Glucose Regulation Using an Intelligent PID Controller

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Abstract

Type 1 diabetes is a condition characterized by a lack of insulin production. This lack of insulin causes glucose concentration in the blood to increase after meals. In order to maintain blood glucose levels, diabetics must inject insulin using needles or an insulin pump. Additionally, the lack of insulin can cause glucose levels to decrease overnight. This project uses a proportional integral derivative (PID) controller to modify the rate of insulin and glucagon infusion when glucose levels are increasing or decreasing, respectively.

A system of 13 differential equations were used to anticipate changes in glucose concentration as insulin and glucagon were injected. The system was simulated for virtual patients over a 24-hour time span in order to test its feasibility in human patients. The PID controller uses the current, past, and anticipated future glucose levels, respectively, in order to better determine the best course of treatment for the virtual patient.

One of the many difficulties in medical technology, however, is that everyone is different. These differences are a result of metabolism and other factors. To account for this fact the controller is designed to change the gain of the different controller components in order to better tailor the treatment to each patient.

Keywords: controller, insulin, glucose

1 Introduction

Diabetes is a chronic condition that affects nearly 10% of the US population [1]. Of these, another 5% of diabetics have Type 1 diabetes which is characterized by the body's inability

to properly regulate the concentration of glucose in the blood without the external administration of insulin [3]. Because of this problem, many researchers have developed models designed to aid in the treatment of diabetes in a number of situations. These range from models that replicate the body's response to large quantities of injections and others which use stochastic methods to account for outside influences like stress levels [7].

In this project, a model proposed by Resalat et al. will be discussed and used in a treatment algorithm. This model, which uses the biological processes affecting blood glucose, is a combination of biological mass transport and chemistry [9]. The method by which patients were generated and the model solved will then be introduced. The treatment, which involves a PID controller being used to maintain healthy glucose levels, will be detailed. This treatment is administered both during the day, when glucose tends to increase, and at night, when glucose decreases. The algorithm accomplishes this by introducing insulin when the glucose increases and introducing glucagon when the glucose decreases. Finally, some simulations will be run without the controller, with an early version of the controller, and with the final controller. After this has been done, the quality of the treatment will be addressed and compared to other solutions being developed.

2 The Model

A total of 13 coupled ordinary differential equations are used in this model. The majority are linear while the last two are nonlinear. These equations involve insulin kinetics and dynamics, carbohydrate absorption, and glucagon kinetics and dynamics. Each set of equations is discussed in more detail below. Please note the dot notation used below indicates a time derivative.

2.1 Insulin Kinetics

Three differential equations govern insulin kinetics [6]. The equations are as follows:

$$\begin{aligned} \dot{S}_1 &= u_I - \frac{S_1}{t_{max}} \\ \dot{S}_2 &= \frac{S_1}{t_{max}} - \frac{S_2}{t_{max}} \\ \dot{I} &= \frac{S_2}{t_{max} V_I} - k_e I \end{aligned} \tag{1}$$

This is a mass transport model using two subcutaneous compartments. S_1 and S_2 are the masses of insulin in each compartment [mU/kg] [1]. I is the concentration of insulin in the plasma [mU/L], and u_I is the rate of insulin infusion [mU/(kg·min)]. The last three

[1] 10 mU is equal to one mL.

parameters, t_{max}, V_I, and k_e are the time-to-maximum absorption [min], distribution volume [L/kg], and elimation rate from the plasma [min^{-1}], respectively. In total, these equations account for the movement of insulin throughout the body.

