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Effectiveness of Intravenous Infusion Algorithms for Glucose Control in Diabetic Patients Using Different Simulation Models

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Abstract

The effectiveness of closed-loop insulin infusion algorithms is assessed for three different mathematical models describing insulin and glucose dynamics within a Type I diabetes patient. Simulations are performed to assess the effectiveness of proportional plus integral plus derivative (PID) control, feedforward control, and a physiologically-based control system with respect to maintaining normal glucose levels during a meal and during exercise. Control effectiveness is assessed by comparing the simulated response to a simulation of a healthy patient during both a meal and exercise and establishing maximum and minimum glucose levels and insulin infusion levels, as well as maximum duration of hyperglycemia. Controller effectiveness is assessed within the minimal model, the Sorensen model, and the Hovorka model. Results showed that no type of control was able to maintain normal conditions when simulations were performed using the minimal model. For both the Sorensen model and the Hovorka model, proportional control was sufficient to maintain normal glucose levels. Given published clinical data showing the ineffectiveness of PID control in patients, the work demonstrates that controller success based on simulation results can be misleading, and that future work should focus on addressing the model discrepancies.

Keywords

Control; Systems; Glucose; Insulin; Diabetes; Model

Introduction

As the field of bioengineering continues to grow, chemical engineers, equipped with the ability to understand, quantify, design, optimize, and control chemical as well as biochemical processes, are well positioned to make strong contributions. Of particular interest is systems engineering. Because the body is constantly working to maintain homeostasis, systems engineering can be applied by treating the body as a system of complex chemical processes, with the objective being to maintain optimal levels of specific biological species.

One of the most important areas where homeostasis is desirable is in the development of therapies for diabetes mellitus, in which the body is unable to maintain normal glucose levels.

Abnormally high glucose levels (hyperglycemia) can lead to heart and kidney failure, blindness, and the necessity to have appendages amputated. Abnormally low levels (hypoglycemia) can result in diabetic coma or even death. Of particular concern is Type I diabetes, in which the body is unable to produce sufficient insulin, the hormone most responsible for regulating glucose levels in the blood.

An important part of the control process is the definition of all controlled, manipulated, measured, and state variables. In perhaps the simplest type of control system, a single output variable is controlled with only one input. Specifically for glucose regulation, glucose would be the lone controlled variable and insulin would be the single manipulated variable. In complex systems, the concentrations of other metabolites can affect glucose levels as well. This multi-output control system can be designed such that all the hormones of significance could be used as manipulated variables to control glucose, amino acid, and fatty acid levels.

Effective explicit closed-loop control can only be realized when the necessary sensors, control algorithms, and actuators (delivery systems) are developed. For an intravenous delivery system, both the sensors and the pumps should be implantable. Sensors should be in place to give the values of all controlled variables at sample times on the order of minutes to provide minute-to-minute control of the variable. The implanted pumps should be able to supply the necessary inputs (hormones) for multiple days in order to prevent having to refill the reservoirs too frequently.

The control algorithm developed or used depends on the availability of measurements for all controlled species (glucose, fatty acids, and amino acids) as well as the ability to effectively infuse the inputs (hormones). The lack of effective fatty acid or amino acid sensors to be implanted makes the use of these species for feedback measurements in multivariable control infeasible at present. While recent research efforts have focused on the implementation of a control system utilizing glucagon, such work is relatively recent, and the large majority of glucose control still focuses on insulin as the single manipulated variable.

The use of models facilitates the investigation of control system effectiveness by allowing simulations to be performed that capture the glucose response to various conditions, including meal consumption and exercise. By implementing the control algorithm as the source of insulin secretion, the effectiveness of the control system with respect to maintaining normal glucose levels can be investigated without the use of experiments.

There has been considerable work over the years in developing effective explicit closed-loop glucose control algorithms for patients with Type I diabetes. Bequette [1] and Parker et al. [2] provide reviews of many of the control algorithms developed. Among them are the proportional plus derivative (PD) algorithms of Albisser [3], the Biostator algorithms [4] that aimed to improve upon Albisser's work, and the PD model of Nomura [5]. These algorithms suffered from being too patient specific, being sensitive to measurement noise, and in having to be reprogrammed as the patient's metabolic parameters changed. A recently proposed PID switching algorithm by Marchetti et al. [6] was demonstrated to perform favorably when faced with meal disturbances, changes in insulin sensitivity, and intra-patient variability in simulations. Among advanced algorithms, Fisher [7] and Ollerton [8] developed optimal control algorithms, but the authors demonstrated the inability of their algorithms alone to successfully control glucose through simulations. Parker et al [9,10] has developed both an MPC and an H_{∞} algorithm, demonstrating effective control on Sorensen's physiologic model.

In addition to simulation studies for control algorithms, real-life trials with controllers have also been performed. Steil et al. [11] has performed trials using PID controllers on diabetic dogs, demonstrating the ability to provide the basal insulin infusion as well as bring levels to normal in response to a meal. El-Khatib et al. has performed trials using adaptive control with

dual insulin and glucagon infusion in pigs [12]. Finally, Hovorka et al. [13,14] has been performing trials using model predictive control with human patients with Type I diabetes, both in intensive care patients and patients with initially elevated glucose levels.

In this work, we investigate the effectiveness of explicit closed-loop control through simulations with existing patient models. Various methods of single input-single output control are applied to study the effectiveness of insulin infusion algorithms with respect to maintaining acceptable glucose levels in different simulated situations encountered by diabetic patients.

Methods

To study the effectiveness of different control algorithms, the control algorithms are used to determine the infusion rate for various patient models. The ability of the each controller to maintain normal glucose levels in response to meal and exercise is simulated and assessed by noting the glucose response and the insulin infusion profile as a function of time for each situation, using each model.

