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Blood glucose regulation with stochastic optimal control for insulin-dependent diabetic patients

Saadet Ulas Acikgoz, Urmila M. Diwekar *

University of Illinois at Chicago, Department of Bioengineering, Chicago, IL, Vishwamitra Research Institute (VRI) - Center for Uncertain Systems: Tools for Optimization & Management (CUSTOM), Westmont, IL, USA

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ABSTRACT

Diabetes is a disease resulting from the impaired mechanism of insulin secretion from the pancreas, which prevents glucose from entering the cells and being utilized and leads to wide swings of blood sugar and many complications such as heart disease and stroke, kidney disease and amputations. In order to prevent these complications and achieve a better quality of life for diabetic patients, effective regulation of blood glucose is essential. This study aims to achieve a better blood glucose control profile by incorporating the time-dependent uncertainties in diabetic patient parameters into formulations of optimal control using a novel approach which originates from finance literature. The time-dependent uncertainties are represented using stochastic processes called Ito processes and the mathematical formulation for this problem is presented. The usefulness of this approach is shown using experimental data from a diabetic patient and stochastic and deterministic optimal control profiles are computed. The stochastic profile results in fewer variations in blood glucose from the reference value of 4.5 mmol/L as compared to the deterministic profile in the presence of parametric uncertainty. This method holds a lot of promise in reducing the wide swings of blood glucose observed in diabetic patients and preventing possible complications of diabetes.

1. Introduction

About 20.8 million people in the US suffer from diabetes, which has many complications such as heart disease and stroke, high blood pressure, kidney disease, nervous system disease and amputations. The hormone insulin has many functions in the body; most importantly it influences the entry of glucose into cells. The lack of insulin prevents glucose from entering the cells and being utilized and leads to excess blood sugar and excretion of large volumes of urine, dehydration and thirst. The current treatment methods for insulin-dependent diabetes include subcutaneous insulin injection or continuous infusion of insulin via an insulin pump. The former treatment requires patients to inject insulin four to five times a day. The amount of injection is usually determined by a glucose measurement, an approximation of the glucose content of the upcoming meal and estimated insulin release kinetics. The continuous insulin infusion pump allows for more predictable delivery due to its constant infusion rate into a subcutaneous delivery site. Keeping the blood glucose levels as close to normal (non-diabetic) as possible is essential for preventing diabetes related complications. Ideally this level is between 90 and 130 mg/dL before meals and <180 two hours after starting a meal. The Diabetes Control and Complications Trial Research Group (1993) followed 1441 people with diabetes for several years. This trial concluded that the patients who followed a tight glucose control program were less likely to develop complications such as eye disease, kidney disease and nerve disease, than the ones who followed the standard treatment, because the former group had kept the blood glucose levels lower.

The ideal treatment for controlling blood glucose levels in insulin dependent diabetic patients would be the use of an artificial pancreas which would have the following components: (a) a glucose sensor to monitor the blood glucose continuously with sufficient reliability and precision, (b) a computer to calculate the necessary insulin infusion rates by an appropriate feedback algorithm and (c) an insulin infusion pump to supply the required amount of insulin into the blood. Safe delivery of insulin in this way requires reliable glucose sensors. Two types of sensors have been developed during the last 30 years, minimal invasive and non-invasive (Koschinsky and Heinemann, 2001). The non-invasive approaches are carried out using optical glucose sensors. These sensors work by directing a light beam through intact skin and measuring the properties of the reflected light that are altered either as a result of direct interaction with glucose (spectroscopic approach) or due to the indirect effects of glucose by inducing changes in the physical properties of skin (scattering approach).

* Corresponding author.
E-mail address: urmila@vri-custom.org (U.M. Diwekar).

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However, these optical sensors are not able to measure glucose with sufficient precision. On the other hand, minimally invasive sensors measure the glucose concentration in the interstitial fluid of the skin or in the subcutis. There is a free and rapid exchange of glucose molecules and interstitial fluid. Therefore, changes in blood glucose and interstitial glucose are correlated. However, there is a time delay between these changes varying from a few seconds to 15 min; which complicates the interpretation of measurement results (Roe and Smoller, 1998). The magnitude of this delay depends on factors such as the absolute glucose concentrations and direction of change. This delay shows intra and inter-individual variability. Furthermore, it has been found that the absolute values of interstitial glucose concentrations vary between 50% and 100% of the intravasal value.

