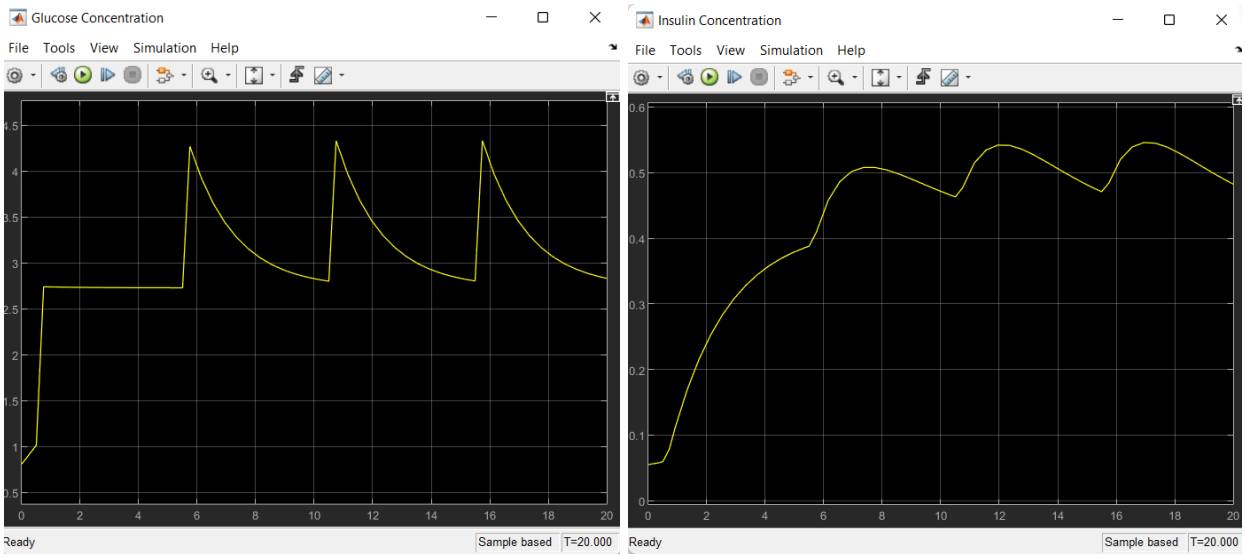

Figure 4b.2.2: Glucose and insulin concentrations corresponding to the impaired insulin-dependent tissue utilization pathway model.

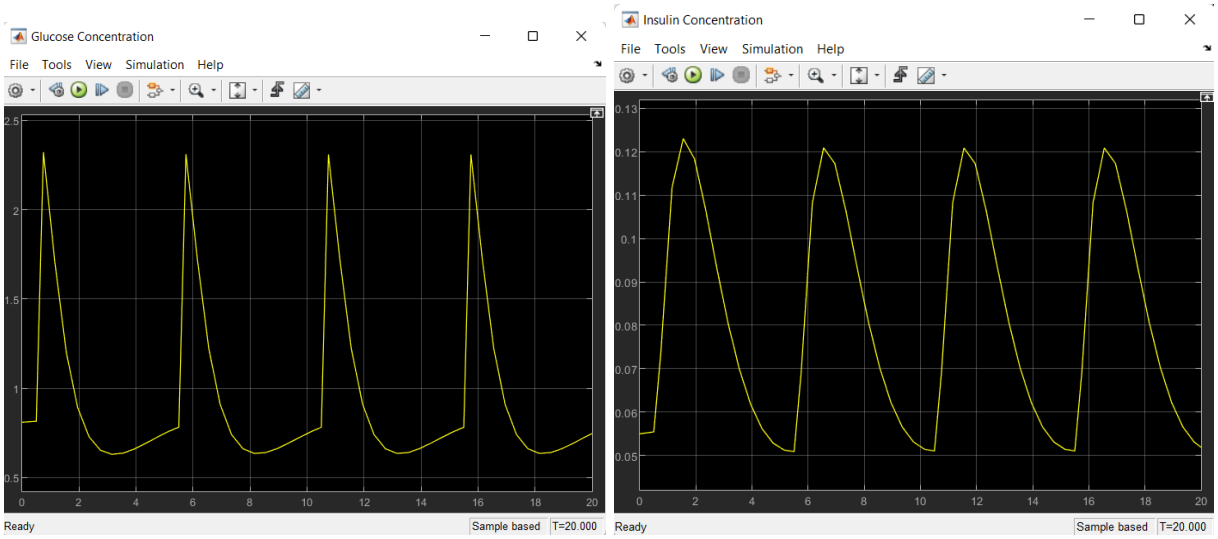

Figure 4b.2.3: Glucose and insulin responses of a healthy person.