Patient Models

Three patient models have been used to assess closed-loop controller performance. The earliest model is the minimal model of Bergman and Cobelli [15]. The modified form by Furler et al. [16] and Lynch and Bequette [17,18] to describe dynamics without pancreatic insulin release is described by equations (1)–(3).

$$\frac{dG(t)}{dt} = -P_1(G(t) - G_b) - G(t)(X(t) - X_b) + D(t) \quad (1)$$

$$\frac{dX(t)}{dt} = -P_2(X(t) - X_b) + P_3(I(t) - I_b) \quad (2)$$

$$\frac{dI(t)}{dt} = -nI(t) + \frac{U(t)}{V} \quad (3)$$

Here, G is the plasma glucose concentration, X is a term proportional to the insulin concentration in the “remote compartment”, which represents the compartment of insulin action (i.e., insulin bound to liver and peripheral cells), and I represents plasma insulin levels. D represents an external glucose source, such as a meal or an oral or injected glucose dose. U represents an exogenous insulin source. The parameters P_1 , P_2 , P_3 , and n represent first order kinetic elimination rates for each state variable, and V represents the insulin circulation volume. Finally, the terms G_b , X_b , and I_b represent the basal (steady-state) values of state variables. Typical patient values for a Type I diabetic patient are given in Table 1.

To simulate control using an explanatory model, the Sorensen model [19] is used. Originally developed as a healthy patient model, it includes three additional ordinary differential equations (ODEs) to describe pancreatic insulin release as a function of glucose. To simulate a diabetic patient, the pancreatic insulin release term is set to zero, and the three ODEs of the secretion are eliminated. The resulting model consists of 19 ODEs describing glucose, insulin, and glucagon dynamics throughout the different organ systems of the body, including the gut, brain, blood, periphery, liver, and kidneys. The compartmental diagrams of the model are given in Figures 1 through 3

Finally, because of its frequency of use among control engineers, Hovorka's model [20,21] is used. The model equations are given in Appendix. The model's two glucose compartments and three insulin action compartments correspond to the most accurate pharmacokinetic descriptions of glucose and insulin, according to Sorensen [19] and Cobelli et al. [22].

Meal Models

To describe the absorption of a meal, the description of the model used by Fisher [7] was chosen, as given in Equation (4).

$$D(t) = \begin{cases} 0 & t < t_{meal} \\ A \exp(-b(t - t_{meal})) & t \geq t_{meal} \end{cases} \quad (4)$$

The term t_{meal} represents the time at which the meal begins digestion. The parameter b represents the absorption rate of the meal, while A represents the size of the meal. Because the integral of the equation from t_0 to infinity gives the total size of the meal, A can be determined as:

$$A = M_{meal}b \quad (5)$$

Bequette [23] adds a 20 minute time constant to the meal to account for the physiological process of digestion before the glucose begins to appear in the blood. This time constant, interpreted as the inverse of the parameter b , is equal to 0.05 min^{-1} . When t is less than t_{meal} , the variable D is zero.

For Sorensen's model, Equation (4) is substituted into the gut glucose equation as a source of oral glucose. Hovorka's model [21] has its own meal model, described by Equation (6).

$$D(t) = \frac{M_{meal}A_{meal}t \exp\left(-\frac{t}{t_{max}}\right)}{t_{max}^2} \quad (6)$$

The variable A_{meal} represents the percent availability of the meal consumed. The variable t_{max} represents the time, from the beginning of the meal consumption, for the absorption rate to reach its maximum. This model represents a meal as a two compartment chain. Each compartment has a kinetic elimination rate coefficient of $1/t_{max}$. Compartment one has no input, and is initially described as the amount of total available glucose. Compartment two has the output of compartment one as its input, and the absorption of glucose into the blood as its output. The meal absorption rate is described as the concentration in compartment two multiplied by its rate coefficient.

Exercise Models

Roy and Parker [24] and Lenart and Parker [25] proposed two different exercise models. The models were developed using the experimental work of Ahlborg et al. [26] and Felig and Wahren [27], describing exercise effects on fuel metabolism. Both models assumed that exercise increases metabolism, and that the increase in metabolic rates is best described as a function of the exercise levels, which are described by the current oxygen consumption levels as a percentage of maximum oxygen consumption level, $PVO_2^{\max}$. The first description is used with the minimal model to match the data. It is combined with Equations (1) through (3) to give the total description of the patient, as shown in Equations (7) through (13)

$$\frac{dG(t)}{dt} = -P_1(G(t) - G_b) - X(t)G(t) + D(t) + G_{prod}(t) - G_{up}(t) \quad (7)$$

$$\frac{dX(t)}{dt} = -P_2(X(t) - X_b) + P_3(I(t) - I_b) \quad (8)$$

$$\frac{dI(t)}{dt} = -nI(t) + \frac{U(t)}{V} - I_e(t) \quad (9)$$

$$\frac{dG_{prod}(t)}{dt} = a_1 PVO_2^{max}(t) - a_2 G_{prod}(t) \quad (10)$$

$$\frac{dG_{up}(t)}{dt} = (a_3 PVO_2^{max}(t) + a_4) PVO_2^{max}(t) - a_5 G_{up}(t) \quad (11)$$

$$\frac{dI_e(t)}{dt} = a_6 PVO_2^{max}(t) - a_7 I_e(t) \quad (12)$$

$$\frac{dPVO_2^{max}(t)}{dt} = \left(\frac{1}{\tau_{ex}} \right) \left(-PVO_2^{max}(t) + PVO_{2,ultimate}^{max} \right) \quad (13)$$

The new state variables G_{prod} , G_{up} , I_e , and PVO_2^{max} represent the glucose production rate, glucose uptake rate, insulin removal rate, and exercise intensity, respectively. Each parameter a_i represents the kinetic rate coefficient for the increase or decrease in metabolic rate for each type of exercise enhanced process. The parameter τ_{ex} is the time constant for changing from one exercise level to another. The final parameter of Equation (13) represents the maximum exercise level that will be achieved. The model is simple, basing rate increases on first or second order kinetics. Given the pharmacokinetic-type description of the exercise model in [24], this model is also applied to Hovorka's model.