The wide-spread use of these glucose sensors is also complicated by biocompatibility issues and skin reactions. Also these sensors should be available at a reasonable cost in order to be applicable to insulin-dependent diabetic patients. The implementation of a closed loop system in daily life conditions requires these reliability, compatibility, cost and safety issues to be resolved.

The aim of this paper is to develop an optimal control system. Optimal control is different from a closed loop feedback control where the desired operating point is compared with an actual operating point and knowledge of the difference is fed back to the system. Optimal control problems are defined in their time domain, and their solution requires establishing an index of performance for the system and designing the course (future) of action so as to optimize a performance index. Therefore optimal control allows us to make future decisions. Using optimal control theory we can minimize the deviations of blood glucose from non-diabetic levels, while penalizing the use of large amounts of infused insulin for safety. Optimal control theory was applied to this problem in literature (Swan, 1982; Fisher and Teo, 1989; Fisher, 1991; Ollerton, 1989; Parker et al., 1999). However, uncertainties in model parameters and variability among different individuals were not considered in these papers. Recent published works in this field point out the difficulties in using a PID type controller due to the imprecision of the models for diabetic systems (Hernjak and Doyle III, 2005). Another recent publication uses a model-based control technique for regulating the blood glucose for patients with Type1 diabetes. The optimal insulin delivery rate is obtained off-line as an explicit function of the current blood glucose concentration of the patient using parametric programming (Dua et al., 2006).

The success of optimal control method depends on the accuracy of the model; therefore, the inherent uncertainties in the patient need to be addressed. If the uncertainties are omitted and if the model cannot accurately represent the glucose and insulin dynamics, this can lead to significant performance degradation. Significant variability of relevant parameters among patients and within a given patient during the course of the day or week has been reported in literature (Simon et al., 1987; Bremer and Gough, 1999). Meals and exercise, the age and weight of the patient also affect the insulin/glucose dynamics. These daily and hourly fluctuations of patient parameters can create difficulties in continuous glucose control. These dynamic uncertainties affect the optimal insulin infusion profiles.

The aim of this paper is to model these uncertainties by a novel approach and incorporating them into formulations of optimal control. Time-dependent uncertainties are commonly encountered in finance literature. Optimal investment rules and Ito's Lemma (Dixit and Pindyck, 1994; Merton and Samuelson, 1990) were developed for pricing options in financial markets, to generalize the Bellman equation or the fundamental equation of optimality for the stochastic case. This new equation constitutes the base of the so called real options theory. Although such a theory was developed in the field of economics, it was recently applied to optimal control problems encountered in other branches of science. For example, in chemical engineering literature, time-dependent uncertainties in batch processing and pharmaceutical separations were represented by Ito processes and time-dependent stochastic optimal control profiles were obtained. Using this approach, the performance of separation processes where stochastic optimal control was applied, has increased significantly as high as 69%. Using Ito processes, ideal and non-ideal systems were represented and thermodynamic parameter uncertainties associated with locally optimal parameter estimates as a result of nonlinear regression were addressed (Ulas and Diwekar, 2004; Ulas et al., 2005).

This approach could also be extended to optimal glucose control in insulin dependent diabetic patients. The blood glucose profiles can be represented using Ito processes and stochastic optimal control profiles could be derived to achieve better treatment for diabetes. The outline of this paper is as follows. Section 2 presents a mathematical model for glucose–insulin dynamics. Section 3 considers the uncertainties in diabetes glucose control and uses experimental data to estimate the model parameters for deterministic and stochastic models. In Section 4, the stochastic and deterministic optimal control problem formulation is presented and in Section 5 numerical results are shown. In Section 6, the implications of the results and the advantages of using the Ito processes and stochastic optimal control profiles are discussed. In Section 7, conclusions are presented.

