Insulin is a hormone that plays a crucial role in metabolism. The major insulin disorders, type 1, and type 2 diabetes are one of the leading health issues in the world, and as such, to understand the design of an insulin pump, we will need to first understand insulin and sugar metabolism in the body.

When we consume sugar, it undergoes the process of digestion in the mouth, stomach and ends up in the duodenum of the small intestine, where a large of amount sugar absorption occurs. Sugar is absorbed into the blood stream by enteroctyes, where it either diffuses into the interstitial space of muscles and tissue to be metabolized into energy via the electron transport chain, or it is stored in the liver in the form of glycogen, where it can undergo the process of gluconeogenesis, and be converted back into sugar when needed. Finally, glucose in the blood is removed via the kidneys.

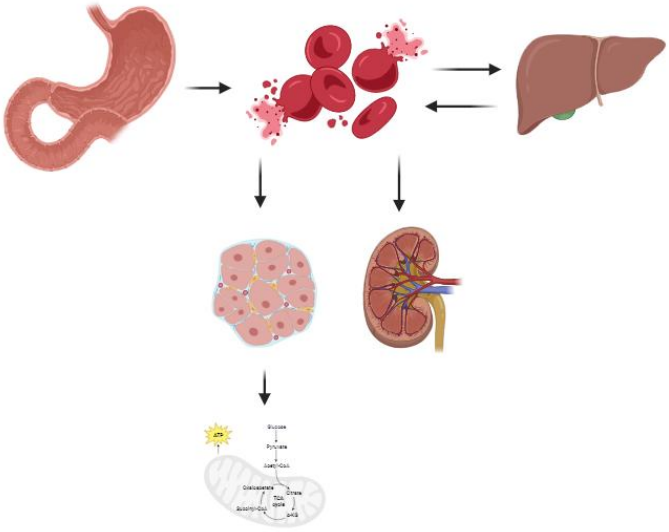


Figure 1. Glucose pathway

The role insulin plays in this glucose path is in the muscle and tissue uptake of glucose. Insulin is secreted by β-cells in the pancreas. When cells detect elevated blood glucose levels, they release insulin into the blood stream. While some tissue types are able to take in blood glucose without the presence of insulin, GLUT4 transmembrane protein presenting cells, mostly found in the muscle and tissue of soft organs, require the assistance of insulin to transport blood glucose into the cell for metabolism. Without glucose, these cells undergo necrosis, as they do not receive sufficient nutrients, despite it being present in the blood.

The pancreas first secrete insulin into the hepatic portal vein, where insulin enters the liver and is degraded. The remaining insulin travels around blood stream, leaving to enter the interstitial space, where it can bind to cells, enabling the GLUT4 transmembrane proteins.

The mathematical model of insulin's function is presented in Dalla Man et al's paper "Meal Simulation Model of the Glucose-Insulin system". In this paper, the authors present the equations associated with their compartment model of insulin and glucose dynamics as seen in Figure 2.

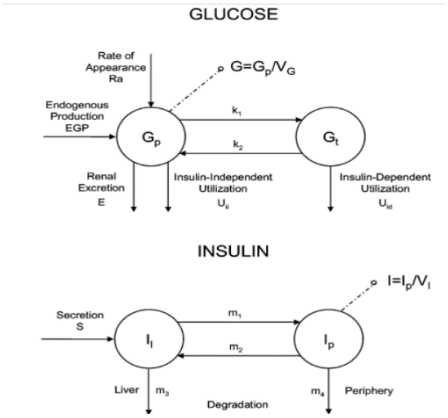


Figure 2. Insulin – Glucose compartment model

The model can be described with a system of differential equations describing the net glucose and insulin flow in each compartment.