The model in reference [25] was developed for use with the Sorensen model. It is similar to the model in reference [24] in that it is based on PVO_2^{max} , which is also described by Equation (13) in this model. However, there are some key differences that need to be mentioned. First, the reported blood flow rates had to be modified according to literature of reported blood flow for different exercise levels. Second, by the very nature of differences between the two model types, specifically their equations describing metabolism, the metabolic effects of exercise with respect to glucose production and uptake and insulin elimination had to be developed to fit the Sorensen model form. To do this, specific dimensionless multiplicative factors representing exercise contributions had to be developed. For glucose uptake, the multiplicative factor is described by Equation (14).

$$M_{PGU}^E = 1 + \frac{PGU_E(m_{EM})}{PGU_b} \quad (14)$$

The parameter m_{EM} represents the mass of exercise muscle and PGU_E represents the exercising muscle glucose uptake rate. It is described by Equation (15)

$$\frac{dPGU_E(t)}{dt} = \left(\frac{1}{\tau_{EGU}} \right) (-PGU_E(t) + ePGU_E) \quad (15)$$

The variable τ_{EGU} is the time constant associated with increasing glucose uptake from one exercise level to another level. The variable $ePGU_E$ represents the maximum uptake rate for a particular level of exercise. The effect of exercise on glucose production is found the same way, using the basal production rate and the mass of exercising muscle. The primary difference is that the production rate of exercising muscle is set equal to the uptake rate of exercising muscle, assuming glucagon is able to produce enough glucose to supply the amount needed in increased uptake. This is shown in Equation (16).

$$M_{HGP}^E = 1 + \frac{PGU_E m_{EM}}{HGP_b} \quad (16)$$

Finally, regarding insulin removal, insulin peripheral uptake was modified to account for the observation that uptake increases by a factor of 3.4 when 100% of a person's muscle is active [25]. This is shown in Equation (17).

$$PIU = \frac{I_p \left(1 + 2.4 \left(\frac{m_{EM}}{m_{TM}} \right) \right)}{\left[\frac{1-F}{FQ_p} - \frac{\tau_p^I}{V_{PI}} \right]} \quad (17)$$

The parameter m_{TM} represents the total mass of muscle of the individual. The remaining model parameters are defined in Appendix B. The authors [25] modified the parameter F in order to maintain constant insulin uptake rates in response to increased blood flow rates. All exercise parameters for the models in references [24] and [25] are given in Table 2.

Control Algorithms

To investigate the effectiveness of control in response to meals and exercise in diabetic patients, several control algorithms were employed. The algorithms were used to determine the infusion parameter $U(t)$ for each model.

The first method studied was a simple feedback control system utilizing the proportional plus integral plus derivative (PID) control algorithm. The feedback process control diagram is shown in Figure 4. The PID algorithm is described by Equation (18).

$$U(t) = U_{basal} + K_c \left[(y(t) - y_{setpoint}) + \frac{1}{\tau_i} \int_0^t (y(t) - y_{setpoint}) dt + \tau_d \frac{d(y(t) - y_{setpoint})}{dt} \right] \quad (18)$$

The parameter K_c is the proportional gain, τ_I is the integral time, and τ_D is the derivative time. The variable y corresponds to the system outputs. In this case y corresponds to the system's glucose concentration. The controller is based on the error in y relative to its set point. To maintain basal conditions, $y_{setpoint}$ is set to be the basal glucose concentration. The controller was designed for each model by subjecting the model to a step change in the insulin infusion rate, and then fitting the data by a first order plus time delay (FOPTD) model, as shown by Equation (19).

$$y = \begin{cases} 0 & (t \leq \theta) \\ KM \left(1 - \exp\left(-\frac{t-\theta}{\tau}\right) \right) & (t > \theta) \end{cases} \quad (19)$$

Here, K is the process gain, defined as the change in the output variable in response to a unit change in the manipulated variable. M is the magnitude of the step change, τ is the time constant, defined as the time for the output to reach approximately 63% of its steady state value, and θ is the time delay in the process. Given the step response data, the parameters of a FOPTD model were regressed. Once the FOPTD model parameters were determined, the controller tuning parameters K_c , τ_I , and τ_D could be calculated using the Internal Model Control (IMC) PID tuning guidelines given in reference [28]. The controller tuning equations are shown in Equations (20) through (22).

$$K_c = \left(\frac{1}{K} \right) \frac{\tau + \frac{\theta}{2}}{\tau_c + \frac{\theta}{2}} \quad (20)$$

$$\tau_I = \tau + \frac{\theta}{2} \quad (21)$$

$$\tau_D = \frac{\tau\theta}{2\tau + \theta} \quad (22)$$

The parameter τ_c is the desired closed-loop process time constant. Increasing the value of τ_c results in increasingly conservative control. For parameter tuning, τ_c was taken to be equal to the process time delay. Once the PID tuning parameters were initially determined, they were tuned by increasing and decreasing the different actions in order to meet the desired control objectives. These objectives are discussed in the next section. Although PID tuning parameters were initially determined using the FOPTD model, all simulations were performed on the full-scale ode systems.

The second type of algorithm used was feedforward control. Feedforward control is based on the idea that, given a known value of the disturbance, a controller can be designed such that corrective action is taken before the disturbance enters the process. Ideally, the disturbance never affects the process. While this may not be achieved in reality, feedforward control is able to significantly reduce the effects of measured disturbances on a process. Figure 5 shows a schematic of feedforward control, and Figure 6 shows a feedforward control scheme combined with a feedback scheme.

The feedforward control algorithm was defined by converting the patient model into transfer functions for the manipulated variable and the disturbance variable. For low order models this

can usually be performed manually. For higher order models, such as the Sorensen model, it is best to develop FOPTD models for the different input variables, and determine the control law based on the simplified models. Once the transfer functions for each input is determined, the feedforward controller is determined from Equation (23).

$$G_{ff} = -\frac{G_D}{G_U} \quad (23)$$

In Equation (23) the variable G_D represents the disturbance transfer function, and G_U represents the manipulated variable transfer function. As previously mentioned, this control setup is usually used in combination with a feedback controller. The combined feedback/feedforward method was also employed as a potential control system.

As a final method of control, a physiological pancreatic secretion model was used to determine the body's natural response to glucose. For this controller, Sorensen's pancreas model [19] was used. The equations and model parameters for pancreatic insulin release for a healthy patient are given below, with parameter definitions and values given in Table 3:

$$r_{PIR} = \frac{S(G_H)}{S(G_H^B)} r_{PIR}^B \quad (24)$$

$$S = \begin{cases} [M_1 Y + M_2 (X - I)] Q & X > I \\ M_1 Y Q & X \leq I \end{cases} \quad (25)$$

$$Y = (X)^{1.11} \quad (26)$$

$$X = \frac{(G_H)^{3.27}}{(132)^{3.27} + 5.93(G_H)^{3.02}} \quad (27)$$

$$\frac{dI}{dt} = \beta(X - I) \quad (28)$$

$$\frac{dQ}{dt} = K(Q - Q_0) + \gamma P - S \quad (29)$$

$$\frac{dP}{dt} = \alpha(Y - P) \quad (30)$$

Control Objectives

The overall objective of control with respect to insulin dependent diabetes is to mimic a healthy pancreas as much as possible. In this regard, the controller should be able to keep glucose levels at the patient's basal level during normal fasting conditions. Ideally, the patient should remain in the normal range after meal consumption and during exercise as well. Specifically, the controller should be able to match the pancreas in three areas: the maximum and minimum glucose concentrations observed in response to the disturbance, the duration of hyper/hypoglycemic episodes, and the maximum insulin infusion observed.

