Active Insulin Infusion Using Optimal and Derivative-Weighted Control

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ABSTRACT

Close control of blood glucose levels significantly reduces vascular complications in Type I diabetes. A control method for the automation of insulin infusion that utilizes emerging technologies in blood glucose biosensors is presented. The controller developed provides tighter, more optimal control of blood glucose levels, while accounting for variation in patient response, insulin employed and sensor bandwidth. Particular emphasis is placed on controller simplicity and robustness necessary for medical devices and implants.

A PD controller with heavy emphasis on the derivative term is found to outperform the typically used proportional-weighted controllers in glucose tolerance and multi-meal tests. Simulation results show reductions of over 50% in the magnitude and duration of blood glucose excursions from basal levels. A closed-form steady state optimal solution is also developed as a benchmark, and results in a flat glucose response. The impact and tradeoffs associated with sensor bandwidth, sensor lag and proportional versus derivative based control methods are illustrated. Overall, emerging blood glucose sensor technologies that enable frequent measurement are shown to enable more effective, automated control of blood glucose levels within a tight, acceptable range for Type I and Type II diabetic individuals.

Keywords: Diabetes, Optimal Control, Automated, Insulin Infusion, Sensor Lag

1. INTRODUCTION

If not managed properly, diabetes can lead to complications such as nerve damage, brain damage, amputation and eventually death. Diabetes related complications are a worldwide

epidemic with high medical, economic and social costs [1-3]. Tight control of blood glucose levels has also been shown to reduce the mortality of diabetic, and non-diabetic, intensive care unit patients by up to 50% [4]. Diabetic individuals monitor food intake and daily activity to maintain blood sugar levels at an adequate level. For ease of management, subjects are encouraged to stick to strict routines and diets to minimize manual monitoring and injections, reducing intervention and difficulty. This regime can lead to severe limitation of the subjects' lifestyle, an "institutional" psychology, and the difficulty of consistently maintaining a strict daily regimen over several years.

Though devices that can measure glucose level and administer insulin exist, they do just that – measure and inject - with no automated interface between the two. A diabetic individual is required to carry out the procedures manually, introducing drudgery and the error due to human miscalculation and limitations. Hence, a system that automatically monitors and controls a diabetic individual's blood sugar level allows the patient to more fully engage in the "normal" routines of life with reduced risk of long-term adverse end-results.

Current treatments for Type I diabetes involve monitoring the plasma glucose level and injecting insulin as needed. Normally, patients follow a strict regimen to prevent complications, however the effectiveness of this regimen is a function of the patient's intuition and experience. A typical day for a diabetic individual might involve injecting long-acting insulin approximately three times and injecting rapid-acting insulin before meals, to reduce the post-prandial blood glucose spike. The patient is required to make intuitive decisions when they deviate from normal diet or exercise patterns, and modify their regimen to suit the irregularity. As a result, error is introduced and control is often not optimal, even for conscientious patients.

Most commonly available glucose sensing devices operate by measuring the blood glucose content of a small finger-prick blood sample, an irritating method upon frequent use. As a result, some diabetic individuals measure blood sugar as infrequently as once per day, or less. However, recent advances have resulted in semi-invasive systems such as the GlucoWatch Biographer from Cygnus [5]. This device offers sampling rates up to one reading every 20 minutes, and can measure and store data continuously for up to 12 hours before new sensor pads are required.

This research develops optimal and robust control algorithms for the automated infusion of insulin to Type I and Type II diabetic individuals. Wireless technology, insulin pumps, embedded computation and emerging non-invasive glucose monitoring systems may be interconnected and a closed loop control system realized. Ultimately, an effective control system should be able to automate over 95% of a diabetic individual's regular insulin care, freeing them from significant stress and to better handle any exceptions that arise. The potential for future implementation(s) of an implanted artificial pancreas is investigated in terms of the feasibility of the interface and the tradeoffs between control performance, and sensor and actuator limits.

Current diabetes management typically seeks to limit blood glucose levels to be less than 5.8-6.0 mmol/L, however tighter control to the basal level of 4.5 mmol/L would significantly limit the damage that can result from long-term exposure to elevated blood glucose levels. Such relaxed higher blood glucose levels are considered acceptable, as blood glucose management without automation does not typically deliver the data, or the ability to constantly modify insulin infusion rates, necessary for tighter control. In addition, regular,

automated blood glucose measurement provides the consistent volume of data necessary for such tight control, in contrast to the sometimes infrequent and inconsistent self-measurement reported by clinicians. Automation can have a significant impact on the treatment of juveniles with Type I diabetes where children have less ability to fully manage the disease and, as a result, the stress and difficulty of management can fall on parents and others. In all cases, an automated approach can provide clinical staff with a far greater abundance, and consistency, of data, and the resulting ability to provide better treatment and feedback.

Whether it is in the area of understanding, modeling or managing diabetes [6,7] years of research in this area has led to no shortage of theoretical solutions [8-17]. However, due to either the complexity of the proposed implementation, current technological limitations, models that are not physiologically verified, lack of required data, or the cost/complexity of realizing the results, these solutions are not yet practicable.

Several researchers have examined the analysis and automation of insulin administration as reviewed by Lehman et al. [18]. Many of the systems presented use control as a means of providing clinical advice or testing the efficacy of a new protocol [19-24]. A more complex, higher performance real-time control example uses model predictive control on a 19th order model of the glucose-regulatory system resulting in a 40% peak reduction and 23% reduction in settling time to basal level [25]. Optimal control using grid search theory, robust H-infinity control, and variable structure controllers have also been studied, each using different models [11, 24-28]. In each case, the focus has been on controlling absolute blood glucose excursion rather than slopes. The models used typically require either patient specific parameters that are not generically available, and/or knowledge of glucose or exercise inputs that would not

be known a priori. Finally, none study the impact of more frequent measurement enabled by recent advances in sensing technology or the potential for improved results.

The following sections present the physiological model employed, the optimal control solution and the heavy derivative PD controllers developed. Subsequent sections examine the impact of sensor bandwidth, sensor lag and other forms of error.

2. MODEL OF THE GLUCOSE REGULATORY SYSTEM

Models of the glucose regulatory system can be categorised as either comprehensive or simple models. Comprehensive models, though they are very accurate in regimen evaluation, are generally unsuited for real-time control, requiring several time points of input to generate the insulin infusion profile. Additionally, they are not generic requiring patient-specific data and known glucose inputs. The aim of this research is to develop control schemes based on models that capture the essential system dynamics, do not require unavailable data, and are applicable to a wider variety of subjects. Simple models capture these essential dynamic behaviours, providing a more suitable for real-time control design and analysis.