Insulin Independent Tissue Utilization

The value of λ from equation (2) is changed to zero in order to simulate the imparied insulin independent tissue utilization rate pathway (See *Figure 4b.3.1*). Glucose concentration was not greatly affected (Compare *Figure 4b.3.2* to *Figure 4b.3.3*), since the rate of tissue utilization of glucose was majorly insulin dependent.

$$Tissue\ utilization\ rate\ (insulin - independent) = \lambda x \qquad (2)$$

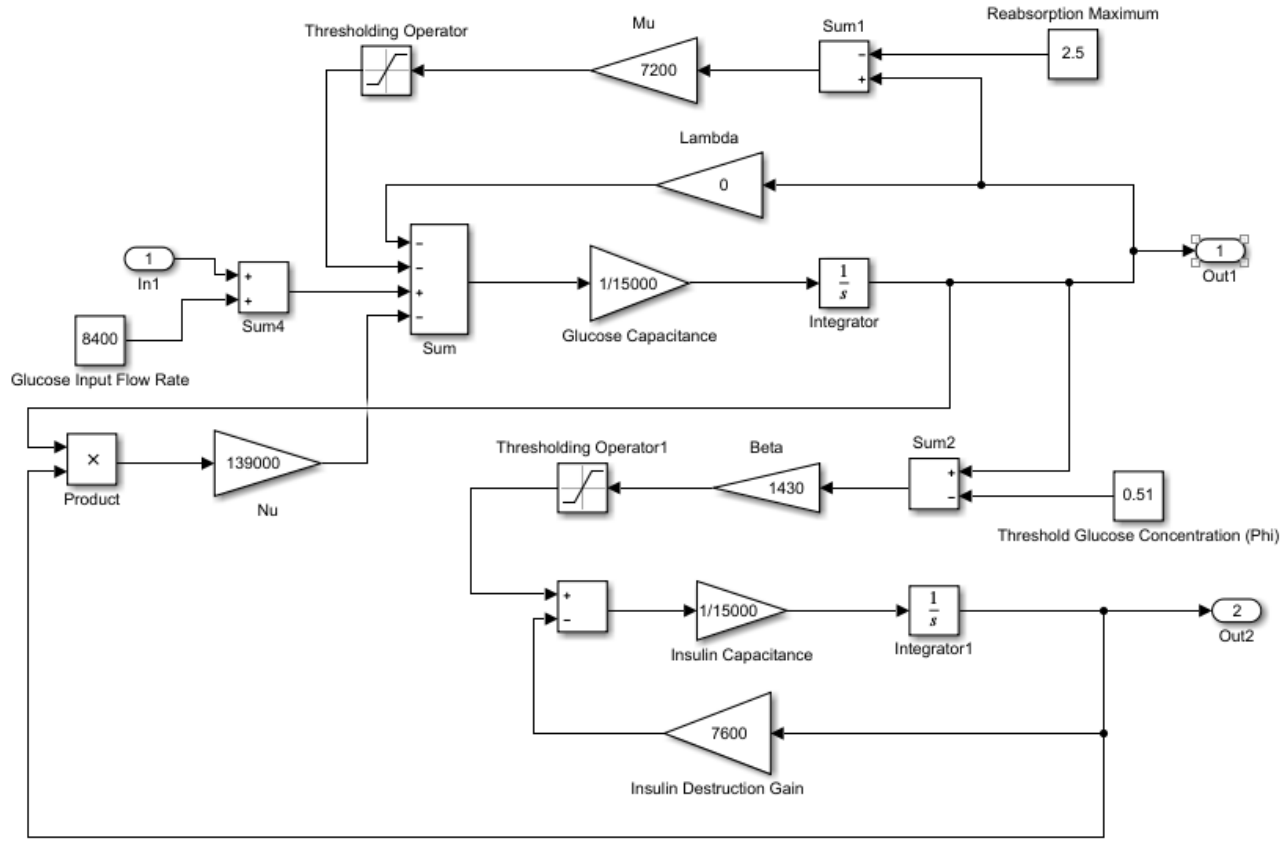

Figure 4b.3.1: Impaired insulin-independent tissue utilization pathway model.