2. Mathematical model for glucose–insulin dynamics

Perhaps the most commonly used control relevant model for glucose–insulin dynamics is the minimal model which was presented by Bergman et al. (1981). This model considers two subsystems (compartments) to represent glucose insulin dynamics and is given below:

$$\frac{dG}{dt} = -(\theta_1 + I_a)G + \theta_1 G_b + \frac{P(t)}{V_G} \tag{1}$$

$$\frac{dI_a}{dt} = -\theta_2 I_a + \theta_3 (I - I_b) \tag{2}$$

$$\frac{dI}{dt} = \frac{u(t)}{V_I} - nI \tag{3}$$

The initial conditions are: $G(0)=G_0$, $I_a(0)=I_{a0}$ and $I(0)=I_0$. In these equations G is the plasma glucose concentration, I is the plasma insulin concentration and I_a is proportional to the concentration of insulin in the remote compartment or the "active insulin pool". In Eqs. (1) and (3), $P(t)$ and $u(t)$ are the rates of infusion for exogenous glucose and insulin respectively. V_I is the insulin distribution volume, V_G is the glucose distribution volume and n is the fractional disappearance rate of insulin. The constants G_b and I_b are the basal values of plasma glucose and plasma insulin concentrations, respectively. The patient dependent model parameters are represented by θ_1, θ_2 and θ_3.

In this work, a physiological model based on the minimal model is used for optimal control problem formulation. This model was developed to provide a suitable framework to characterize the individual diabetic patients quantitatively and predict the blood glucose profile which is expected to be produced by an adjustment in the diet and/or insulin regimen (Lehmann and Deutsch, 1992). This model is called the automated insulin dosage advisor (AIDA) model and more information about this

model can be found in the website http://www.2aida.net/. The equations for this model are presented below.

In this model, the change in glucose concentration with time is given by the differential equation:

$$\frac{dG}{dt} = \frac{G_{in}(t) + NHGB(t) - G_{out}(t) - G_{ren}(t)}{V_G} \quad (4)$$

In this equation G is the plasma glucose concentration, NHGB is the net hepatic glucose balance, G_{in} is the systemic appearance of glucose via glucose absorption from the gut. G_{out} is the overall rate of peripheral and insulin dependent glucose utilization and G_{ren} is the renal excretion of glucose. V_G is the volume of distribution of glucose. The overall rate of glucose utilization is

$$G_{out} = \frac{G(c \cdot S_p \cdot I_{eq} + G_I)(K_M + G_X)}{G_X(K_M + G)} \quad (5)$$

In this equation a Michaelis–Menten relationship is assumed between glucose utilization and plasma glucose concentration with a constant K_M. G_I is the insulin dependent glucose utilization, G_X is a reference glucose level, S_p is a patient dependent model parameter, which represents the peripheral insulin sensitivity. The equations describing the insulin kinetics for the AIDA model are the same as the minimal model (Eqs. (2) and (3)). I_{eq} is the insulin level equilibrated with the steady state active insulin $I_{a,ss}$. The steady state active insulin is assumed to be the same as I_a (the insulin concentration in the remote compartment) since only rapid acting insulin preparations are considered in this paper. Therefore we can write

$$I_{eq}(t) = p_2 * I_a(t)/p_3 \quad (6)$$

Another patient dependent model parameter S_h, which represents the hepatic sensitivity is used to determine the net hepatic glucose balance (NHGB), which depends on the glucose concentration G and effective insulin level ($S_h * I_{eq}$). The data for NHGB is summarized in Fig. 1.

The glucose input G_{in} via the gut wall following a meal is modeled by

$$G_{in} = k_{abs} \cdot G_{gut} \quad (7)$$

$$\frac{dG_{gut}}{dt} = G_{empt} - k_{abs} \cdot G_{gut} \quad (8)$$

In these equations G_{gut} is the amount of glucose in the gut following a meal, G_{empt} is the rate of gastric emptying, k_{abs} is the rate constant of glucose absorption from the gut.

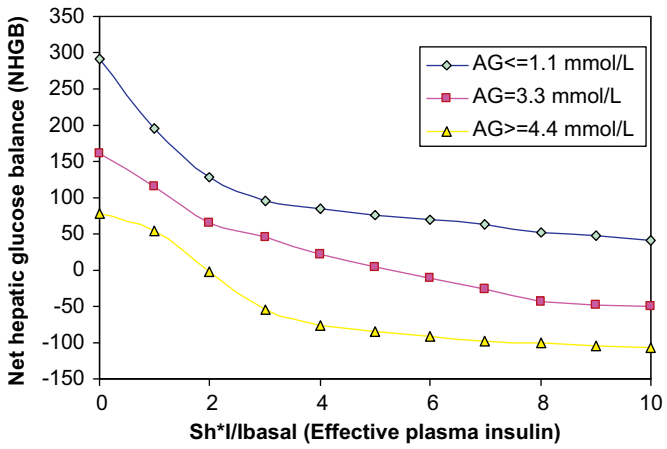

Fig. 1. Net hepatic glucose balance (mmol/h) as a function of the arterial blood glucose level, AG, and plasma insulin level I (Guyton et al., 1978; Lehmann and Deutsch, 1992).