A well known, and more importantly, physiologically verified model originated from the work of Bergman et al. [15]. It utilises the concept of a remote compartment for the storage of insulin to account for the time delay between injection of insulin and its utilization to reduce blood glucose levels. Equations (1)–(3) show the equations used to define the system.

$$\dot{G} = -p_1 G - X(G + G_B) + P(t) \quad (1)$$

$$\dot{X} = -p_2 X + p_3 I \quad (2)$$

$$\dot{I} = -n(I + I_B) + u(t)/V_I \quad (3)$$

where :

G = concentration of the plasma glucose above the basal level. ($mMol\ L^{-1}$)

G_B = basal level for plasma glucose concentration ($mMol\ L^{-1}$), i.e. G + G_B is the total glucose in the blood plasma, where G_B = 4.5 typically

X = utilization effect of insulin in a remote compartment (min^{-1})

I = concentration of the plasma insulin above basal level ($mU\ L^{-1}$)

I_B = basal level for plasma insulin concentration ($mU\ L^{-1}$)

$P(t)$ = exogenous glucose infusion rate ($mMol\ L^{-1}\ min^{-1}$)

$u(t)$ = exogenous insulin infusion rate ($mU\ L^{-1}\ min^{-1}$)

p_3 = subject dependant model parameter ($mU^{-1}\ L\ min^{-2}$)

V_I = insulin distribution volume (L)

n, p_1, p_2 = subject dependant model parameters (min^{-1})

The parameters, p_1, p_2 and p_3, may be changed to represent different conditions of the glucose regulatory system. For diabetic subjects:

$$p_1 = 0,\ p_2 = 0.025,\ p_3 = 0.000013 \quad (4)$$

These and other parameters are obtained from medical research [10,13,15].

The model in Equations (1)-(3) is a revised version of works by Bergman *et al.* [15] and Furler et al. [14]. It was developed for modelling insulin sensitivity, a measure of how

efficiently the body responds to an insulin input after taking a glucose tolerance test. The model is simple, yet accurately represents the essential dynamics of the human glucose regulatory system for a variety of patients.

The three equations represent insulin production and infusion, insulin storage in a remote compartment, and glucose input and insulin utilization in a second compartment. Insulin inputs are either endogenous from the pancreas, or exogenous from a pump or injection and are represented in Equation (3). Equation (2) defines the dynamics and delay in the transport of insulin from the subcutaneous layer to the blood plasma and subsequent utilization. Equation (1) represents the glucose levels in the blood stream and the dynamics of its reaction with insulin. Figure 1 graphically outlines the glucose regulatory dynamics for the model of Equations (1)-(3).

The values of n, V_I, G_B, I_B employed for all simulations are defined, for an average-weighted male, as follows [10]:

$$V_I = 12 \text{ L}, n = 5/54 \text{ min}^{-1}, G_B = 4.5 \text{ mmol L}^{-1}, I_B = 15 \text{ mU L}^{-1} \quad (5)$$

The controller uses a simple feedback loop that employs the blood glucose level above basal, G, and its' derivate, $\dot{G}$, as sensor inputs, and the exogenous insulin infusion rate, $u(t)$, as the control output. Glucose deviation from basal levels, G, and its slope, $\dot{G}$, are the only data readily available to control the system. As a result, the controller measures the output from Equation (1) while directly influencing the dynamics in Equation (3) via the control action. In between are the time delay and additional dynamics of the remote compartment represented in Equation (2).

To verify the model the controller output is set to zero, with $p_1=0.028$, $p_2=0.025$ and $p_3=0.000013$ to model normal human response [8], and simulated with an initial plasma glucose level of $G(0) = 15$ *mmol/L* including the basal contribution. The results shown in Figure 2 match the results obtained for a normal subject [11, 14]. The insulin infusion plot represents insulin produced by the pancreas as the controller output is zero and normal human response is enabled by the parameters selected. Note that the Plasma Glucose Concentration graph shows the amount of glucose in the blood in units of mmol/L of glucose above the basal level. The basal level is the fasting amount of glucose typically maintained in the absence of additional glucose input. As expected, Figure 2 shows that when a normal person has blood glucose above the basal level the pancreas acts to produce insulin to return the blood sugar to the basal level. The transition is smooth over approximately 180 minutes (3 hours) with no hypoglycemic overshoot.

3. DERIVATION OF CONTROL SCHEMES

In this section, three control schemes are presented, one closed-form semi-optimal solution and another two input-output forms where the control input is not a direct function of the model parameters, but determined by measured outputs.

There are many complex influences between glucose and insulin concentration for any person, normal or diabetic. However, the steady state glucose concentration in the body is mainly determined by how much insulin is present. In order to lower glucose concentration in the blood, insulin needs to be released, injected or infused. Hence, the controller defines the insulin infusion rate, $u(t)$, based on the measured inputs G and $\dot{G}$. The goal is to minimise

excess glucose, G, and its rate of change, $\dot{G}$, and ensure that excursions from the basal value, G_b, are minimised in magnitude and duration with no hypoglycemic overshoot below the basal level.

Sustained blood glucose levels of around 8 mmol/L, or more, can result in significant physiological damage. A value below G_B can lead to loss of consciousness and, if large enough, possible brain damage. Therefore, blood sugar levels must be maintained in a tight range around the basal level, minimizing the size and duration of excursions in either direction. This approach matches the concept that the ideal blood glucose curve for a reasonable glucose input is typically considered to be relatively, if not completely, flat [3].

3.1 Relative Proportional Control (RPC)

One of the better-known, more effective diabetes control systems is relative proportional control (RPC) [10]. This basic, widely used form of proportional control law is based on the idea of strictly limiting the absolute blood sugar level by applying resisting "forces" (insulin) in weighted proportion to the magnitude of the excursion from the desired (basal) level. The control inputs are defined:

$$u(t) = u_0\left(1 + \frac{G}{G_b}\right), \qquad u_0 = nVI_b \tag{6}$$

This controller is based on a relative proportional control (G/G_b) with a constant term. In this case, there is no input based on the derivative, or rate of change, of blood glucose level $\dot{G}$.

Note that when $G = G_b$ the blood sugar is at the desired level and the insulin infusion rate is u_0, the basal infusion rate necessary to maintain blood glucose at a constant level.