$$\frac{dGp}{dt} = EGP(t) - Ra(t) - U_{ii}(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \qquad (1)$$

$$\frac{dGt}{dt} = -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t) \qquad (2)$$

$$\frac{dI_L(t)}{dt} = -\big(\mathrm{m1} + \mathrm{m3(t)}\big) \cdot I_L(\mathrm{t}) + \mathrm{m2} \cdot \mathrm{Ip(t)} + \mathrm{S(t)} \qquad (3)$$

$$\frac{dI_p(t)}{dt} = -(\mathrm{m2} + \mathrm{m4}) \cdot I_p(\mathrm{t}) + \mathrm{m1} \cdot I_L(\mathrm{t}) \qquad (4)$$

$$\mathrm{I}_d = \begin{cases} \frac{\mathrm{dI_1}}{dt}(\mathrm{t}) = -\mathrm{ki} \cdot [\mathrm{I_1(t)} - \mathrm{I(t)}] \\ \frac{d\mathrm{I}_d}{dt}(\mathrm{t}) = -\mathrm{ki} \cdot [\mathrm{I}_d(\mathrm{t}) - \mathrm{I_1(t)}] \end{cases} \qquad (5)$$

Equations (1) and (2) describe the dynamics of the plasma and tissue glucose respectively. Equation (1) suggests that the rate of change of plasma glucose is determined by the sum of the endogenous glucose production due to gluconeogenesis (EGP), rate of appearance, ie. Rate of consumption (Ra), insulin independent uptake (Uii), renal excretion (E), and diffusion between the plasma and tissue determined by rate constants k1, k2. Equation (2) suggests that the rate of change of glucose in tissue is a function of the insulin dependent uptake (Uid) and rate of diffusion between plasma and tissue.

For the insulin equations, equation (3) suggests that rate of change of liver insulin is a function of the amount of insulin in the liver (Il) being degraded dictate by constants m1, 3, and the insulin from the plasma (Ip), the rate of flow of which is dictated by m2, as well as secretion, from the pancreas (S).

Finally, insulin is secreted both immediately after a meal and over a long period afterwards. This dynamic is captured by equation (5), where I1 represents the immediate insulin release, and Id, represents the slow insulin release over time. While these equations have numerous parameters, the ones of most note are S(t), and Uid(t), as these represent the insulin secretion and utilization, and will be of particular interest to diabetes and the discussion of insulin pumps.

The most common conditions relating to insulin are type1 and type2 diabetes. Type 1 diabetes is an autoimmune condition where the person's immune cells attack the β-cells of the pancreas, leaving the individual unable to produce insulin. In Type 2 diabetes, due to a chronically elevated blood sugar level, muscle and tissues have become resistant to insulin, despite binding to insulin, the glucose uptake mechanism that insulin enables is not as effective, resulting in lower uptake of blood sugar.

In terms of our mathematical model, we can model both of these diseases by changing various parameters. While many of the above constants differ between healthy and diabetic patients, the most notable parameters are insulin secretion (S) and utilization (Uid). Firstly, in type 2 diabetes, the patient secretes insulin similar to a healthy individual, however, the tissue and muscle cells are unable to process the glucose as effectively as a healthy individual. This decrease in efficiency is reflected in a change in the Uid function. Uid is defined in Dalla Man et al with the following equations:

$$U_{id}(t) = \frac{\mathrm{Vm(X(t))} \cdot \mathrm{Gt(t)}}{\mathrm{Km(X(t))} + \mathrm{Gt(t)}} \quad (6)$$

$$\mathrm{Vm(X(t))} = \mathrm{Vm0} + \mathrm{Vmx} \cdot \mathrm{X(t)} \quad (7)$$

$$\frac{\mathrm{dX(t)}}{dt} = -\mathrm{p2U} \cdot \mathrm{X(t)} + \mathrm{p2U[I(t) - Ib]} \quad (8)$$

Here Vm and Km represent constants that change as a function of the concentration of interstitial insulin (X). Equation 8 describes the rate of change of interstitial insulin concentration, as a function of the amount of interstitial insulin and the difference between plasma insulin concentration and the plasma insulin concentration at baseline or fasting. In a diabetic person, the parameter we would expect to see differ from a healthy person is p2U, which describes insulin's rate of action on glucose. A higher value indicating less utilization per glucose. From the data tables in Dalla Man et al. we see that in type 2 diabetic patients, p2U = 0.0840, compared to the healthy value of 0.0331.