The duration of the period ($Tmax_{ge}$) where gastric emptying is constant and maximal ($Vmax_{ge}$) is a function of the carbohydrate content of the meal that is ingested, which is denoted with Ch (millimoles of glucose equivalent carbohydrate).

$$Tmax_{ge} = \frac{Ch - 1/2 * Vmax_{ge} * (Tasc_{ge} + Tdes_{ge})}{Vmax_{ge}} \quad (9)$$

In Fig. 2, the rate of gastric emptying as a function of time and carbohydrate intake is shown. $Tasc_{ge}$ and $Tdes_{ge}$ are the respective branches of the gastric emptying curve which have default values of 30 min. For small values of carbohydrate intake below 10 g, the gastric emptying curve is a triangular function.

Using linear interpolation, the rate of gastric emptying is defined for meals containing Ch millimoles of carbohydrate (>10 g), according to the time elapsed from the start of the meal.

$$G_{empt} = (V\,max_{ge}/Tasc_{ge})t; \quad \text{when } t < Tasc_{ge} \quad (10)$$

$$G_{empt} = V\,max_{ge}; \quad \text{when } Tasc_{ge} < t \le Tasc_{ge} + T\,max_{ge} \quad (11)$$

$$G_{empt} = V\,max_{ge} - (V\,max_{ge}/Tdes_{ge})(t - Tasc_{ge} - T\,max_{ge}); \quad \text{when } Tasc_{ge} + T\,max_{ge} \le t < Tasc_{ge} + Tmax_{ge} + Tdes_{ge} \quad (12)$$

$$G_{empt} = 0 \text{elsewhere} \quad (13)$$

Finally, the rate of renal glucose excretion, G_{ren} is modeled as

$$G_{ren} = GFR(G - RTG); \text{if } G > RTG \quad (14)$$

$$G_{ren} = 0; \text{elsewhere} \quad (15)$$

In this model, GFR is the glomerular filtration rate (creatinine clearance that is the volume of filtrate made by the kidneys per minute) and RTG is the renal threshold of glucose concentration.

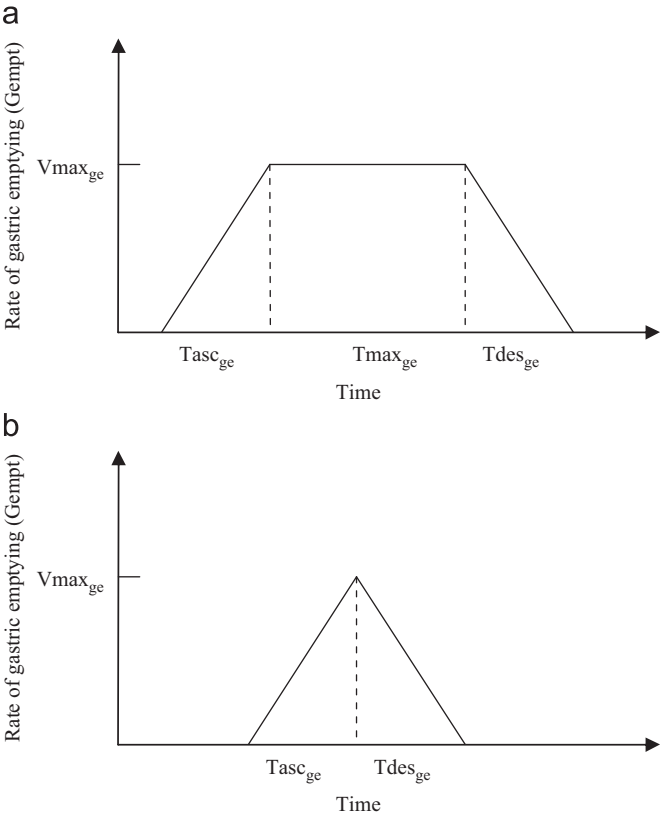

Fig. 2. Rate of gastric emptying, G_{empt} as a function of time, (a) for carbohydrate intake ≥ 10 g and (b) for carbohydrate intake < 10 g.