These objectives were considered when designing different controllers for different patient models, using average parameters. First, the insulin infusion rate allowing glucose to remain at basal levels was determined. Then, beginning with a simple feedback algorithm, a controller was developed to try to satisfy the objectives with respect to a meal disturbance. If the controller type was not successful, a different type of controller was tested. If the controller was successful, it was then used to maintain glucose levels for exercise.

After the performance of the control strategies was determined, the model was investigated in order to determine why a given control strategy was or was not successful. With these investigations in place, different conclusions can be drawn regarding the ability to apply explicit process control to a diabetic patient.

Computational Methods

To perform the control simulations, three different computational steps needed to be performed. First, each dynamic model was programmed in order to simulate its behavior when no controller is present. Second, each control system was designed. Finally, the control system was implemented with each patient model in order for closed-loop simulations to be performed.

MATLAB was used to perform all simulations. The MATLAB function ode45 [29], which is based on the 5th order Runge-Kutta Dormand-Prince Pair, was used to solve the sets of differential equations. To determine the steady state insulin infusion rates, each state variable was set to zero, and the equations were algebraically solved to determine the basal state values. Given the basal state values, the basal infusion rate could easily be calculated from state equations involving insulin infusion.

For the Sorensen model, because of the nature of the equations, initialization required an iterative process. The insulin basal values of the diabetic patient are assumed to depend on the steady state infusion rate. The nature of the glucose equations are such that a plasma glucose value is needed to determine the glucose value of the other states. Thus, the iteration is performed for a specific infusion rate by guessing a plasma glucose value, using it to determine the initial values of glucose concentrations in the various tissues (liver, periphery, gut, etc.), and then using those values to determine if the plasma glucose values match. Sorensen [19] discusses it more fully, including iteration diagrams.

To design the PID controllers, FOPTD models were developed using the Microsoft Excel Solver to minimize the sum of squared residuals. Sorensen provided the FOPTD models for his diabetic patient model in reference [19]. As previously mentioned, the PID parameters were determined using reference [28]. PID control was implemented in MATLAB by treating $U(t)$ as the manipulated variable. Feedforward control and feedforward-feedback control were implemented using MATLAB Simulink. MPC was implemented using the Model Predictive Control Toolbox in MATLAB. To simulate the healthy patient response, the healthy patient Sorensen model was used.

Results

Generation of Healthy Patient Response

The healthy glucose and insulin responses for a 50 g oral glucose disturbance and an exercise session are given in Figure 7–Figure 9. The healthy model glucose response shows a maximum increase to slightly below 12 mmol/L. While this is high for a meal, it is a reasonable expectation for a glucose load of this size, as shown by oral glucose tolerance test (OGTT) data in literature [19,30]. As glucose levels fall, they fall slightly below 4 mmol/L before leveling off at the basal rate. All of this occurs within two hours of the ingested oral glucose load. The healthy patient exercise simulations in Figure 8 and Figure 9 show exercise periods of 30 minutes and two hours, respectively, at a moderate intensity of 60% VO_2^{max} . As the figures show, the glucose level stays above the hypoglycemic realm during and after exercise. Glucose levels fall slightly initially as the blood flow rates change. This is followed by a sharp rise in glucose resulting from the rapid increase in glucose production relative to uptake. After exercise, a short spike is observed as the blood flows return to normal. This is followed by a sharp drop resulting from total glucose production decreasing much faster than total uptake. As uptake rates return to normal, the steady state condition is approached. Thus, the control objectives become the following: keep glucose levels between 3.8–12 mmol/L, return to normal levels within two hours, and keep insulin infusion near the upper limit of 150 mU/min.

Control of Glucose Using the Minimal Model

Using the model parameters of Table 1, the steady state insulin infusion rate to maintain glucose levels at 4.5 mmol/L was determined to be approximately 16.667 mU/min. Note that for $P_I = 0 \text{ min}^{-1}$, the model assumes that only insulin-dependent uptake occurs. As such, any glucose in excess of what the current insulin infusion can act on will simply remain in the circulation. In this way, the glucose compartment of a Type I diabetic patient can be considered similar to a storage tank.

Figure 10 shows the simulation of a diabetic patient ingesting 50 g of glucose orally with only the basal infusion of insulin to enhance glucose uptake. Upon ingestion, the glucose concentration approaches a new steady state at approximately 28 mmol/L. When insufficient insulin is available to enhance glucose uptake, nothing beyond the basal glucose uptake will occur. Because glucose-dependent uptake is assumed to be non-existent, the additional glucose is simply added to the circulation, as in the situation in which more of a substance is added to a storage tank.

Figure 11 shows the glucose response to a step change in the insulin infusion rate. Within the investigated time frame, the unit increase in insulin infusion causes a continuous linear decrease in glucose. The glucose level reaches zero in approximately 10,000 minutes, as shown in Figure 12. A result of these phenomena is that the system behaves as an integrating system during the observation period, as noted by the large time constant. The parameters of the FOPTD model are given in Table 4, as are the PID control parameters. The glucose response to the 50 g glucose ingestion with the tuned PID controller is shown in Figure 13. The two lines included in the glucose plot represent the upper and lower limits observed by a healthy patient in response to the same glucose input. The controller gain and derivative time were maximized to decrease the glucose excursion to as small in magnitude as possible. The integral time of 3300 minutes essentially eliminates integral action. The addition of integral action results in heavy oscillations in the glucose response that often results in severe hypoglycemia being realized, as well as steady state offset. At the optimal control configuration, the glucose excursion still rises above the specified upper limit. The insulin infusion rate had no upper limit, and the resulting infusion rate of nearly 600 mU/min is not sufficient to prevent the excursion. The

infusion rate is clearly above the rate of the healthy patient and may be infeasible as an upper limit for an infusion pump.