2.2 Insulin Dynamics

The insulin dynamics model evaluates how glucose concentrations change as a result of insulin being present in the plasma. Again, three equations govern this model [6].

$$\begin{aligned} \dot{X}_1 &= -k_{a1}X_2 + S_{f1}k_{a1}I \\ \dot{X}_2 &= -k_{a2}X_2 + S_{f2}k_{a2}I \\ \dot{X}_3 &= -k_{a3}X_3 + S_{f3}k_{a3}I \end{aligned} \tag{2}$$

Here, the input variable X_1 [min^{-1}] represents the effect of insulin on glucose distribution, X_2 [min^{-1}] is the effect of insulin on glucose disposal, and X_3 [unitless] is the suppression of endogenous glucose production (EGP). Similar to before, $k_{a1},\ k_{a2},\ k_{a3}$ [min^{-1}] are the rates at which insulin is entering a compartment as well as the rate at which the insulin's effects are being eliminated, where the compartment corresponds with the relevant X variable. Finally, the variables S_{f1} [mU/(L·min)], S_{f2} [mU/(L·min)], and S_{f3} [mU/L] represent the sensitivity of the body to the concentration of insulin.

2.3 Glucagon Kinetics

The absorption rate of subcutaneously injected glucagon into the plasma is represented by this triad of equations [9]:

$$\begin{aligned} \dot{X}_{1g} &= -(k_{1g} + k_{ge1})X_{1g} + u_g \\ \dot{X}_{2g} &= k_{1g}X_{1g} - k_{2g}X_{2g} \\ \dot{X}_{3g} &= k_{2g}X_{2g} - k_{ge2}X_{3g} \end{aligned} \tag{3}$$

Similar to the insulin kinetics model, X_{1g} and X_{2g} [mg/kg] are the mass of glucagon in different compartments. However, X_{3g} [mg/kg] is the mass of glucagon in the plasma. The variables k_{1g} and k_{2g} [min^{-1}] are transfer rates between the two compartments, and k_{ge1} and k_{ge2} [min^{-1}] are the elimination rates from these compartments. Lastly, u_g [mg/(kg·min)] is the basal infusion rate of glucagon infusion from a pump.

2.4 Glucagon Dynamics

This model shows the relationship between the concentration of glucagon in the plasma and the endogenous glucose production (EGP) [9]. The equations in the model are shown below:

$$\begin{aligned}\dot{Y} &= \frac{10^6 \cdot k_c \cdot S_{fGG}}{V_{dGG}} X_{3g} - k_c Y \\ Z &= \dot{Y} \\ \dot{Z} &= k_g k_{2g} X_{2g} - k_g k_{ge2} X_{3g} - k_c Z\end{aligned} \tag{4}$$

First, Y [mg/kg] is equal to the effect glucagon has on EGP. The clearance rate of glucagon from the compartment is given by k_c. S_{fGG} [L/(ng·min)] is the patient's sensitivity to glucagon. V_{dGG} [L/kg] is glucagon's volume of distribution. The parameter k_g is equal to the coefficient of X_{3g} in the above equation.

2.5 Carbohydrate Absorption

The carbohydrate absorption model measures the changes in blood glucose caused by the behavior of insulin and glucagon as well as natural glucose uptake. This nonlinear model was proposed by Hovorka et al. [6].

$$\begin{aligned}\dot{Q}_1 &= -X_2 Q_1 - F_{01}^c - F_R + K_1 2 Q_2 + U_G + EGP_0(1 - X_3 + Y + k_{g3} Z) \\ \dot{Q}_2 &= X_1 Q_1 - k_{12} Q_2 - X_2 Q_2\end{aligned} \tag{5}$$

Q_1 and Q_2 [mmol/kg] are the masses of glucose in the plasma and compartment, respectively. EGP_0 [mmol/(kg·min)] is the basal endogenous glucose production with an insulin concentration of zero. F_{01}^c is the natural glucose uptake, and F_R is the renal glucose clearance rate. Both of these are given in units of mmol/(kg·min). The variable U_G [mmol/(kg·min)] is the glucose absorption rate from individual meals. The equation used to model this absorption is

$$U_G = \frac{D_G A_G (t - t_0) e^{-\frac{t - t_0}{t_G}}}{t_G^2} \tag{6}$$

D_G is the estimated carbohydrate intake [mmol/kg], A_G is the carbohydrate availability [unitless], t_0 is the time a meal occurs [min], and t_G is the time-to-maximum appearance of Q_1 [min].