3.2 Optimal Control

Since the model employed represents the essential dynamics of the human glucose regulatory system, the optimal solution for *u(t)* can be obtained analytically. First, Equation (3) is solved and the exact solution for *I(t)* determined in terms of the exogenous insulin infusion *u(t).*

$$I(t) = I_B\left(e^{-nt} - 1\right) + \frac{e^{-nt}}{V_I}\int_0^t e^{nt'}u(t')dt' \tag{7}$$

Similarly, using Equation (2), the solution for *X(t)* is obtained in terms of *I(t)* and using Equation (7) can be directly expressed in terms of *u(t).*

$$X(t) = \frac{p_3 I_B}{p_2 - n}\left(e^{-nt} - e^{-p_2 t}\right) + \frac{p_3 I_B}{p_2}\left(e^{-p_2 t} - 1\right) + \frac{p_3}{V_I\left(p_2 - n\right)}\int_0^t u(t')\left\{e^{-n(t-t')} - e^{-p_2(t-t')}\right\}dt' \tag{8}$$

Since the goal is to minimize G and $\dot{G}$, the assumption of $G = \dot{G} = 0$ at steady state is applied to Equation (1) to obtain a steady state optimal solution, leaving:

$$P(t) = G_B X(t) \tag{9}$$

Substituting Equation (8) into Equation (9) and using the Laplace transform and its inverse, to simplify the convolution integrals, the optimal steady state exogenous insulin infusion profile is obtained:

$$u(t) = \frac{V}{p_3 G_b}\left[\ddot{P}(t) + \dot{P}(0) + (n + p_2)(\dot{P}(t) + P(0)) + np_2 P(t)\right] + u_0 \qquad (10)$$

The optimal solution includes first and second derivatives of the exogenous glucose input *P(t)*. However, it is unrealistic to implement since *P(t)* is not known a priori, and because it is not practical to remove insulin (or add glucose) as is suggested if some terms become negative. Equation (10) is also an explicit function of the time constants and other model parameters subjecting it to potential modelling error. This solution does act as a benchmark for the performance of other controllers.

Note that the steady-state insulin infusion without exogenous glucose input, $u(t) = nV_I I_B = u_0$, corresponds to the result obtained from Equation (10) if $P(t) = 0$. The optimal solution will provide an optimal insulin infusion profile for any case where the initial conditions match the steady state assumptions. However, the result also assumes continuous sensor measurement and feedback, rather than discretely spaced readings, which will influence simulation results.

3.3 Heavy Derivative PD Controller

The most effective controller developed, of several approaches, is a basic PD controller where heavy emphasis is placed on the derivative term.

$$u(t) = u_0\left(1 + k_p G + k_d \dot{G}\right) \tag{11}$$

This controller incorporates proportional and derivative control with independent weightings and the basal infusion u_0. Heavy emphasis implies that the derivative gain, k_d, is significantly larger than the proportional gain, k_p. As a result, this controller focuses almost exclusively on controlling the slope of the blood glucose curve rather than its absolute magnitude. This approach is a far different one than normally taken and made possible by the emerging capability to measure blood sugar far more regularly via semi- or non- invasive means.

There are several benefits provided by derivative emphasized control for this non-linear, delayed system. Most importantly, a large increase in glucose is observed before a large proportional term, enabling a faster response time for the controller. Derivative terms can be susceptible to noise, but in this case with appropriate filtering and technology it should not be an issue. More specifically, the use of low pass finite or infinite impulse response (FIR or IIR) filters, along with a variety of other well known filtering methods can be used to reduce noise arising from glucose measurement error. Such filtering should be relatively straightforward given the well-characterized measurement errors for approved glucose measurement methods. In addition, the sampling period, even at 1-20 minutes, is long enough to make additional measurements and average results if necessary. The only potential significant issue with filtering over several samples is the small lag, or delay, that can occur in the filtered signal.

4. NUMERICAL TESTS AND ALGORITHM VERIFICATION

This section presents results from several different simulation tests to determine the efficiency and effectiveness of these controllers in limiting blood glucose excursion and duration.

4.1 Oral Glucose Tolerance Test

The oral glucose tolerance test (OGTT) is a large step input test of the glucose regulatory system often performed to diagnose diabetes. A fasting subject consumes 400–800 kilocalories of glucose and the response is observed. This beta-cell function test represents a significant challenge to the pancreas.

The OGTT input may be modelled by the lognormal distribution curve defined in Equation (2) and shown in Figure 3.

$$P(t) = P_m e^{-a(\ln(bt)-c)^2} \tag{12}$$

Where P_m is the peak value and a, b and c are constants, which determine the slopes and curvature. This function is employed because it is smooth, continuously differentiable, and has zero initial conditions, making it easily implemented and physiologically representative. It is easily modified to represent faster or slower absorption rates of exogenous glucose.

Figure 4 shows the glucose response for a OGTT using the PD controller with sensor measurements every 1 and 20 minutes, and for the RPC system measuring every 20 minutes. The nearly flat optimal control result is shown as well. There is also a graph of no controller, labelled “Accumulation of glucose input”, which shows glucose input profile. Figure 5 shows the insulin infusion rate for the RPC and PD controller, where the step shape is due to the 20 minutes between sensor measurements and changes to the insulin infusion (control) input.

Note that the insulin infusion rate is smoother and more like an injection for the PD controller in both cases and particularly when sensor measurements are made every minute.

In judging controller performance the critical factors are the magnitude of the excursion for a given input and the time required to return to basal blood sugar levels. The PD controller limits the excursion and returns to the basal level much faster, in each case, due to the higher infusion rates generated by large initial slopes of the glucose curve.

As seen in Figure 4, the optimal controller has an almost flat response. The insulin infusion rate for the optimal solution is not shown, however, it is effectively an injection of approximately 3 units of insulin followed by a small glucose infusion over 25 mins. Though the optimal solution cannot be practically implemented, it does show that the optimal solution approaches current injection practice in a way that achieves near perfect glucose response given the controllers knowledge of the glucose input *P(t).*

Figure 5 also shows that as the sampling rate increases, the insulin infusion profile tends towards injections with the optimal solution resulting in an injection of 3 units at the beginning of the simulation. These results match current methods of managing diabetes that have evolved over time, where insulin is injected before meals.

Sensor bandwidth, or sampling period, is varied since the current *GlucoWatch* measures blood sugar levels every 20 minutes. The one-minute bandwidth graph shows what can be achieved when future technology allows measurements at this rate. Smaller sampling periods have less impact as the sampling period becomes small relative to system time constants that are larger than 1 minute.

The K_p and K_d gains for the PD controller are set at different values based only on the sensor bandwidth employed. The derivative term is emphasized due to its importance in enabling a faster response to rising blood glucose levels. As expected, with increasing sampling time the derivative emphasized PD controller performance deteriorates more than the relative proportional control as derivatives lose some usefulness as the sampling period grows.

4.2 Multi-Meal Tests

The input for these simulations is designed to give the system a more strenuous physiological test such as two meals within 6 hours. The inputs vary in magnitude from 50-400 calories and are given in two groups, at t = 0,10,30 minutes and for the second meal at t = 210 and 300 minutes. At the end of 6 hours, the total intake of glucose into the body is over 1000 calories with 1000 calories input over the first 4 hours. Figure 6 shows the glucose input profile for these meals and the results are shown in Figures 7-9.

Figure 7 shows that the PD controller works slightly better than a normal person, in terms of peak reduction as well as settling time with a sensor bandwidth of 1 minute. This result illustrates the potential of this controller to replace physiological dysfunction. Figure 7 also includes a plot of the response for a normal subject under the same conditions.

Figure 8 compares results at different sensor bandwidths and Figure 9 shows the insulin infusion profiles. These figures show similar trends to the OGTT results, where the more the insulin infusion profile tends towards injections, the better the control of blood sugar. For the optimal controller, inset in Figure 9 with a scaled glucose input profile, the insulin input is

essentially two injections closely following the onset of each meal. The optimal controller glucose curve in Figure 8 is nearly flat and as the sensor sampling period approaches zero this solution should not vary at all to glucose inputs.