Given the relatively poor performance of PID control to effectively control the glucose response, at even high infusion rates, feedforward control was employed in order to provide control before the glucose excursion is realized. Because the feedforward controller design equation is based on process and disturbance variable transfer functions, the minimal model was subjected to a step increase in the disturbance variable, and a first order plus time model was estimated from the response. The model parameters are given in Table 4. Because there is no time delay in the disturbance model, the resulting feedforward equation would be physically unrealizable, as the negative delay implies the controller responds in anticipation of a disturbance that has yet to be measured. The controller is approximated by adding the 30 minute process delay to the time constant to get the following feedforward controller, which is physically realizable.

$$G_{ff} = \frac{1.08 \times 10^5 (3331s + 1)}{6.44(1.08 \times 10^5 s + 1)} \quad (31)$$

Figure 14 shows the glucose response with feedforward control only, and Figure 15 shows the response when feedforward control is implemented with a PID controller to provide control of both the excursion and the glucose levels. As Figure 14 shows, because the controller is based only on the disturbance, there is no counter-regulation as glucose is falling to prevent hypoglycemia. In addition, the gain is still not large enough to prevent the excursion, and it appears that infusing insulin in response to the oral glucose at the time of appearance does not offer any advantages to PID control. Figure 15 shows that as PID control is implemented with feedforward control, a tradeoff exists between approaching hypoglycemia and approaching hyperglycemia. The originally developed feedforward controller, when used in conjunction with PID control, prevents the hyperglycemia excursion, but at the cost of severe hypoglycemia. Because this can lead to coma or death, such an occurrence is not an option in design. To prevent this from happening, the feedforward controller gain was reduced by two orders of magnitude, and the results are nearly identical to those of PID control alone. Therefore, feedforward control appears to offer no advantages to PID control.

Finally, the nonlinear pancreas model of Sorensen [19] was used to simulate a controller that emulates human behavior. It should be noted, however, that an investigation of the pancreas model reveals that pancreatic insulin release is simply being modeled as a nonlinear proportional-plus-derivative (PD). Nonetheless, given its success in predicting OGTT responses in healthy patients, it was employed in its exact form, as shown in Figure 16. Both hyperglycemia and severe hypoglycemia are predicted, meaning that either the Sorensen pancreas is not an accurate portrayal of the healthy pancreas, or that certain shortcomings of the minimal model prevent it from being controlled, even by natural means.

There are shortcomings to the minimal model that may render control impossible. First is the assumption that P_1 is zero for a Type I diabetic patient. This parameter set was given by Furler et al. [16] and has been used by other control engineers, including Fisher [7], Ollerton [8], and Bequette [17,18]. As previously mentioned, this implies that glucose can neither be produced nor taken up independently of insulin. Both Sorensen and Hovorka assume that glucose can contribute to uptake and production in the absence of insulin, and both models are preferred to the minimal model today. Allowing P_1 to be nonzero would naturally lead to increased glucose uptake at high insulin, as well as increased production at low insulin. This leads to the large time constants when fitting the FOPTD models. Also problematic with the minimal model is that the single kinetic rate coefficient for all insulin binding, P_3 , is consistently on the order

of 10^{-4} min^{-1} , a full two orders of magnitude slower than other processes. This leads to the time delays seen with the FOPTD regressions. Sorensen and Hovorka improve upon this by including multiple action terms, which allow certain processes to occur much quicker than others, as binding is not considered slow for each process. From a control standpoint, this could be overcome by being able to adjust the manipulated variable before the disturbance is encountered, such as through the priming bolus that nearly every successful control implementation with the minimal model has used. This could also be used to provide feedforward control if the controller was able to measure the disturbance in real time, but the disturbance was subject to some time delay that prevented it from affecting glucose immediately. Physiologically, this may be what the incretins, especially glucagon-like peptide-1, are actually doing. Perhaps by being released in response to glucose in the gut, and then causing insulin release, insulin is being released into the blood before the glucose has been passed from the GI tract.

Control of Glucose Using the Sorensen Model

The Sorensen model for a diabetic patient is unique in that the steady state conditions are a function of the steady state infusion rate. This is in contrast to the minimal model, in which a specific rate is given for a specific basal set of conditions, and the integrating behavior of the model results in the rapid increase or decrease in glucose concentration. To remain consistent, the basal condition of 4.5 mmol/L and 15 mU/L were chosen for glucose and insulin respectively. Trial and error was then used to determine which steady infusion rate yielded this basal condition. The basal insulin infusion was found to be approximately 21.45 mU/min.

Figure 17 shows the Sorensen model glucose response to a 50 g glucose source. By inspection of the figure, two things are evident. First, there is no integrating behavior, as the glucose level is restored to normal in spite of only the basal insulin. This shows that glucose is able to mediate uptake independently of insulin. Second, the excursion is minimal, already lower than any controller was able to achieve for the minimal model. Given the relatively low magnitude of the excursion, the first type of control attempted was simply proportional control, without any integral or derivative action. The response with this controller is shown in Figure 18 with a controller gain of 13 (mU/min)/(mmol/L). The Sorensen model is easily controlled using the simplest control algorithm that can be developed. Neither hyper- nor hypoglycemia are ever approached, and the maximum insulin infusion is less than even the maximum of the pancreas model used to describe a healthy patient.

The ease at which the Sorensen model is controlled can be explained by an investigation of the model glucose response at steady state with no insulin infusion, as shown in Figure 19. Given no insulin, the Sorensen model predicts a glucose concentration below 10 mmol/L. In reality, untreated Type I diabetic patients typically achieve glucose levels between 20 and 70 mmol/L [30]. Given this discrepancy, the Sorensen model appears to overestimate the effect of glucose levels on the body's glucose uptake rates into liver and muscle cells, as less insulin is required to bring glucose to a certain level than is expected in a patient.

Mathematically, these shortcomings appear in the liver glucose uptake equations and curve fitting of Sorensen's development work [19]. First, an investigation of the Sorensen model plots of the effect of glucose on uptake shows that the data does not fit the mathematical representation, with the model predicting nearly twice the glucose uptake than what was observed in data for high glucose values. Second, data were not used to fit the insulin contribution to uptake. Assumptions based on canine studies were used to develop the equation specifying that tripling the insulin concentration results in a doubling of the uptake rate over time. Finally, a plot of the predicted uptake vs. actual uptake shows a poor fit, in which the predicted uptake is usually greater than the actual uptake observed.