In type 1 diabetes, utilization is normally, however, the individual is unable to secrete insulin independently. As a result, we expect the S(t), secretion, to be affected.

$$S(t) = \gamma * \mathrm{Ipo} \quad (9)$$

Where γ is physical constant representing transfer rate between liver and portal vein and Ipo is the amount of insulin the hepatic portal vein. In a type 1 diabetic patient S(t) = 0 by definition, and as a result, $\gamma = 0$. Referring back to equation (3), (4), all terms in the equation describe the interchange of insulin between liver and plasma, except the term secretion of new insulin is S(t). If S(t) is 0, the diffusion of insulin between liver and plasma would also be 0, causing insulin in the system overall to be 0.

In practice, changes in insulin secretion, causes changes in glucose, which causes further down stream effects until the system reaches equilibrium, while the parameters mentioned above are the most of note for each condition, realistically, nearly all parameters will vary between healthy and diabetic patients.

The insulin pump is a device that controls blood insulin. Upon detecting abnormally low levels of blood insulin, the insulin pump calculates an appropriate level of insulin via a control algorithm and delivers it into the patient's blood stream.

The insulin pump control system can roughly be modeled to the Figure 3. diagram. After detecting the amount of glucose in blood, the control system calculates the error and determines the appropriate amount of insulin concentration.

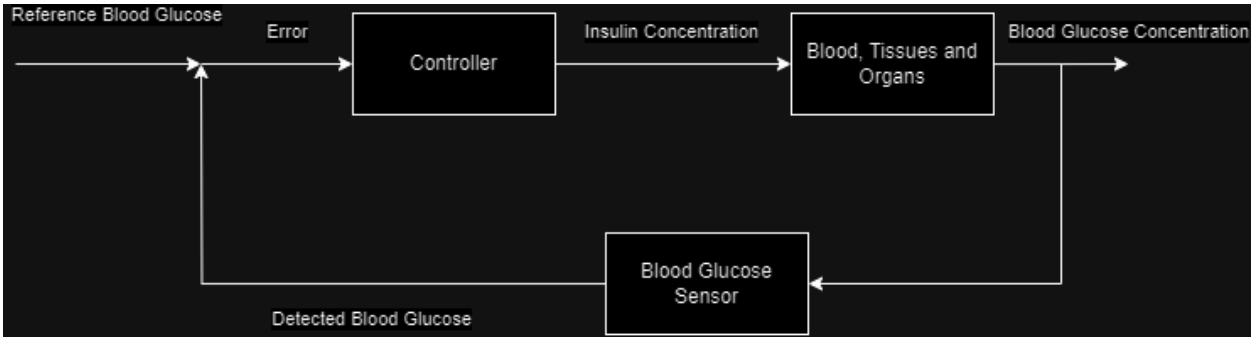


Figure 3. General control system design of the insulin pump

Typically, we model an organ according to an electrical model of the organ where there is an equivalent to Voltage, current, resistance, where a transfer function can be obtained via Laplace transforms and Kirchoff's voltage and circuit laws. When addressing the issue of the insulin – glucose pathway, the electrical analogies become tenuous. Both insulin and glucose behave as current, with no clear voltage equivalent. Insulin is released by the body, regulated through hormonal signals and circadian rhythms, rather than a potential across a circuit. As a result, instead of a circuit, it is easier for the control system to be designed as a PID controller with the components being modeled through compartment models using the equations from Dalla Man et al. to describe flow between compartments.