The default parameter values for GFR and RTG is 100 ml/min and 9.0 mmol/L.

3. Uncertainties in diabetes glucose control

It is well known that there is considerable variability among daily values of glucose. Due to this variability, even the same insulin dose with the same meal and the same amount of physical exercise may result in different blood glucose responses on consecutive days. Furthermore, blood glucose levels vary among different patients according to meals, exercise levels, age and stress. For example, experimental data for continuous blood glucose monitoring over the course of 48 h is given in Fig. 3 for two patients (Service et al., 1970). These patients are identified as unstable diabetic patients judged by the relative difficulty of diabetes management. These patients were eating typical meals and receiving subcutaneous injections four times a day. The times of meals and insulin injections are given in Table 1. Even though the insulin regimen and meal compositions were kept the same on each day, considerable variability is observed in blood glucose values.

This natural inter- and intra-patient variability needs to be addressed in developing an optimal glucose control profile. Since the interactions between insulin, meals, exercise and other factors and their effect on blood glucose is a dynamic phenomenon, it involves dynamic uncertainties or variations. These dynamic uncertainties (variabilities) could be represented using stochastic processes.

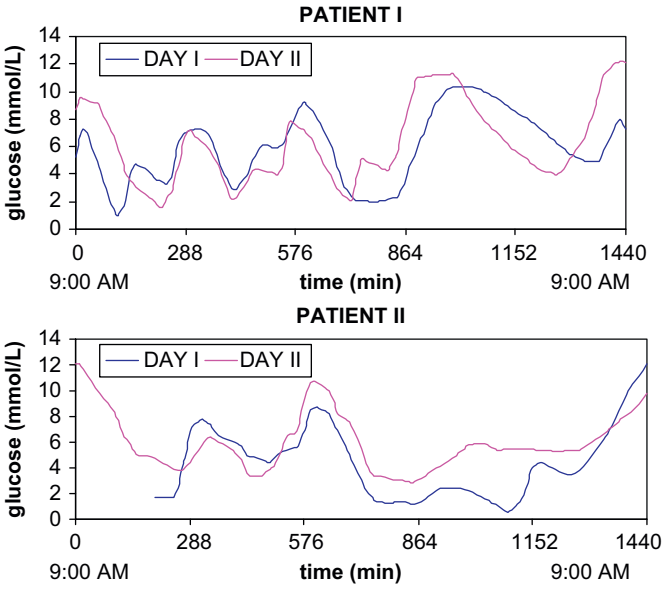

Fig. 3. Variability of blood glucose among patients and within a given patient over the course of 48 h (Service et al., 1970). These patients have been eating typical meals and given subcutaneous insulin injections four times a day. The insulin regimen and meal compositions were kept the same each day.

3.1. Modeling dynamic uncertainties with stochastic processes

A stochastic process is a variable that evolves over time in an uncertain way. One of the simplest examples of a stochastic process is the random walk process. The Wiener process, also known as Brownian motion (Fig. 4a shows one form of Brownian motion) is a continuous limit of the random walk and is a continuous time stochastic process. A Wiener process can be used as a building block to model an extremely broad range of variables that vary continuously and stochastically through time. An example of this is the price of technology stock. It fluctuates randomly, but over a long time period has had a positive expected rate of growth that compensates investors for risk in holding the stock. A Wiener process has three important properties:

1. It satisfies the Markov property. The probability distribution for all future values of the process depends only on its current value. Stock prices can be modeled as Markov processes, on the grounds that public information is quickly incorporated in the current price of the stock and past pattern has no forecasting value.
2. It has independent increments. The probability distribution for the change in the process over any time interval is independent of any other time interval (non-overlapping).
3. Changes in the process over any finite interval of time are normally distributed, with a variance that increases linearly with the time interval.

From the example of the technology stock above, it is easy to show that the variance of the change distribution can increase linearly, in a manner similar to Brownian motion with drift shown in Fig. 4(a). However, given that stock prices can never fall below zero, price changes cannot be represented as a normal distribution. To get around this difficulty, it is reasonable to assume that changes in the logarithm of prices are normally distributed. Thus, stock prices can be represented by logarithm of a Wiener process.