These shortcomings are not listed to say that the Sorensen model is incorrect. As shown by the author during model validation, the healthy patient model fits healthy patient data very well. However, it is the observation of the authors that the approximation of the pancreas-removed healthy patient model as a diabetic patient model is not adequate. This approximation has been used to demonstrate control success in several instances. However, given the observed results, nothing beyond proportional control should be needed, as it provides adequate control against meal disturbances. Given the ease of control and the possible physiological shortcomings, the Sorensen model was not used in further studies.

Control of Glucose Using the Hovorka Model

The steady state initial condition was determined by defining the basal glucose level, and then setting each dynamic equation to zero. The basal insulin infusion was found to be 7.3 mU/min. Given the basal condition, the model glucose response to the 50 g glucose ingestion with a basal amount of insulin being provided is shown in Figure 20. Like the Sorensen model, glucose mediated uptake does appear to play a role in naturally decreasing glucose levels in response to the input. However, the process is more gradual than that shown by the Sorensen model, implying that role of glucose in uptake is not emphasized as strongly as it is by the Sorensen model.

Given the small magnitude of the glucose excursion, proportional control was initially employed to try to control the process described by the Hovorka model. The results are shown in Figure 21. Simple control based only on a proportionality of the glucose residuals is shown to be all that is needed for tight glucose control. Neither hyper- nor hypoglycemia are approached, and glucose values are brought to normal very rapidly. Figure 22 and Figure 23 show the controller's ability to regulate glucose during 30 minutes and two hours of moderate ($PVO_2^{\max} = 60$) exercise, respectively. It appears that a new steady state is reached after exercise. As the exercise duration is increased, the new steady state is increasingly lower, with hypoglycemic steady state levels approached during the two hour simulation. Mathematically, this results from the glucose uptake rate dynamics being modeled much slower than the rate used in the exercise model used with the Sorensen model. The result is that the increased uptake levels do not restore themselves as rapidly as they would if the Sorensen model was used to create the exercise model. If the model parameters were modified to match the physiological considerations used in Parker's exercise model fit with the Sorensen model [25], this offset would not occur, as the glucose levels would return to normal much faster.

The ease of control with the Hovorka model brings into question the validity of the model. By comparison, several works previously mentioned employed proportional control with additional features of derivative and/or integral action [3,11], and these algorithms suffered shortcomings, including not being able to maintain normal glucose levels as effectively as the simulations presented. Furthermore, Hovorka himself focuses a great deal of his efforts toward the use of advanced controllers in the patient setting [13,14]. Predictive and adaptive controllers would not be necessary if all glucose control was completely possible simply using a proportional algorithm.

In addition, if the model is indeed accurate, then how inaccurate can the Sorensen model actually be when very similar simulation results were produced? One major difference between the models is that when insulin is removed, the glucose concentration becomes steady at 22.4 mU/L for the Hovorka model, a quantity that is consistent with physiological observations. So whether the Hovorka model is inaccurate or not, the Sorensen model still has fundamental issues that should be resolved before its use is acceptable.

One noticeable characteristic of the Hovorka model is the use of relatively low insulin infusions to achieve a certain glucose level. The basal insulin level calculated for this Hovorka model is

considerably smaller than the values determined for the minimal and Sorensen models, as well as the reported average values of basal secretion from the pancreas [30]. In addition, the amount of insulin used to reject the glucose disturbance was less than a third of the insulin secretion of the healthy pancreas model used by Sorensen. Based on these findings, the Hovorka model may have a problem with overpredicting the effects of insulin on metabolism. One difference between the model of Hovorka and the model used in this work is that Hovorka's model is based on subcutaneous infusion, whereas the control simulations assume intravenous infusion. This difference was accounted for by eliminating time constants associated with insulin transport from the subcutaneous tissue to the blood. It may be possible that the over prediction of insulin loss during the subcutaneous infusion may cancel the overprediction of action from the actual plasma insulin. All control simulations and their characteristics used to assess performance are summarized in Table 5.

Conclusions

Control of glucose during an ingestion of an oral glucose load was simulated using the minimal model, the Sorensen model, and the Hovorka model. Using the minimal model, no method of closed-loop control proved effective at keeping glucose levels below a hyperglycemic limit without also experiencing severe hypoglycemia. These results may result from assuming no glucose-dependent uptake or production of glucose. The assumption of a single insulin action that is characterized by very slow kinetic rates results in long time delays for the model. With the Sorensen model, control can easily achieved by simply using proportional control. However, given the relatively low glucose values at zero insulin, as well as the poor agreement between liver glucose uptake data and the Sorensen uptake model, the Sorensen model adapted for Type I diabetic patients has physiological shortcomings that prevent the simulation results from being considered accurate. Using the increasingly popular Hovorka model for control simulations resulted in proportional control being highly effective at maintaining normal glucose levels in response to both a meal and exercise. However, the ability of low insulin levels relative to pancreatic secretion to effectively control glucose brings up the possibility that the Hovorka may overestimate the role of insulin in glucose metabolism.

Assuming that Hovorka's model is indeed accurate, explicit-closed loop control appears to be a feasible method of use in the treatment of insulin dependent diabetes mellitus. However, such control will depend on other factors, including the development of effective implantable sensors and an implantable infusion pump. In addition, the ability of the controller to handle measurement noise, sensor time delays, and delays in the changing the pump flow rate will also have to be investigated.