It is worth noting that the RPC performance is relatively resistant to changes in sampling period from 1 minute to 20 minutes. The PD controller result almost doubles in magnitude and requires slightly more time to return to basal level. The PD controller with a sample period of 20 minutes also has a slightly hypoglycemic response where the graph dips just below the basal value.

The primary results from this testing are that the algorithm is robust to significant multiple inputs with the same gains as designed for OGTT inputs and that as sampling period decreases the insulin input profile for the PD controller approaches that of injections at the beginning of a meal input. This latter result tends to match current accepted clinical practice for the management of Type I diabetes in New Zealand and elsewhere. In particular, the PD controller with derivative weighting provides a basal input, u_0, in the absence of elevated blood sugar and leads to injection-like insulin infusion profiles when glucose inputs are applied. In clinical practice low, basal insulin infusion is required to prevent diabetic ketoacidosis (DKA) in the absence of insulin in the system, while injections of rapid acting insulin are used to handle meals and other post-prandial glucose spikes. Basal levels are typically maintained, clinically, via long-acting insulin injections. As a result, the behaviour of the derivative weighted PD controller mimics current clinical practice that has evolved over several years with a basal infusion level augmented in injection like insulin infusion profiles for hyperglycemic events due to exogenous glucose input. Hence, there exists a great similarity between the insulin infusion profile for the PD and optimal controllers, and typical

clinical recommendations using current practice. The primary difference is that these controllers are able to effectively take advantage of a greater amount of blood glucose data using a model-based controller.

4.3 Sensor Lag

A *GlucoWatch* measurement lags approximately one sample period due to the method by which it obtains the value, and this lag is simulated with a 20 minute sampling period for the PD controller to determine its impact on control efficacy, with results shown in Figure 10. As expected, control response lags further allowing greater glucose excursions in both magnitude and duration. The RPC is also shown for reference along with the zero-lag PD controller.

4.4 Sensor Failure

There is a possibility of sensor failure where sweat or other interference may cause a measurement to be skipped. Figure 11 shows results for one and three successive sensor failures, with the PD controller and a 20 minute sampling period, occurring 30 minutes after the multi-meal simulation begins. The failures are timed for worst-case impact versus the glucose input profile. A single sensor failure results in an acceptable range in glucose control, however three successive failures results in a larger and longer excursion and greater hypoglycemic overshoot. In both the sensor lag and sensor failure case the results clearly indicate the over-reaction resulting from the delay in noting the rise in blood glucose level. These results delineate how reliable the sensors must be to ensure safety and performance.

4.5 Comparison of Control Methods

It is seen that the heavy derivative PD controller outperforms the RPC. Figure 12 shows the glucose response for the RPC controller with a variety of different proportional gains and a 20-minute sampling period. The RPC definition in Equation (6) has a gain of 1.0 on the relative proportional term. However, as the gain is increased for better peak performance hypoglycemic overshoot grows because even as the glucose levels are decreasing toward basal a proportional controller is still infusing insulin. The result is hypoglycemia due to over-insulinising a system with significant delay. Hence, simply increasing proportional gain is not a practicable solution.

Figure 12 also shows the curve associated with the PD controller, which is able to command significant insulin infusion earlier than a proportional dominated controller providing better peak response control and limiting hypoglycemic overshoot. Due to the large derivative gain the PD controller cuts the insulin infusion to zero when $\dot{G}$ is significantly negative it allows a more gentle drift back to the basal level when the glucose level starts dropping. This approach enables better control and, with greater sensor bandwidth, drives the control input to match current, effective diabetes management with infusion profiles that are essentially pre-meal injections with a basal infusion rate at other times.

Overall, the control methods presented are found to be both simple and effective. This control approach is less affected by patient specific parameters and as a result parameter variation is better tolerated. For example, the PD controller is simulated with parameters for a non-diabetic individual and the resulting exogenous insulin infusion is effectively zero. Different types of insulin however cause difficulty where the control gains are tuned

assuming insulin that acts in about 12 minutes, with faster or slower acting insulin employed in simulation.

5. CONCLUSIONS

The emergence of glucose sensors capable of providing blood glucose readings at a very high rate is investigated for their ability to automate insulin infusion for diabetic individuals. Such sensors open the possibility of controlling the slope of the glucose response curve, rather than focusing strictly on absolute blood glucose level. Two controllers are derived, consisting of an optimal solution and a simple PD controller where the derivative term heavily outweighs the proportional term. A proportional controller is also simulated to highlight the effectiveness of controlling the slope of the glucose curve rather than the absolute blood glucose level.

Oral glucose tolerance test and multi-meal inputs are employed to test the response of each controller for a variety of sensor sampling periods. The impact of different sampling periods, sensor lag, and the relative impact of proportional and derivative control is delineated to determine the limiting values necessary for practical implementation. An optimal control law is derived and used as a benchmark although it is not feasible for real-time implementation. The optimal solutions, simulated with 1-minute sampling period, are essentially flat, representing the limiting case for tight, active control of blood glucose levels.

The primary result is that a simple PD controller, heavily emphasising the derivative term, can effectively and robustly manage a variety of glucose input profiles slightly better than even a normal person. More specifically, the PD controller is shown to control glucose excursions up to 50% better than proportional-based control schemes and slightly better than the normal

human system as represented by the model employed. Finally, as the sampling period drops, the insulin infusion profiles for this type of PD controller mimic current diabetes management utilizing pre-meal injections and low infusions at other times, verifying the basic approach. As a result, far tighter control of blood glucose excursions from basal levels can be used to reduce the impact of long-term exposure to (slightly) elevated blood glucose levels. In addition, such an automated approach enables far more consistency in blood glucose management, particularly for juveniles or others who may not be responsible for managing their condition.

Further work is required to refine several aspects, including detailed study into robustly handling different types of insulin. In addition, further simulation of these controllers using more comprehensive models is required to further verify the methods developed. Finally, examining more complex controllers will further improve the controlled response and approach the optimal solution.