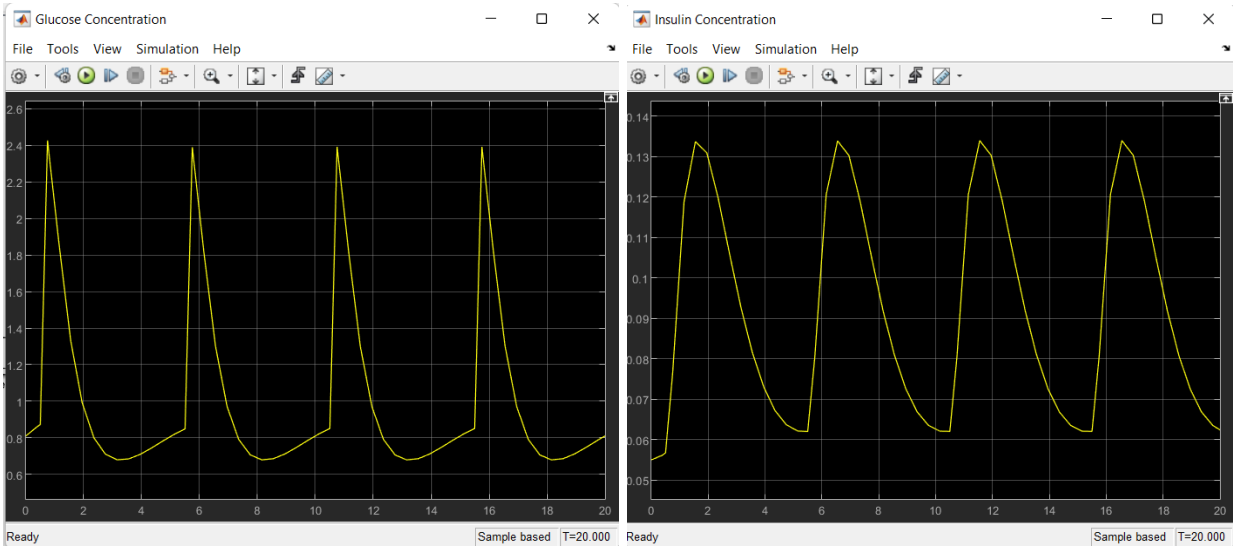

Figure 4b.3.2: Glucose and insulin concentrations corresponding to the impaired insulin-independent tissue utilization pathway model.

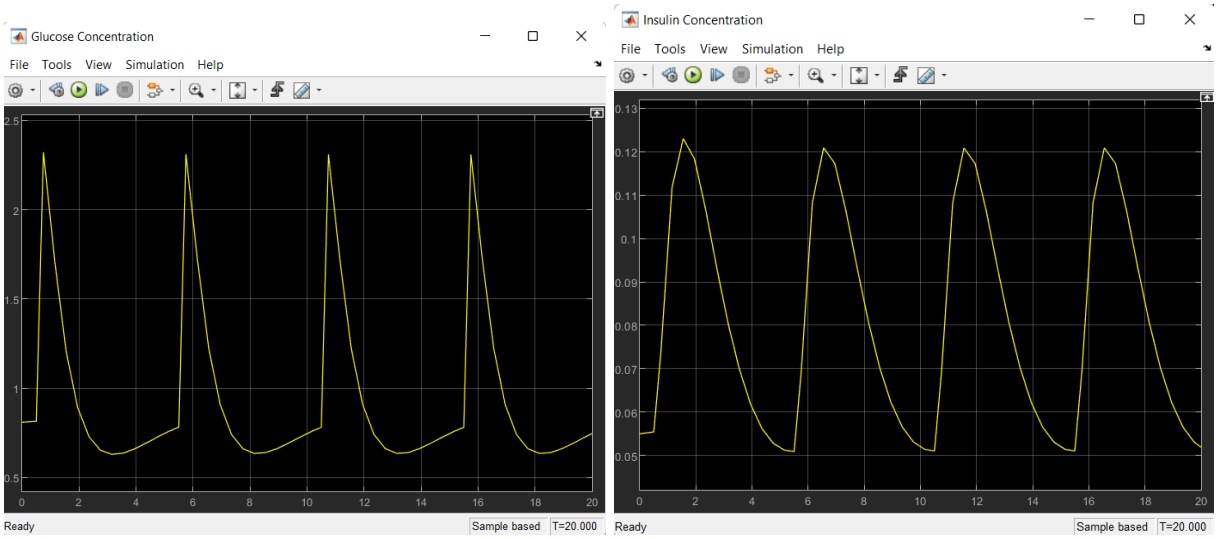

Figure 4b.3.3: Glucose and insulin responses of a healthy person.

Discussion

a) **Using the results from section 2b, identify an aspect of the control of glucose that is not captured by this model. What modifications to the model would be required to address these issues? If these modifications were made, how would you expect the output in section 2b to be different?**

In section 2b, we have observed that glucose levels rise due to a glucose infusion. This increase stimulates insulin production and secretion. The rising levels of insulin promotes the uptake of the glucose into the cells. As a result glucose levels return back to their normal value and remain at a constant value until the next infusion.