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APPENDIX

HOVORKA MODEL EQUATIONS

Mass Balances

Glucose

$$\frac{dQ_1(t)}{dt} = - [F_{01}^C(t) + x_1(t)Q_1(t)] + k_{12}Q_2(t) - F_R(t) + U_G(t) + EGP_0[1 - x_3(t)] \quad (\text{A.1})$$

$$\frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t) \quad (\text{A.2})$$

$$G(t) = \frac{Q_1(t)}{V_G} \quad (\text{A.3})$$

Insulin

$$\frac{dI(t)}{dt} = \frac{U(t)}{V_I} - k_e I(t) \quad (\text{A.4})$$

Insulin Action

$$\frac{dx_1(t)}{dt} = -k_{a1}x_1(t) + k_{b1}I(t) \quad (\text{A.5})$$

$$\frac{dx_2(t)}{dt} = k_{b1}x_2(t) + k_{b2}I(t) \quad (\text{A.6})$$

$$\frac{dx_3}{dt} = k_{c1}x_3(t) + k_{c2}I(t) \quad (\text{A.7})$$

Metabolic Sources and Sinks

$$F_{01}^C(t) = \begin{cases} F_{01} & G \geq 4.5 \frac{\text{mmol}}{L} \\ \frac{F_{01}G(t)}{4.5} & G < 4.5 \frac{\text{mmol}}{L} \end{cases} \quad (\text{A.8})$$

$$F_R(t) = \begin{cases} 0.003(G(t) - 9) & G \geq 9 \frac{\text{mmol}}{L} \\ 0 & G < 9 \frac{\text{mmol}}{L} \end{cases} \quad (\text{A.9})$$

$$U_G(t) = \frac{M_{meal}A_G t \exp\left(-\frac{t}{t_{max}}\right)}{t_{max}^2} \quad (\text{A.10})$$

Figure 1. Flow diagram of the Sorensen insulin model [3]. Material flow is represented by the arrows. The dotted lines represent an interface at which mass transfer between intercompartmental spaces can occur. The solid line within a compartment represents a barrier that prevents intercompartmental mass transfer.

Figure 2.
Flow diagram of the Sorensen glucose model [3].

Pancreatic
Glucagon Release
(r_{PGR})

Plasma Clearance
(r_{PGU})

Figure 3.

Flow diagram of the Sorensen glucagon model [3]. Arrows represent inflow and outflow of material through a compartment. The dotted lines represent an interface for mass transfer for the two compartmental spaces of the glucagon compartment.

Figure 4. Schematic diagram of a PID feedback control process. At a point where two arrows intersect, the plus or minus indicates that the particular signal is being added or subtracted at the junction. The output signal is compared to the setpoint, and a PID control action is taken based on this measurement to produce U. U and the disturbance both interact with the process to result in the new output value.

Figure 5. Schematic of a feedforward control process. The plus signs at the intersection of arrows means the two signals are added. The controller output, U , is determined by the disturbance. The process then interacts with both the disturbance and the output variable to produce the system output.

Figure 6. Schematic of combined feedforward and feedback control. The feedforward control signal is determined for a measurement of the disturbance, and the feedback control signal is based on output signal error relative to the set point. The two signals are combined to give $U(t)$, the process input. The process interacts with the input and the disturbance to produce the output signal, Y .

Figure 7.

Sorensen model simulated response of a healthy patient to a 50 g oral glucose load ingested at $t = 60$ min. Glucose is expected to rise to nearly 12 mmol/L, fall to slightly below 4 mmol/L, and return to basal rate within 2 hours of ingesting the load. The insulin infusion rate rises sharply to 150 mU/min before sharply falling and giving a proportional 2nd phase response.

Figure 8.

Simulation of healthy patient glucose and insulin responses to a thirty-minute session of moderate ($60\% \text{VO}_2^{\text{max}}$) exercise. Exercise begins at 160 minutes and stops at time 190 min. Maximum glucose rise is between 5 and 5.2 mmol/L, while lowest point on the profile is greater than 4 mmol/L, so hypoglycemia is never observed. Insulin peaks at 60 mU/min, in response to increased hepatic production and higher peripheral blood flow.

Figure 9. Simulation of healthy patient glucose and insulin responses to a thirty-minute session of moderate (60% VO_2^{max}) exercise. Exercise begins at 160 minutes and stops at time 280 min. Maximum glucose rise is between 5 and 5.5 mmol/L, while lowest point on the profile is greater than 3.6 mmol/L, so hypoglycemia is never observed. Insulin peaks under 80 mU/min, in response to increased hepatic production and higher peripheral blood flow.

Figure 10.

Minimal model glucose profile of a Type I diabetic patient ingesting a 50 g glucose sample. Ingestion begins at 200 minutes. In the presence of no additional insulin beyond the basal infusion, the patient approaches a new steady state glucose concentration in the hyperglycemic realm.

Figure 11.
Glucose response of the minimal model to a unit step increase in the insulin infusion rate.

Figure 12.
Long-term glucose response of the minimal model to a unit step increase in the insulin infusion rate.

Figure 13.

PID-controlled glucose response of the minimal model to a 50 g glucose ingestion at time 200 min. $K_c = 12$ (mU/min)/(mmol/L), $\tau_I = 3300$ min, and $\tau_D = 40$ min.

Figure 14.
Minimal model simulation of feedforward-controlled glucose response to 50 g glucose ingestion at time 200 min.

Figure 15.

Minimal model simulation of feedforward-feedback-controlled glucose response to 50 g glucose ingestion at time 200 min. The line with x's shows the original feedforward controller, while the solid line shows the modified controller developed by reducing the controller gain to prevent hypoglycemia.

Figure 16. Minimal model glucose response to a 50 g glucose ingestion with pancreatic type controller. The horizontal lines on the top graph show the upper and lower glucose limits for good control.

Figure 17.

Sorensen Model glucose response to 50 g glucose ingestion at time 200 min. The horizontal lines in the top graph represent the upper and lower limits for good glucose control.

Figure 18.

Sorensen model proportional-controlled glucose response to 50 g glucose ingestion at time 200 min. The horizontal line on the top graph represents the lower limit glucose concentration to prevent hypoglycemia. The upper limit is the top of the graph.

Figure 19.
Sorensen model glucose steady-state response when there is no insulin being infused.

Figure 20.

Hovorka model glucose response to 50 g glucose ingestion. Insulin is infused at a constant rate to keep the insulin concentration at the basal level. The two horizontal lines in the upper graph show the upper and lower limits of glucose to prevent hyper- and hypoglycemia.

Figure 21. Hovorka model proportional-controlled glucose response to a 50 g glucose ingestion. The lower glucose limit for good control is given by the horizontal line on the top graph.

Figure 22.

Hovorka model proportional-controlled glucose response to moderate exercise. Exercise intensity level is at 60% of VO_2^{max} , and is 30 minutes in duration. Neither the upper nor the lower glucose limits can be seen on the screen, as they are both outside the range of the data.

Figure 23.

Hovorka model proportional-controlled glucose response to moderate exercise. Exercise intensity level is at 60% of VO_2^{max} , and is 120 minutes in duration. For the longer duration, the two models predict the approach of a steady state in the hypoglycemic realm.