3 Methods

3.1 Runga-Kutta-Fehlberg (RK45)

The differential equations were solved numerically using a Runga-Kutta-Fehlberg (RK45) algorithm programmed into MATLAB. A fourth order Runga-Kutta algorithm is a commonly used differential equation solver. However, the RK45 algorithm differentiates itself by allowing for varied time steps rather than fixed steps [5]. This fact makes the RK45

algorithm better suited to test the rapid changes in insulin and glucose that occur at the beginning of the simulation and after meals.

3.2 Patient Generation and Simulation

Many of the parameters in the system were not constants but rather a range of values that vary based on different biological factors. Because of this, a random value from each range was assigned to a patient at the beginning of each simulation. This ensured a variety of patients were tested and the code was not designed to treat one patient better than another. Through this method, the controller was programmed to treat both patients with high metabolisms as well as those with low metabolisms.

The patient was then simulated separately from the controller code via a function with insulin and glucagon injections being passed to the patient throughout the process. However, the simulation only checked the blood glucose of the patient every five minutes to confirm the simulation matched the patient. This was done so insulin and glucagon injections were based on accurate readings rather than simply the simulation's expected values.

3.3 Controller Design

In order to implement a PID controller, gains had to be determined for each of the three components. The initial gains were $0.5, 0.05$, and 14, respectively. These gains were chosen for two different reasons. First, the derivative values were on the order of five times smaller than the proportional component. Thus, it needed a larger gain to give it weight in the controller. Similarly, the integral component was substantially larger leading to its small gain. The second reason is that the system has a 20 minute delay between insulin injection and when it affects glucose levels. Thus, too little insulin being injected immediately after a meal would lead to too high of a blood sugar while too much insulin after a meal was digested would lead to a rapid decrease in glucose. Thus, the derivative gain had to be relatively large while the integral gain needed to be low. Originally, the Ziegler-Nichols tuning method was to be used in determining these values. This method is commonly used in physical systems and can be applied to math models. Unfortunately, the method is designed to work with cyclic functions [2]. The gradual reduction in glucose over time precludes such behavior though, so another method was proposed.

Once the initial gains were set, the simulation began to progress based on ingested meals and patient blood sugar readings. After each peak glucose reading from a meal, the simulation evaluated the expected and actual glucose levels as well as the derivatives of the two during the rising period. Based on the difference between these values, the proportional and derivative gains were altered. If the actual glucose was greater than the expected, the proportional gain was increased. If it was lower, the opposite occurred. The same was done if the actual derivative did not match with the expected derivative. In addition, if the patient's glucose

got too high, the integral gain was increased in order to keep glucose lower on subsequent meals.

4 Results

4.1 Pre-Controller Simulations

Before showing how the controller behaved in the patient it is important to gain an understanding of how the system behaves without outside intervention. Figure 1 shows a simulation of the system prior to any controller implementation.