In real life when there are longer breaks between subsequent glucose infusions (e.g. dietary nutrient intake), there will be a longer fasting (postabsorptive) state. Without any external infusion of glucose, the blood glucose concentration becomes prone to drop below the normal levels, as the cells will constantly require and use glucose as an energy source to survive. To prevent this from happening, our bodies initiate catabolic activities through Glucagon secretion to obtain energy from stored energy sources. Through mechanisms such as glycogenolysis and gluconeogenesis, the blood glucose levels increase. This increase stimulates insulin production and release. To address this shortcoming of the model, we can add a separate subsection to model an internal mechanism of glucose release (pulse generator source block) that is only activated when the blood glucose is below a certain level (thresholding operator block), mimicking the activity of the Glucagon hormone. With these modifications, even when there is no external glucose infusion, we would expect to see rises and falls in a normal glucose control mechanism as the glucose will be released due to internal catabolic activities. We would expect the insulin levels to rise and fall to maintain the changes in glucose concentration in between normal boundaries.

b) **Based on your simulations in section 4a, state whether each of the management strategies proposed (insulin injections, diet, and exercise) are appropriate for each type of diabetes (type I and type II). Justify your answers.**

Type I

Patients with Type I diabetes have an impaired pancreas. Therefore they lack the ability to produce sufficient insulin for themselves.

Insulin injections are an appropriate management strategy in Type I diabetes as they provide frequent monitoring and adjustable levels of insulin. As a result of the injections glucose levels can be maintained within healthy boundaries as we observed in section 4a.1.

Diet management through limitation of glucose intake, is not an appropriate strategy as it does not fix the pancreas nor lead to more insulin secretion, therefore doesn't show drastic effects on the insulin levels. It is, however, useful to maintain healthy glucose levels. This strategy is prone to errors, as there is no accurate monitoring and no exact way to predict how the amount of glucose intake would affect the blood glucose levels precisely. Besides, as each patient is different, with

varying abilities to produce insulin, this strategy would not be as effective or feasible as the insulin injections, as each person will be required to implement diets according to their own needs.

Physical exercise is also not an appropriate strategy, as it shows similar effects to the diet management strategy on the Type I diabetes model. Although it does show better results than the diet management, as it decreases the dependency on insulin by initiating insulin-independent glucose utilization pathways, it is still insufficient. Similar to the diet management strategy, this modification also is not accurate or precise enough when compared to the insulin injections. Each patient has different physical abilities as well as varying ability to produce insulin. Therefore although it is a useful strategy to maintain glucose levels close to healthy boundaries, it is not enough to regulate glucose levels on its own.

Type II

Patients with Type II diabetes have a healthy functioning pancreas. However, due to impairments in insulin receptors, cells have limited ability to respond to rising insulin levels and initiate glucose uptake mechanisms.

Insulin injections are somewhat an appropriate strategy for Type II diabetes in terms of regulating glucose levels, but it is not very efficient as the pancreas already is able to produce higher levels of insulin. Injecting more insulin, would take some pressure off of the pancreas and it would increase the likelihood of cell response to uptake glucose. Although it will not drastically change the blood glucose levels, insulin injections might be necessary for some patients so that their pancreas would not fail when trying to produce excessive amounts of insulin.

Diet management is not an appropriate strategy, as it doesn't initiate cells to take more glucose. Without sufficient glucose, cells cannot provide the energy to sustain metabolic activities. As we have discussed for Type I diabetes, diet management does help to maintain blood glucose levels closer to a healthy level. As there will be less need for insulin, due to lower glucose levels, this strategy is also beneficial as it prevents the pancreas from working excessively. However, the pancreas would still be required to work more than a healthy pancreas to initiate

Physical exercise is an appropriate strategy for Type II diabetes as it initiates insulin-independent glucose uptake pathways in the cells. Although it has some shortcomings in real life, such as varying physical ability of individuals, under the assumption it can be done it provides almost healthy results for the blood glucose regulation. As it initiates facilitated diffusion mechanisms, it increases the glucose intake to the cells. As the glucose intake will no longer be only dependent on insulin, damaged receptors will not hinder the intake mechanism as much as before. This strategy is also effective to maintain a healthy pancreas, as the mechanisms are no longer dependent on just insulin, pancreas can work at a healthier rate to produce the lowered required amounts of insulin.

c) **Based on the results of your analysis in section 4b, comment on the impact of each of the three glucose removal pathways on glucose concentrations. Which pathway has the most influence? Comment on the implications of these results for diabetes.**

By observing the results of three different pathways being imparied, we can conclude that the insulin dependent tissue utilization rate pathway is the most effective and influential. This is because only when this pathway is impaired, the resulting glucose and insulin concentrations are greatly affected. When the other two pathways are impaired, the system is still healthy and functional. Type II diabetes is essentially a disease with imapired insulin dependent tissue utilization rate, which means the cells do not use the insulin as effectively to eliminate glucose in the plasma.