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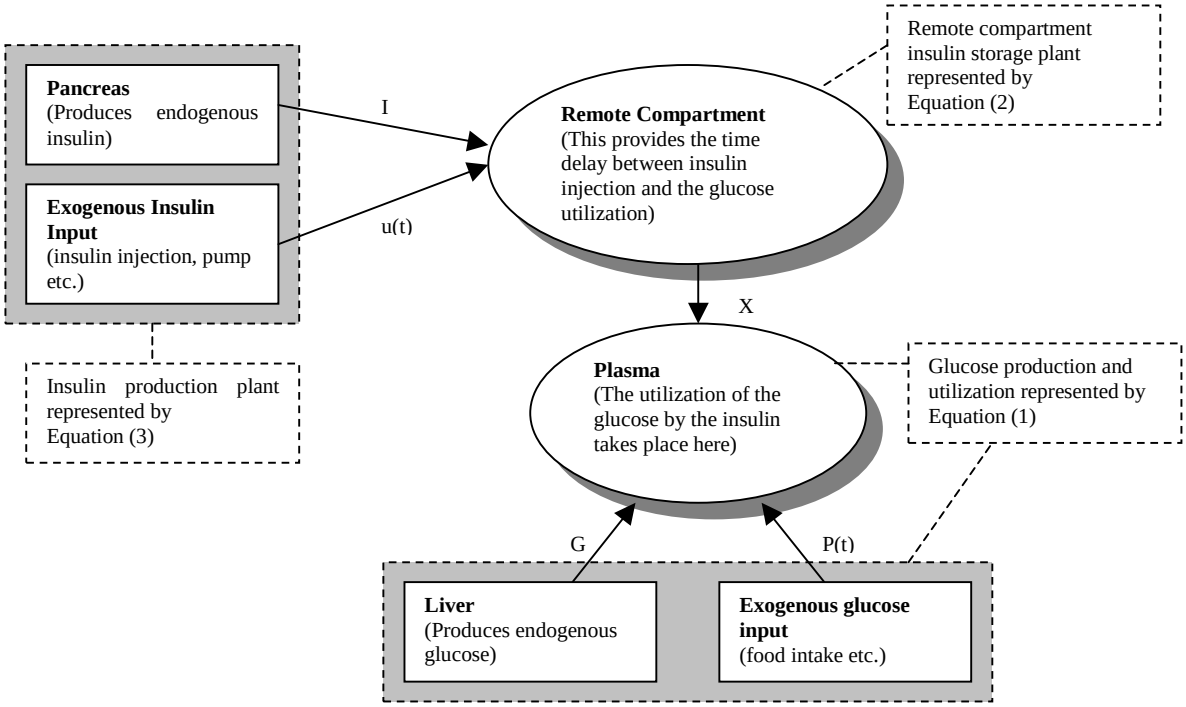

Figure 1: Diagram of the modelled dynamics for the human glucose regulatory system

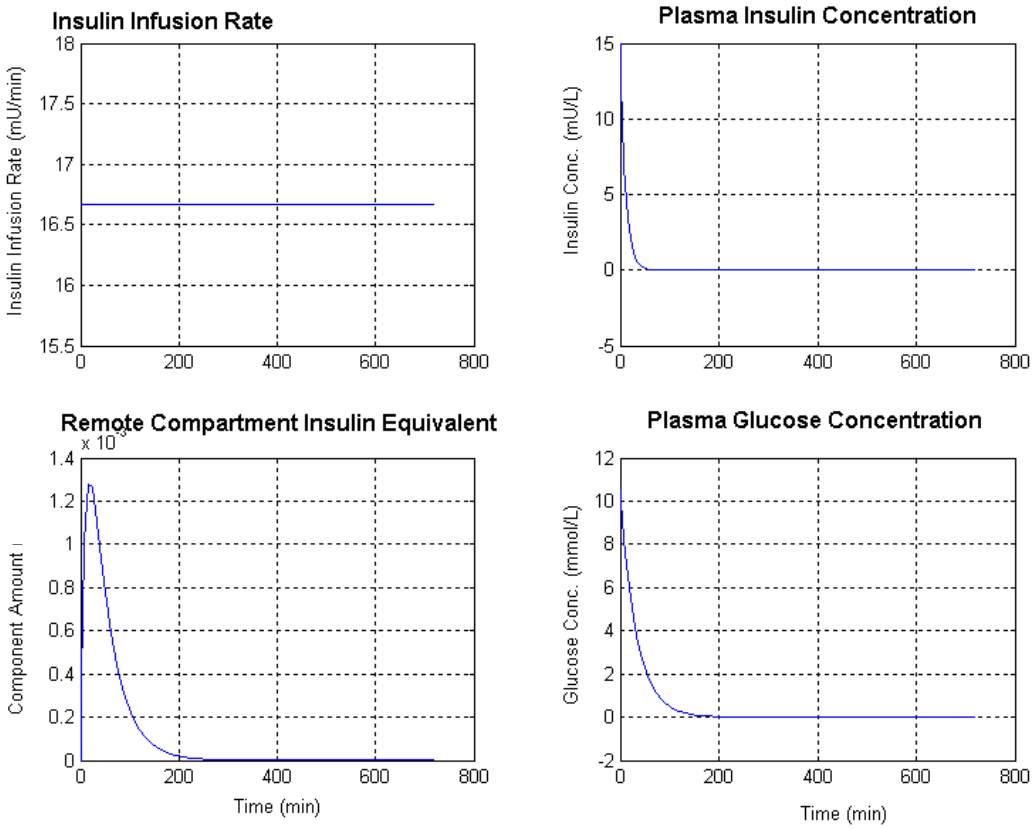

Figure 2: Response for a non-diabetic individual with $G(0)+G_b$ = 15 mmol/L.

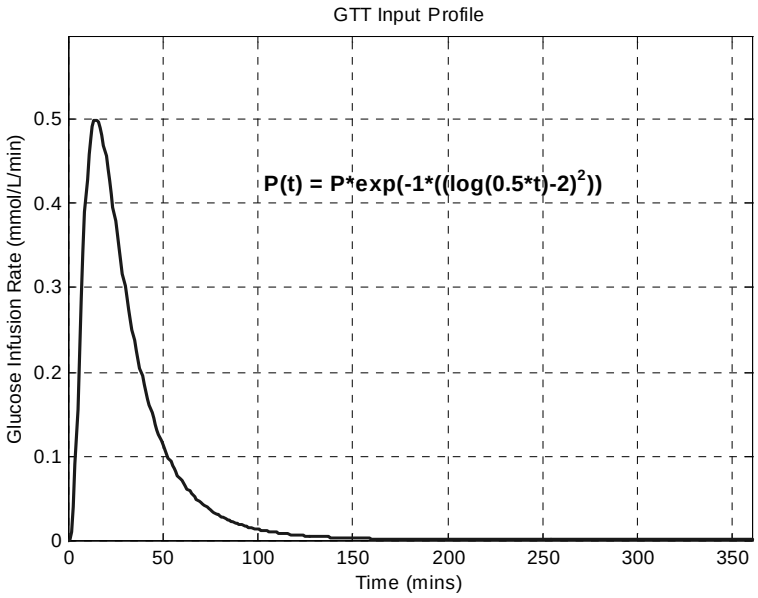

Figure 3: Glucose input model of OGTT curve used in simulations.