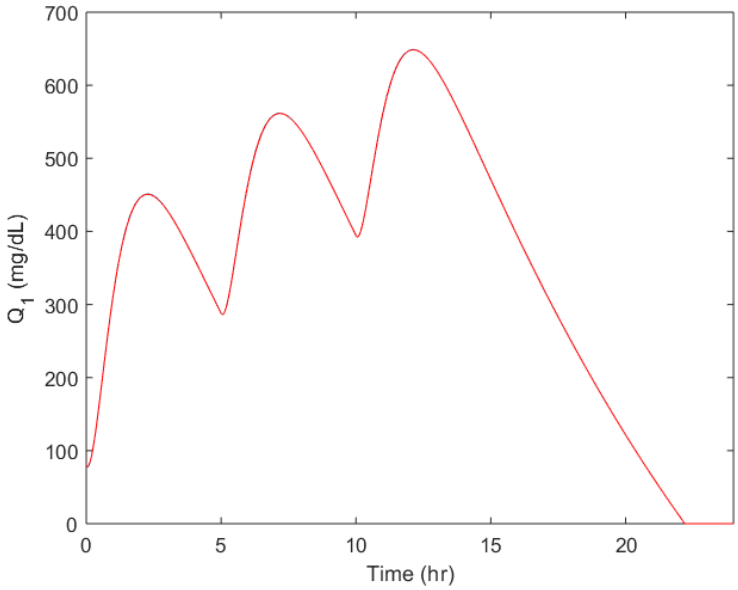

Figure 1. A plot of a diabetic's blood-sugar over time with no insulin

Blood-sugar is measured in mg/dL on the y-axis as per medical standards. This simulation lasts an entire day starting at 7 A.M. and finishing at the 24 hour mark. A meal was also administered at 7 AM, 12 PM, and 5 PM. The meals administered were 100 grams of carbohydrates. As can be seen, the meals cause a rise-time of about two hours prior to a decline caused by the first term in the Q_1 equation in equation set (5). The glucose does not reach its pre-meal value before another meal is ingested though. Because of this, the glucose reaches a peak value for the day of about 650 mg/dL following dinner. Despite this, the body's lack of ability to produce its own sugar causes a rapid decline afterward which in turn causes the blood sugar to reach zero before the next morning. The span of time between peak value and critical condition of the patient is about nine hours.

When adding the simulation's expected values to the plot, it was important to ensure expected values did not diverge from the patient's actual state. Figure 2 shows an example of this happening.

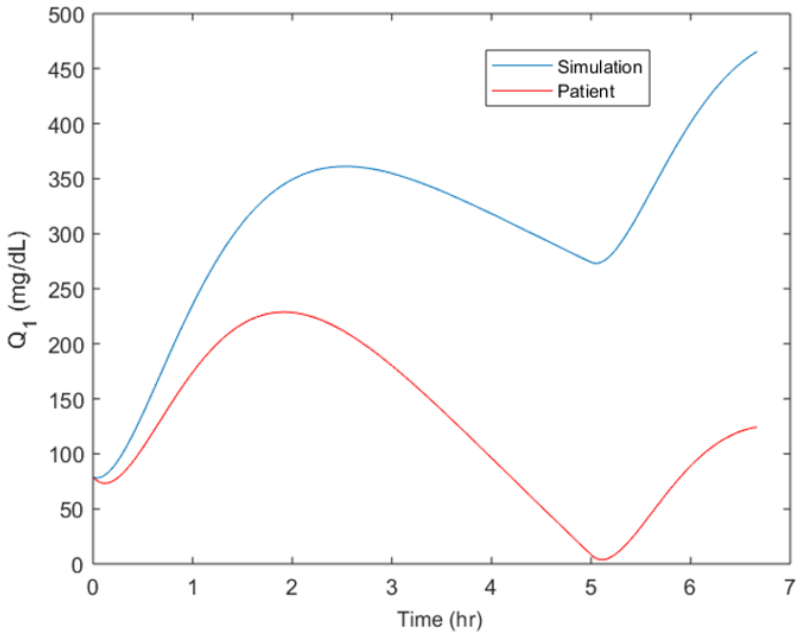

Figure 2. A plot showing the diverging of signals

As can be seen above, when the simulation does not fit itself to the glucose of the patient, the signals diverge. If insulin were to be injected at this point, the simulation would think a large amount of insulin is needed given its high glucose. However, the patient is in a healthy range for the majority of this time. Thus, the patient would receive more insulin than necessary, causing them to reach a glucose level of 0 mg/dL. By sampling the patient's blood-sugar the simulation does not risk this occurring. All this must be done because the parameters of each patient are unknown by the system, as would be the case in a clinic.