Stochastic processes do not have time derivatives in the conventional sense and, as a result, they cannot be manipulated using the ordinary rules of calculus as needed to solve stochastic optimal control problems. Ito (1951, 1975) provided a way around this by defining a particular kind of uncertainty representation based on the Wiener process as a building block.

An Ito process is a stochastic process, $x(t)$, whose increment, dx, is represented by the equation:

$$dx = a(x,t)\,dt + b(x,t)\,dz \tag{16}$$

Table 1
The amounts and times of insulin injections and meals for the experimental data given in Fig. 3.

Insulin injections					
Times	07:45	12:45	17:45	22:45	
Patient I	6 U (R)	5 U (R)	5 U (R)	6 U (SL)	
Patient II	8 U (R)	6 U (R)	6 U (R)	8 U (SL)	
Meals					
Times	8:00	13:00	16:00	18:00	23:00
Patients I&II	Basal caloric requirement+30%				

(R: regular (short-acting) insulin, SL: semilente (intermediate acting insulin).

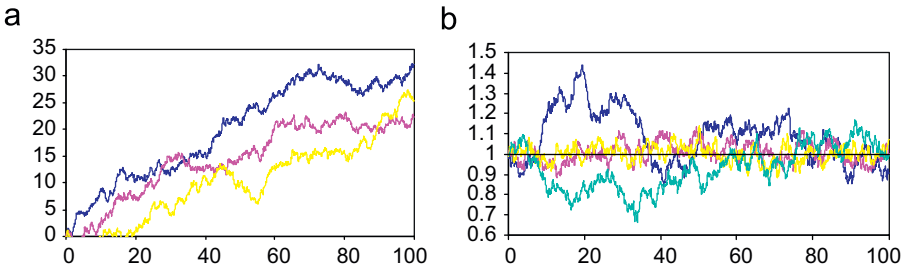

Fig. 4. (a) Sample paths of simple Brownian motion, (b) Sample paths of mean reverting process.

where dz is the increment of a Wiener process, and $a(x, t)$ and $b(x, t)$ are known functions.

By definition, $E(dz)=0$ and $(dz)^2=dt$ where E is the expectation operator and $E(dz)$ is interpreted as the expected value of dz. The simplest generalization of Eq. (16) is the equation for Brownian motion with drift given by

$$dx = \lambda\, dt + \sigma\, dz \tag{17}$$

where λ is called the drift parameter, and σ is the variance parameter. Fig. 4a shows the sample paths of Eq. (17). Other examples of Ito processes are the geometric Brownian motion with drift (Eq. (18) given below) and the mean reverting process (Eq. (19) and Fig. 4(b)).

$$dx = \lambda x\, dt + \sigma x\, dz \tag{18}$$

$$dx = \eta(\overline{x} - x)\, dt + \sigma\, dz \tag{19}$$

where η is the speed of reversion and $\overline{x}$ is the nominal level that x reverts to.

Ito's Lemma states that if $f(x(t), t)$ is an Ito process as shown in Eq. (16), then

$$df(x(t),t) = \left(a(x,t)\frac{\partial f}{\partial x} + \frac{\partial f}{\partial t} + \frac{1}{2}b(x,t)^2\frac{\partial^2 f}{\partial x^2}\right)dt + b(x,t)\frac{\partial f}{\partial x}dz \tag{20}$$

Therefore, using Ito's Lemma, we can differentiate and integrate functions of stochastic processes and derive optimal control profiles. This approach can be applied for deriving a stochastic optimal control policy for blood glucose regulation. This is illustrated using diabetic patient data in the following subsection.

3.2. Modeling blood glucose as an ito process

In the previous section, experimental data for blood glucose were given for diabetic patients over the course of 48 h. In order to determine the patient dependent model parameters for the AIDA model given in Section 2, a nonlinear least squares analysis was performed.

The best set of parameters is searched which allow the minimization of

$$S(P) = \sum_{i=1}^{N} (Y(t_i) - f(t_i, P))^2 \tag{21}$$

where N is the number of data points, t_i is the discrete times at which data is taken, Y represents the measured variable to be fitted. The measured variable in this case is the blood glucose. The term $f(t_i, P)$ is the model computed function which fits the data and depends on P, the vector of parameters.