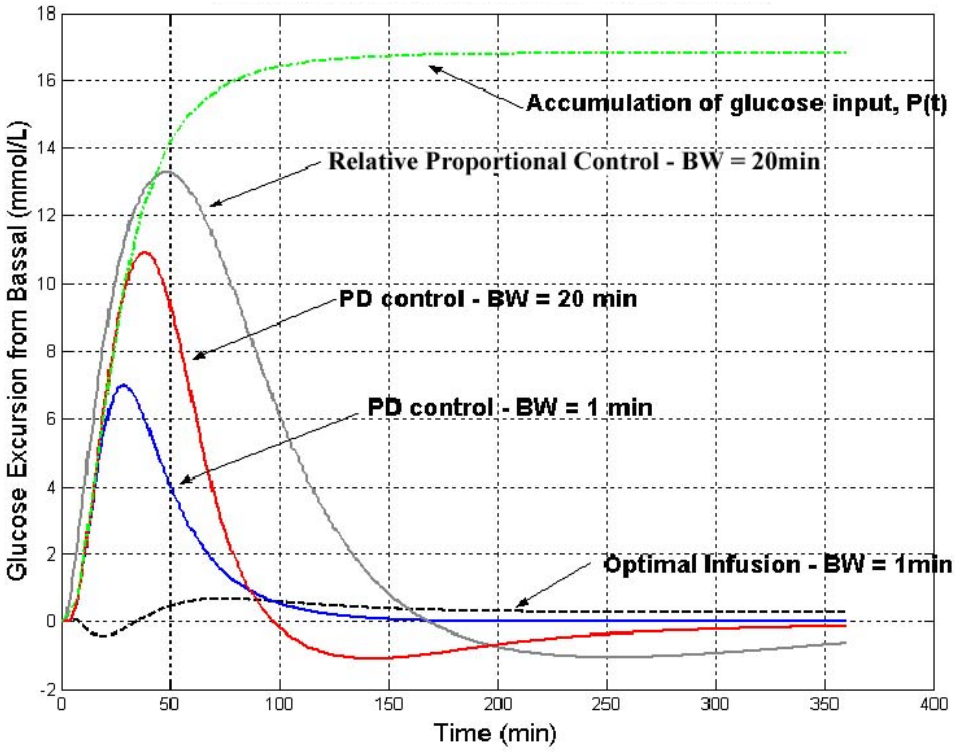

Figure 4: Glucose response for an OGTT.

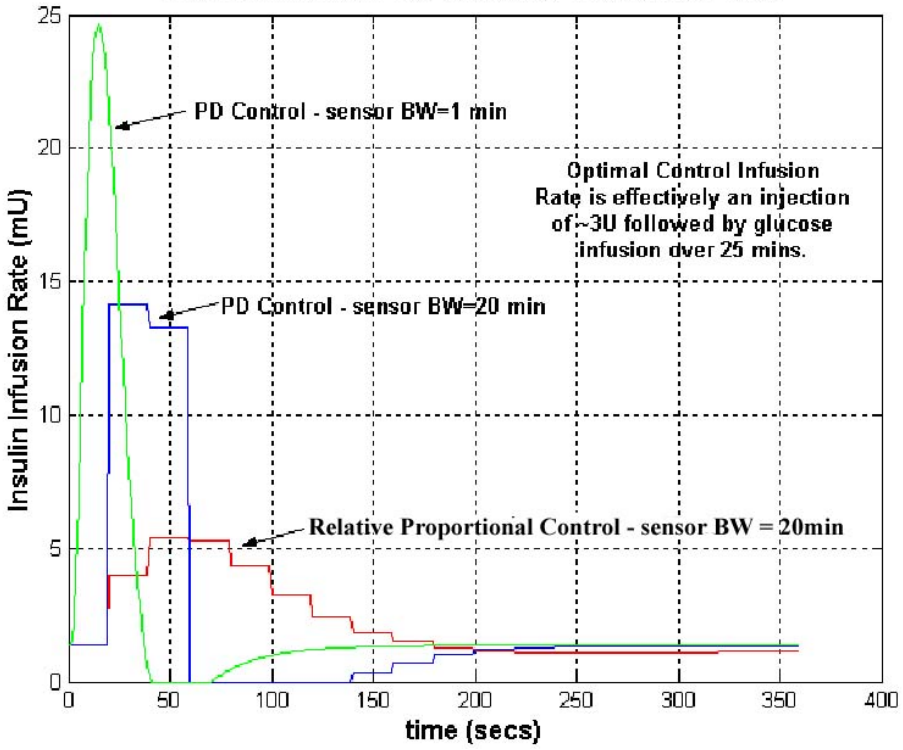

Figure 5: Insulin infusion rate for an OGTT

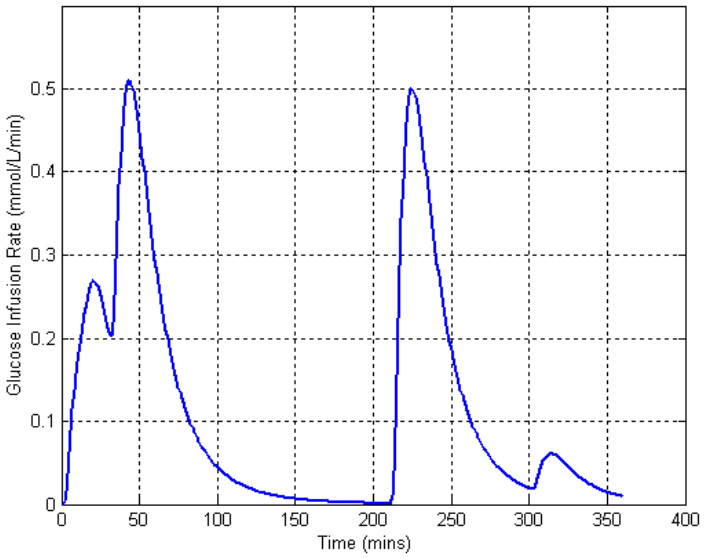

Figure 6: Multi-meal glucose input profile.