4.2 PID Controller Simulations

Following the development of the system, a standard PID controller was programmed to inject insulin during the simulation. Figure 3 shows the plot of a simulation.

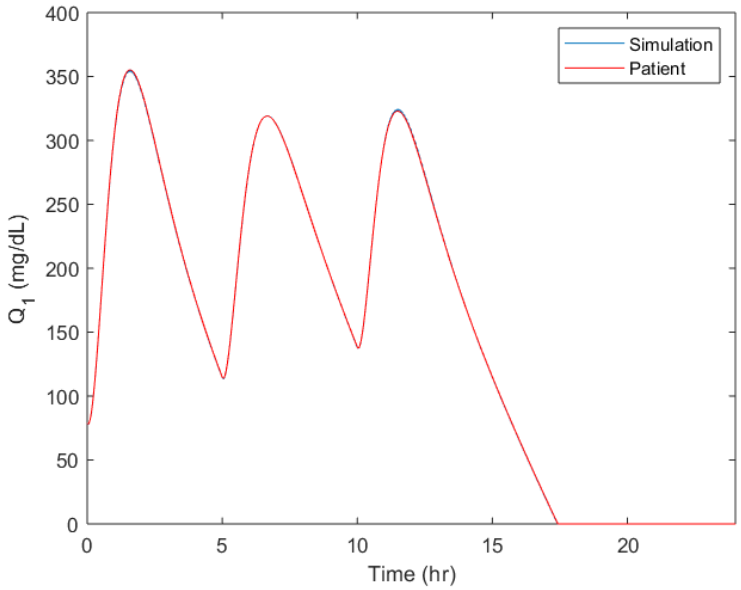

Figure 3. A plot of insulin treatment via PID controller

This plot has a few interesting attributes when compared to Figure 1. While the three peaks still occur after the meals, the peaks are much lower than without a controller. Additionally, the highest peak is the first peak whereas it was the last peak without insulin. This is a result of insulin still being in the blood stream by the time the patient has another meal. The remaining insulin then causes clearance of the glucose faster than the preceding meal. As the simulation continues, the oscillations get smaller even if the peak value remains the same after meals two and three.

Not all patients will react to the same conditions in the same way though. An example of this is shown in Figure 4.

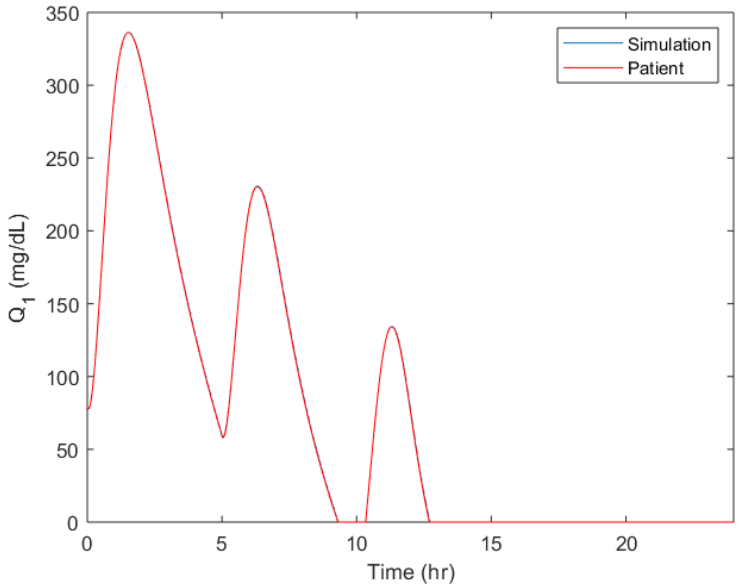

Figure 4. A plot showing another case of insulin treatment

Clearly the outcomes for this patient varied substantially from that of the one shown in Figure 3. By dinner time, the patient has hit a blood glucose of 0 mg/dL. Despite the simulation continuing on, the patient would not have continued on to eat dinner at this point. Using the same gains for patients, therefore, would not work as a solution. To account for these differences, the controller was designed to check expected values against actual values, and alter its gains to account for these differences.