Table 1

Minimal Model Patient Parameters For Type I Diabetic Patients [2]

Parameter	Value	Units
P_1	0	min^{-1}
P_2	0.025	min^{-1}
P_3	0.000013	$\text{L mU}^{-1} \text{min}^{-2}$
n	5/54	min^{-1}
V	12.0	L
G_b	4.5	mmolL^{-1}
X_b	0	Min^{-1}
I_b	15	mUL^{-1}

Table 2

Model Parameters For the Exercise Models For Minimal Model [8] and Sorensen Model [9]

Parameter	Model	Value	Units
a_1	Minimal	6.11×10^{-4}	$\text{mmol L}^{-1} \text{min}^{-1}$
a_2	Minimal	0.9	min^{-1}
a_3	Minimal	5.56×10^{-8}	$\text{mmol L}^{-1} \text{min}^{-1}$
a_4	Minimal	7.22×10^{-6}	$\text{mmol L}^{-1} \text{min}^{-1}$
a_5	Minimal	0.00002	min^{-1}
a_6	Minimal	0.00025	$\text{mU L}^{-1} \text{min}^{-1}$
a_7	Minimal	0.009	min^{-1}
τ_{EX}	Minimal	5/3	min
τ_{EX}	Sorensen	5/4	min
τ_{EGU}	Sorensen	30	min
$ePGU_a (PVO_2^{max} = 8)$	Sorensen	0	$\text{mg min}^{-1} \text{kg}^{-1}$
$ePGU_a (PVO_2^{max} = 30)$	Sorensen	32	$\text{mg min}^{-1} \text{kg}^{-1}$
$ePGU_a (PVO_2^{max} = 60)$	Sorensen	85	$\text{mg min}^{-1} \text{kg}^{-1}$
$Q_G^L (PVO_2^{max} = 30)$	Sorensen	9.8	dL min^{-1}
$Q_G^L (PVO_2^{max} = 60)$	Sorensen	6.1	dL min^{-1}
$Q_G^K (PVO_2^{max} = 30)$	Sorensen	8.1	dL min^{-1}
$Q_G^K (PVO_2^{max} = 60)$	Sorensen	5.3	dL min^{-1}
$Q_G^P (PVO_2^{max} = 30)$	Sorensen	50.6	dL min^{-1}
$Q_G^P (PVO_2^{max} = 60)$	Sorensen	99.1	dL min^{-1}

Table 3**Pancreas Model Parameter Definitions and Values**

Parameter	Definition	Value	Units
r_{PIR}	Pancreatic Insulin Release Rate		$mUmin^{-1}$
r_{PIR}^B	Pancreatic Insulin Release Rate (Basal)		$mUmin^{-1}$
S	Secretion Rate		$Umin^{-1}$
G_H	Arterial Glucose Concentration		$mgdL^{-1}$
Y, X	Intermediate variables		dimensionless
I	Inhibitor		dimensionless
P	Potentiator		dimensionless
Q	Labile Insulin		U
M_1	Model Parameter	0.00747	min^{-1}
M_2	Model Parameter	0.0958	min^{-1}
β	Model Parameter	0.932	min^{-1}
α	Model Parameter	0.0482	min
Q_0	Model Parameter	6.33	U
K	Model Parameter	0.00747	min^{-1}
γ	Model Parameter	0.575	$Umin^{-1}$

Table 4

First Order Plus Time Delay (FOPTD) and PID Tuning Parameters

Parameter	Value	Units
K	-4.5	mU L mmol ⁻¹ min ⁻¹
τ	2139	min
θ	49	min
τ_c	30	min
K_c	12	mU L mmol ⁻¹ min ⁻¹
τ_I	3300	min
τ_D	40	min
K (disturbance)	1.36×10^6	mU L mmol ⁻¹
τ (disturbance)	1.35×10^6	min
θ	22	min

Table 5

Summary of Controller Assessment

Model	Control Method	Max glucose < 12 mmol/L	Min Glucose > 3.9 mmol/L	Max Insulin Infusion < 150 mU/min
Minimal	PID	No	Yes	No
Minimal	Feedforward	No	No	No
Minimal	FF/FB	No	Yes	No
Minimal	Physiologic	No	No	No
Sorensen diabetic patient	Proportional	Yes	Yes	Yes
Hovorka	Proportional	Yes	Yes	Yes

Table A-1**Hovorka Model Variable Definition**

Variable	Definition	Units
G	Plasma Glucose Concentration	mmolL ⁻¹
Q ₁	Glucose Mass In Compartment 1	mmol
Q ₂	Glucose Mass In compartment 2	mmol
F ₀₁	Insulin-indep. Glucose Flux	mmol (Lmin) ⁻¹
F _R	Renal Glucose Clearance	mmol (Lmin) ⁻¹
U _G	Glucose Absorption Rate	mmol (Lmin) ⁻¹
I	Plasma Insulin Concentration	mU L ⁻¹
x ₁	Insulin Action On Glucose Transport	min ⁻¹
x ₂	Insulin Action on Glucose Uptake	min ⁻¹
x ₃	Insulin Action on Glucose Production	min ⁻¹

Table A-2**Hovorka Model Parameter Definitions and Values**

Parameter	Definition	Value	Units
K_{12}	Transfer Rate	0.066	min^{-1}
k_{a1}	Deactivation Rate	0.006	min^{-1}
k_{a2}	Deactivation Rate	0.06	min^{-1}
k_{a3}	Deactivation Rate	0.03	min^{-1}
k_{b1}	Activation Rate	$3.07\text{e-}5$	min^{-1}
k_{b2}	Activation Rate	$4.92\text{e-}5$	min^{-1}
k_{b3}	Activation Rate	$1.56\text{e-}4$	min^{-1}
k_e	Insulin Elimination From Plasma	0.138	min^{-1}
V_I	Insulin Distribution Kinetics	0.12	L kg^{-1}
V_G	Glucose Distribution Volume	0.16	L kg^{-1}
A_G	Carbohydrate Bioavailability	0.8	unitless
t_{maxG}	Time to Maximum Absorption	40	min
EGP_0	Insulin Independent Glucose Prod.	0.0161	$\text{mmol kg}^{-1} \text{min}^{-1}$
F_{01}	Insulin-Independent Glucose Flux	0.0097	$\text{mmol kg}^{-1} \text{min}^{-1}$