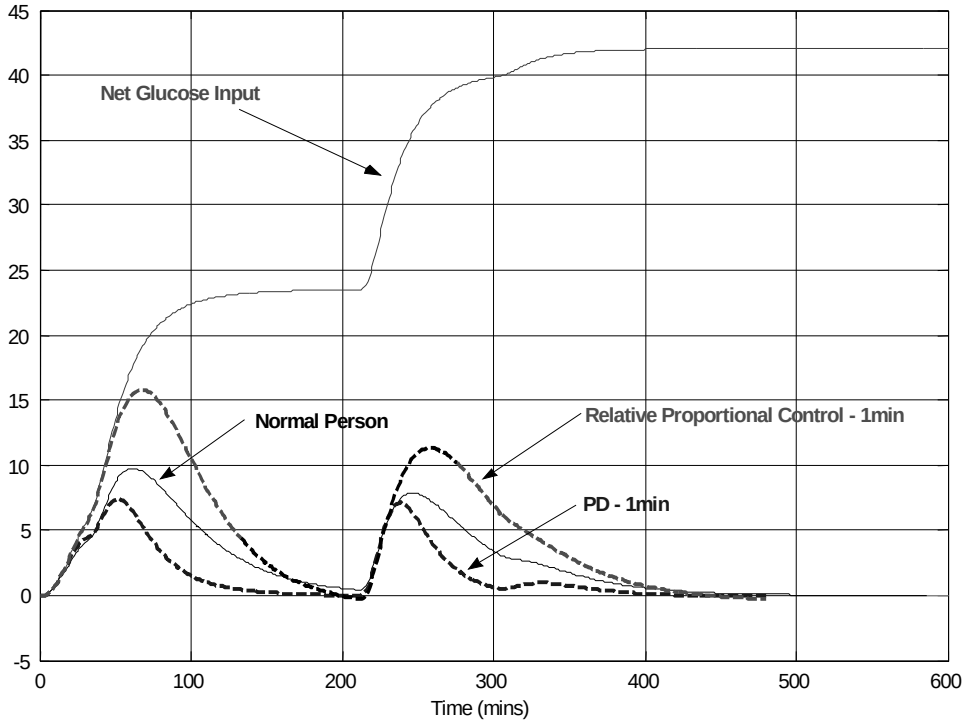

Figure 7: Glucose level of a normal human, and controlled diabetic individual with 1 minute sampling period for each controller type.

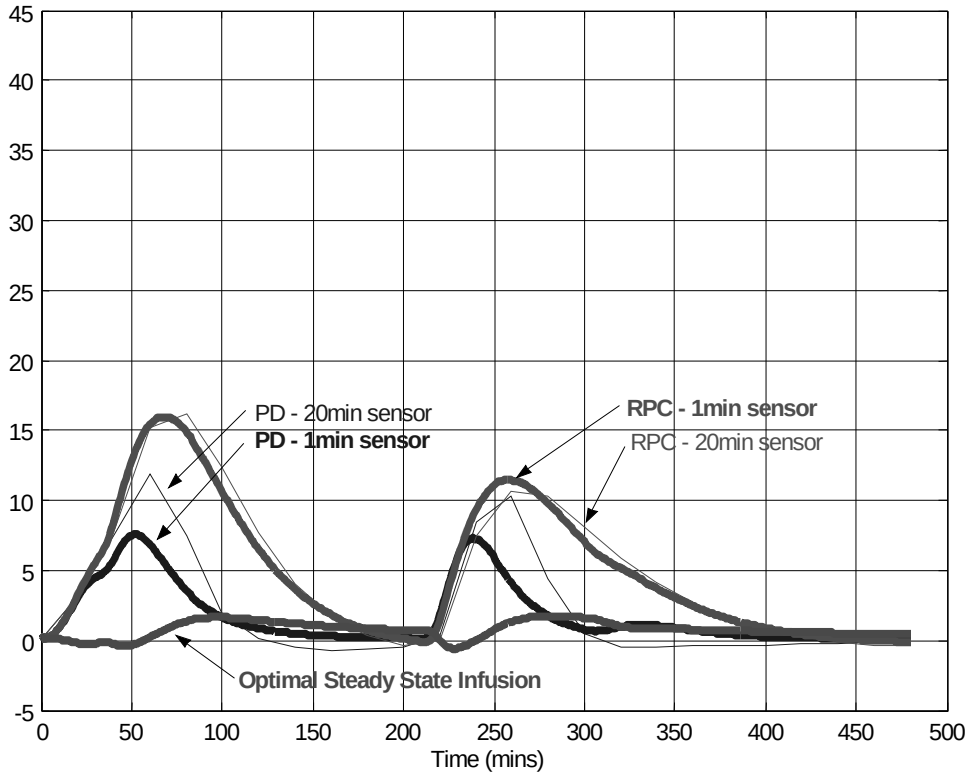

Figure 8: Multi-meal glucose level for controllers at different sampling periods.

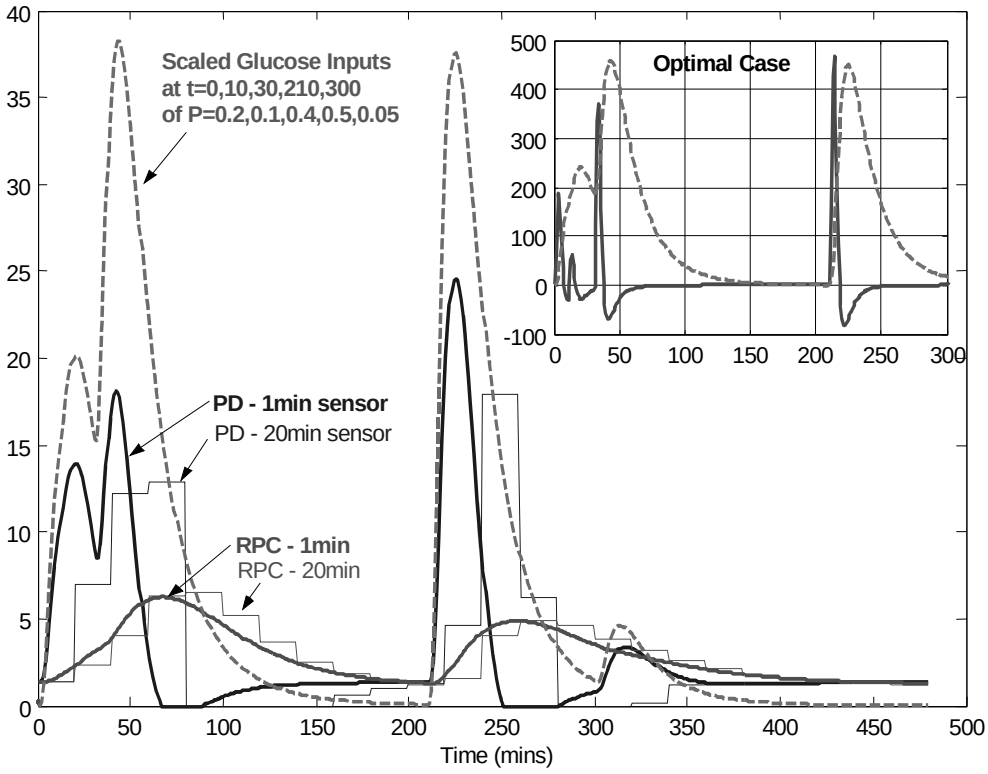

Figure 9: Infusion rate for controllers at different sampling periods for the multi-meal test.