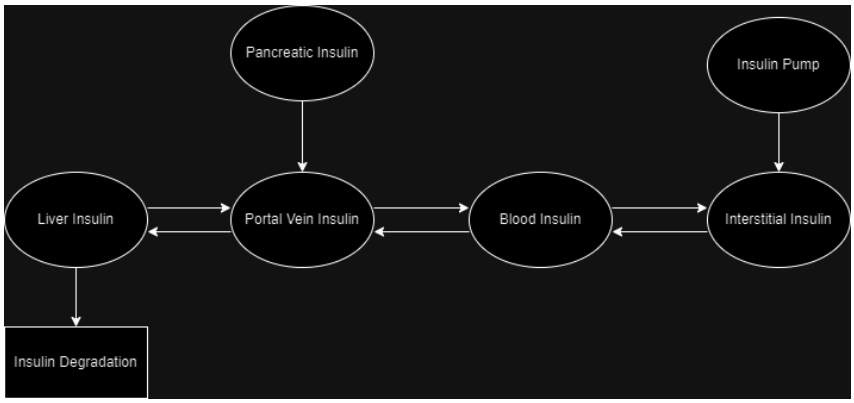


Figure 4. Compartment Model of the Pathway of insulin throughout the body.

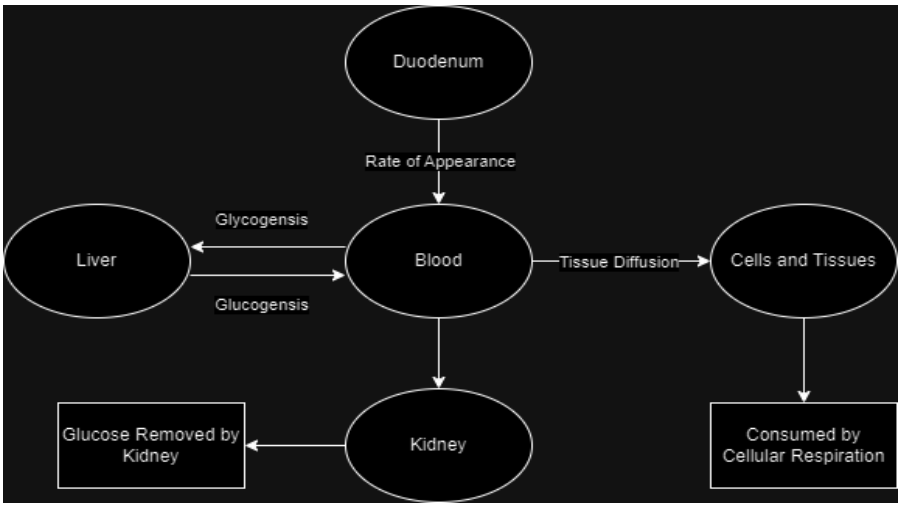


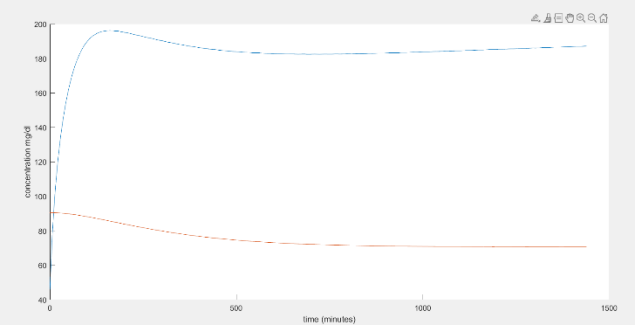
Figure 5. Compartment Model of Pathway of glucose throughout the body

Insulin is modeled with the previous equations (1-8), with initial conditions as $Ip(0) = 5.343\ pmol\ kg$^−1 and $I_L(0) = 7.93\ pmol\ kg$^−1 and Id(0), I1(0) = 90.56 pmol l^-1, X(0) = 0, Gp(0) = 86.496 and Gt(0) = 70.

Differential equations were solved with the constants from the authors and the above initial conditions using MATLAB's ode45 solver, obtaining models for plasma glucose and plasma insulin. The insulin pump is implemented via the S(t) function and the PID controller, where Id is adjusted.

MATLAB of the glucose equation and PID (For the sake of formatting, MATLAB code for the model is not written here. Please refer to complete MATLAB code available in appendix):

From the model we produce the following figures.