Once the insulin controller had been developed to account for different patients, the glucagon controller was developed. Figure 5 shows how the initial glucagon controller functioned.

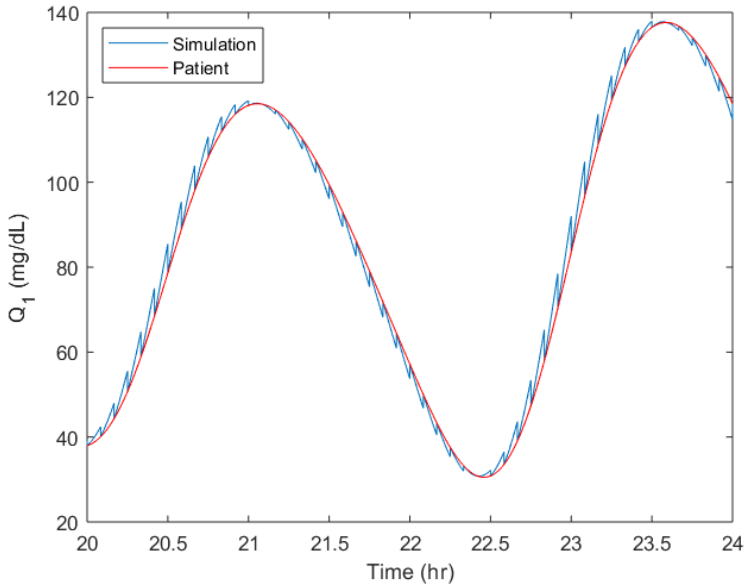

Figure 5. A plot with the preliminary glucagon controller

While the oscillations caused by the glucagon controller and insulin controller together are smaller than that of the insulin controller alone, the oscillations are still larger than desirable. Given that the body is asleep, it is better to have minor glucose changes to ensure the patient is not made to feel sick. For this reason, the same types of corrections were made to the glucagon controller as had been made to the insulin controller.

4.3 Intelligent Controller Simulations

Gains were changed for the insulin controller based on the patient's reaction to insulin injections and glucose clearance. Figure 6 is a plot depicting a simulation from the finalized insulin controller.

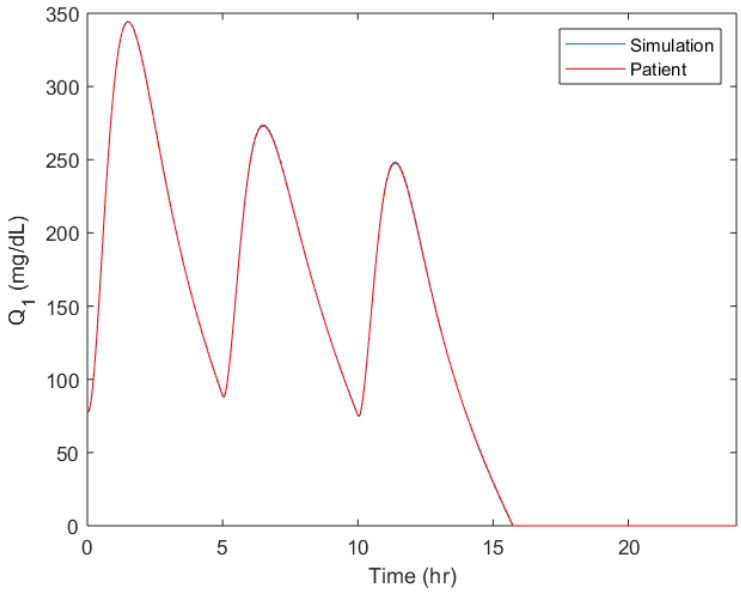

Figure 6. A simulation of glucose with fully functional insulin controller

Glucose levels with the intelligent controller are kept lower during the day than with the standard PID controller. The same initial gains were used for both the preliminary and final controllers to better illustrate how the controller's ability to adjust the gain benefited the patient. Oscillations in glucose levels are kept in a safer range with this controller as the glucose is kept closer to 100 mg/dL than before. However, this better management of glucose results in a zero reading earlier in the evening. This was addressed via the glucagon controller which is shown in Figure 7.