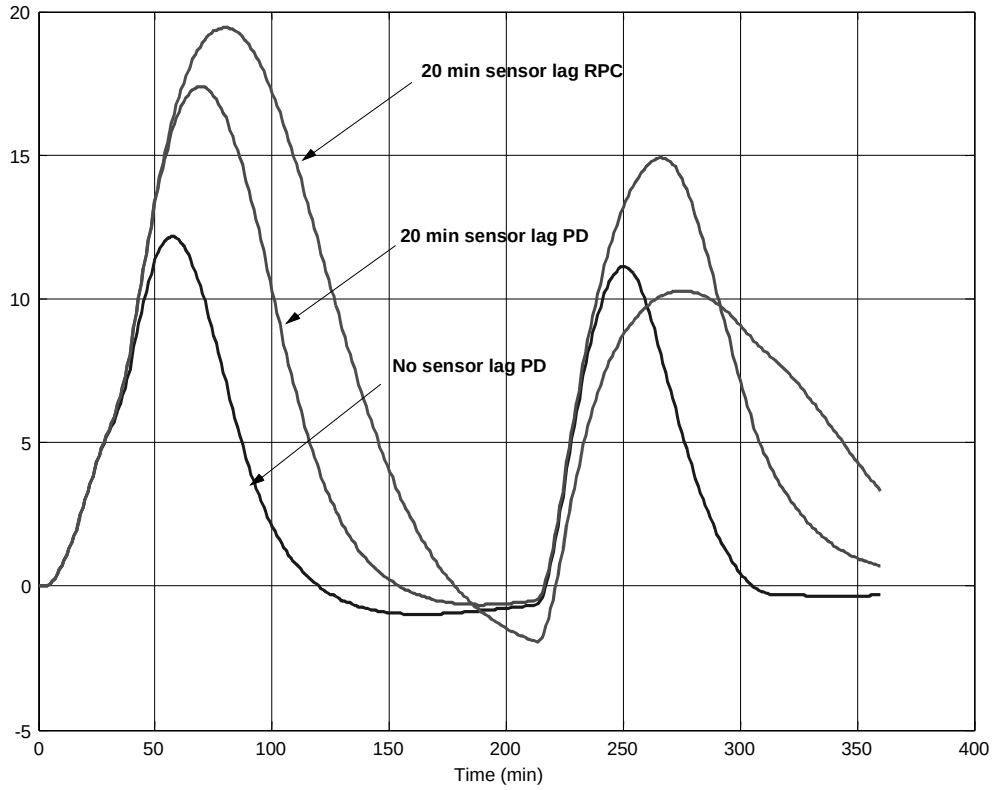

Figure 10: Glucose response with a 20 min sensor lag

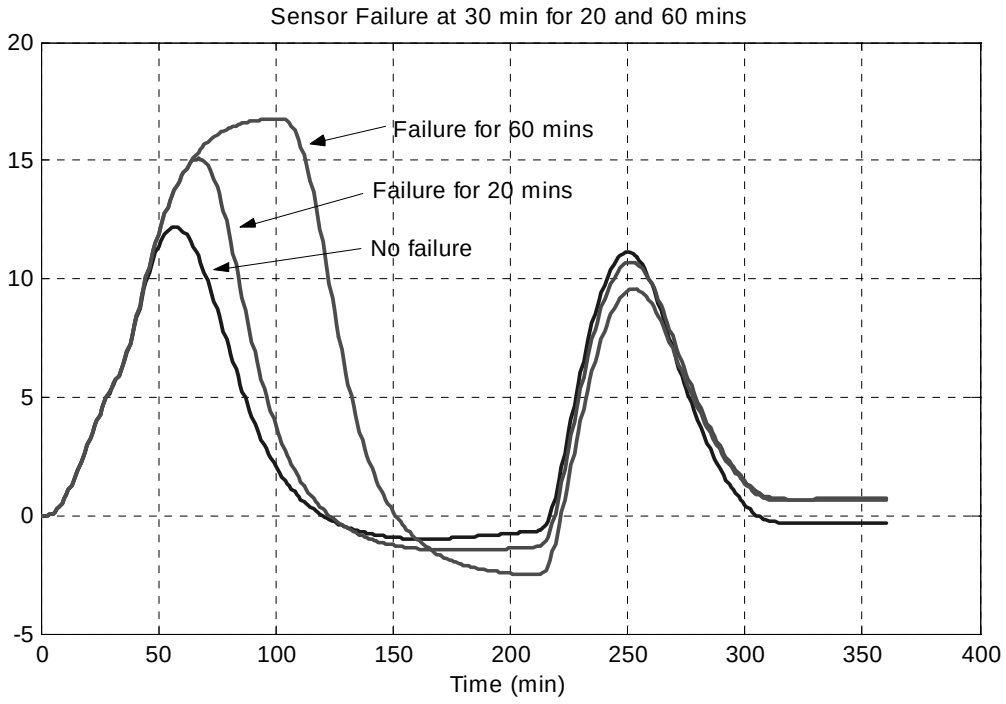

Figure 11: Results for the PD controller with 1 and 3 successive sensor failures, at 30 minutes, in the multi-meal test case.

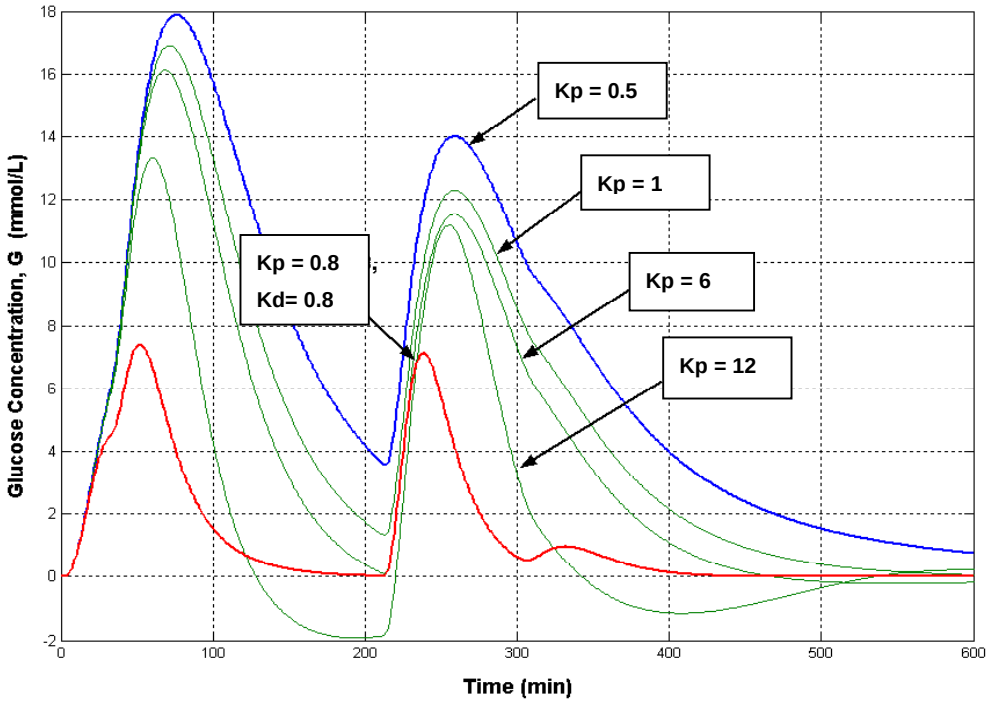

Figure 12: Glucose response of multi-meal testing for derivative and proportional controllers.