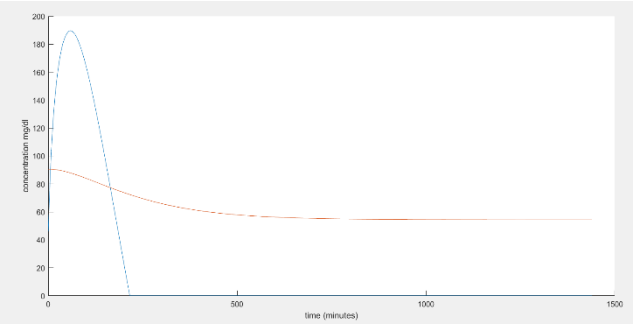
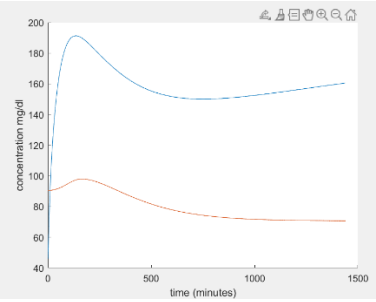


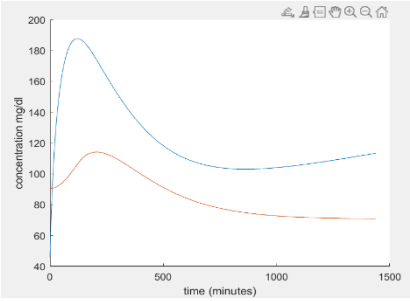
Figure 6A *Figure 6B*

Figure 6. Insulin (orange) and blood glucose(blue) concentrations over time following a meal of 50g of glucose. Figure 1A depicts a diabetic patient, while figure 1B depicts a healthy individual.

We see that after a meal over 120 minutes, indicated by the peak of glucose (blue curve), insulin also rises in both the healthy and the type 2 diabetic patients. However, in the diabetic patient, the insulin is

insufficient to reduce blood glucose, resulting in hyperglycaemia. In the healthy patient, we see that blood glucose was successfully reduced.





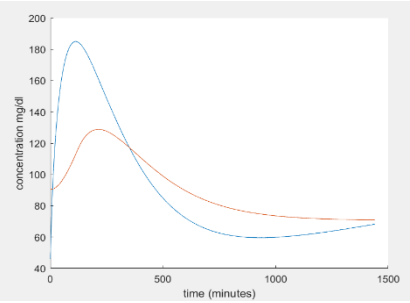
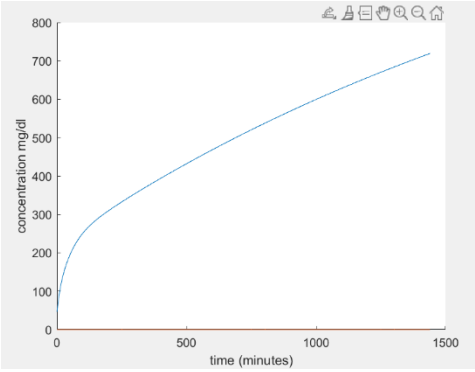


Figure 7A *Figure 7B* *Figure 7C*

Figure 7. Type 2 Diabetic patient's Insulin(orange) and blood glucose(blue) over time after a meal of 50g of glucose. With varying magnitudes of insulin pump injection. Each injection occurred over the first 2 hours. Figure 2A depicts an injection of rate 5 pmol/kg/min, Figure 2B depicts an injection of rate of 10 pmol/kg/min, Figure 2C depicts an injection of rate of 15 pmol/kg/min

In contrast to Figure 6A, we see that the diabetic patient's blood glucose is able to reach more reasonable levels following a meal, due to the insulin pump bolus injection.