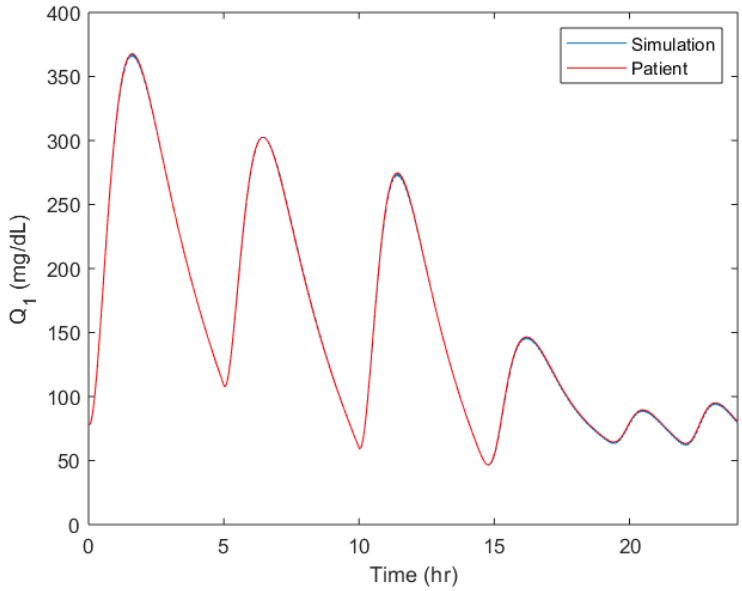

Figure 7. The final glucagon and insulin controller

As can be seen around the 15 hour mark, the first glucagon injection results in a large change in glucose on the order of 100 mg/dL. This is similar to the non-intelligent controller. However, the oscillations quickly shrink and maintain a healthy level through the rest of the night. This simulation also ended the patient's glucose at a similar value to where it started that morning.

5 Future Directions

The simulations were simple to run through MATLAB, but the computational power a computer can offer is not necessarily standard on all phones and especially not insulin pumps. Because of this, a less computationally intensive solution needs to be found which also offers better control and minimizes the fluctuations which occur after meals. One potential solution is model predictive control [8]. Model predictive control uses optimization software to minimize the error function before enacting the steps to actual correct this error [4]. This means the system can run several different simulations to test how different insulin injections will affect the body. Through this method, the minimal amount of insulin can be injected while still achieving the best outcome. Despite the simulations being run repetitively, the optimization algorithm is designed to lessen the computational strain on the device.

Another trend being observed is the development of artificial intelligence in artificial pancreases [10]. Artificial intelligence is being used to analyze the results of injections to determine the values of the parameters within the system of equations. By analyzing patient data over several days, the system can be optimized to achieve the same results as model predictive control.

6 Conclusion

In order to manage Type I diabetes, insulin must be administered into the body. To ensure an accurate prediction can be made of how insulin affects glucose, models have been developed to be used in control algorithms. One potential algorithm uses PID control. Using a PID control algorithm to administer both insulin and glucagon to a diabetic patient allows the patient to maintain better glucose levels throughout the day as well as at night. This can be done by adjusting controller gains as the simulation runs to better match the behavior of the simulation to that of the patient's body. However, based on the results found here, it is possible to improve the algorithm used to keep the patient's glucose within a smaller and lower range. This is possible through both model predictive control and artificial intelligence. Both of these methods are currently being researched and are expected to be used in artificial pancreases in the near future.

7 References

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