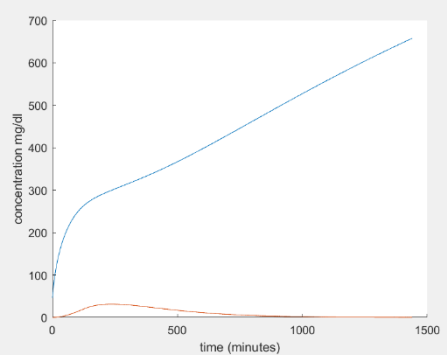
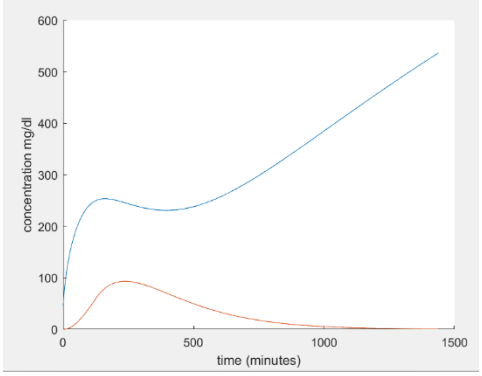


Figure 8A *Figure 8B*



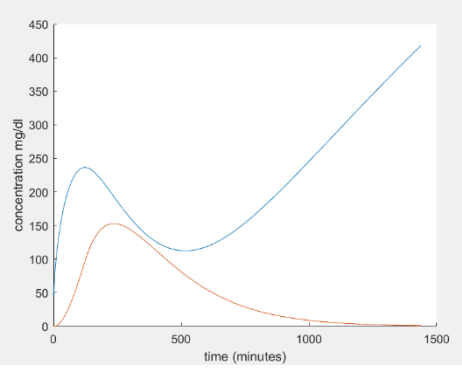


Figure 8C *Figure 8D*

Figure 8. Type 1 Diabetic patient's Insulin(orange) and blood glucose(blue) over time after a meal of 50g of glucose. With varying magnitudes of insulin pump injection. Each injection occurred over the first 2 hours. Figure 3A depicts an injection rate of 0 pmol/kg/min, Figure 3B depicts an injection rate of of 10 pmol/kg/min, Figure 3C depicts an injection rate of 30 pmol/kg/min, Figure 3D depicts an injection rate of 50 pmol/kg/min.

In contrast to the type 2 diabetic patient, bolus insulin injections in the type 1 diabetic patients are able to reduce blood glucose, however, due to the lack of a basal level of insulin, even larger bolus sizes are not able to permanently maintain blood glucose levels. As such, continuous or periodic control of blood glucose is required outside of meals.

While the insulin pump allows for diabetic individuals to receive the assistance needed, there are many issues with the technology. Most prominently, the insulin pump needs to be attached to the individual, with tubing connecting the inside of the body to the insulin supply. This causes severe hindrances to the patient's mobility, causing issues in extraneous physical activities, or during MRI scans, or just day to day inconveniences where an unremovable electronic device may cause issues for the patient. Due to the invasive nature of the tubing, the individual is also susceptible to infection at the site of insertion, needing to provide regular maintenance to the device and to the site of insertion.

The maintenance of an insulin pump is also expensive, as the individual must maintain a supply of insulin, the const of which may build up over time, making the device inaccessible to economically disadvantaged patients.

Finally, with the advent of online technology, modern insulin pumps can record and track data, for example, in the study. Grosman et al. 's 2018 utilized virtual patient data taken from their insulin pumps. This capability raises privacy concerns as an insulin pump may become unethical if the manufacturer records or uses patient data without consent.

The insulin pump has many ethical issues. Both the side effects and the impact on the patient's quality of life is questionable. With the incorporation of internet technology, usage of the insulin could even compromise patient confidentiality if the manufacturers chose to do so. While the good that the insulin pump does outweighs the ethical issues, as the patient's life is still being saved by the device, alternatives such as the insulin injection pens provide the same standard of care without many of the same risks and ethical issues.

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    a. ChatGPT was used in:
        i. the debugging of MATLAB code
        ii. Finding articles on specific topics
        iii. Finding Constants and Physiological values
        iv. Answering questions and concepts surround physiology of insulin