The deterministic model used for parameter estimation is summarized below:

$$\frac{dx_1}{dt} = \frac{-x_1(p_2x_2 + p_5)(K_M + G_X)}{G_X(K_M + x_1)V_G} + \frac{NHGB(p_1, x_3)}{V_G} + \frac{G_{in}}{V_G} - \frac{G_{ren}}{V_G} \tag{22}$$

Table 2
Patient independent constant parameters used in the model.

Constant parameters	Value
K_M (Michaelis constant)	10 mmol/L
G_X (Reference value for glucose utilization)	5.3 mmol/L
V_I (Insulin distribution volume per kg body weight)	0.1421 L/kg
V_G (Glucose distribution volume per kg body weight)	0.22 L/kg
n (Insulin elimination rate constant)	5.4 h^{-1}
a (regular insulin preparation) (h/U^{-1})	0.05
b(regular insulin preparation) (h)	1.7
S((regular insulin preparation)	2.0
a (semilente insulin preparation) (h/U^{-1})	0.07
b(semilente insulin preparation) (h)	2.92
s(semilente insulin preparation)	1.87

$$\frac{dx_2}{dt} = -p_4x_2 + p_3x_3 \tag{23}$$

In these equations, plasma glucose concentration is denoted by x_1, insulin concentration in remote compartment is denoted by x_2 and plasma insulin concentration is denoted by x_3. The parameter vector to be estimated is $P = [p_1 \quad p_2 \quad p_3 \quad p_4 \quad p_5]$. Net hepatic glucose balance (NHGB) is a function of p_1 (a patient dependent parameter), glucose and insulin concentrations and is computed from the experimental data given in Fig. 1. For arterial glucose values in between 1.1 and 4.4 mmol/L, NHGB is computed by interpolation between the values shown in this figure. G_{in}, which is the glucose input by meals is computed in advance using Eqs. (7)–(13) and stored in a file which is the input to the parameter estimation program. The time-dependent insulin profile x_3 is also computed in advance and stored. For the experimental data given in the previous section, the rate of insulin absorption after a subcutaneous insulin injection is modeled according to Berger and Rodbard (1989):

$$\frac{dx_3}{dt} = \frac{s \cdot t^s \cdot (T_{50})^s \cdot D}{t[(T_{50})^s + t^s]^2 V_I} - nx_3 \tag{24}$$

$$T_{50} = a \cdot D + b \tag{25}$$

In Eq. (24), t is the time elapsed from the injection, D is the dose, T_{50} is the time at which 50% of the dose D, has been absorbed. The parameters s, a and b are preparation specific parameters, which define the insulin absorption pattern of different types of insulin (regular, intermediate, lente etc.).

The constant parameters used in Eqs. (21)–(25) are summarized below in Table 2 as provided by Lehmann and Deutsch (1992) and Berger and Rodbard (1989).

Using the model described above and the experimental data given for Patient II (Fig. 3), the parameter estimates are found using a nonlinear curve fitting procedure. The average of two days is taken for model fitting. The comparison of model predicted glucose profile and the experimental data is given in Fig. 5.

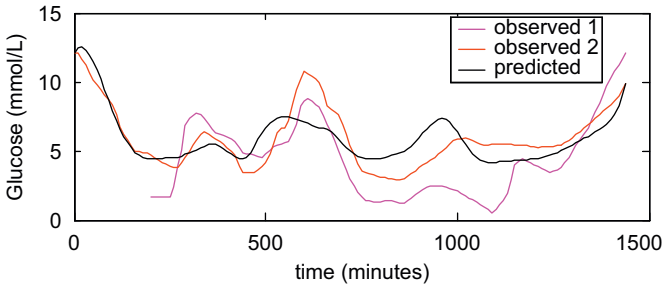

Fig. 5. The results of nonlinear curve fitting procedure; comparison between model predictions and experimental data for Patient II.

Table 3
Optimal parameter estimates.

Parameter	Value
p_1	0.278
p_2 (mmol min^{-1} kg^{-1} mU^{-1} L^{-1})	0.0248
p_3 (min^{-1})	0.000758
p_4 (min^{-1})	0.0148
p_5 (mmol min^{-1} kg^{-1})	0.00986

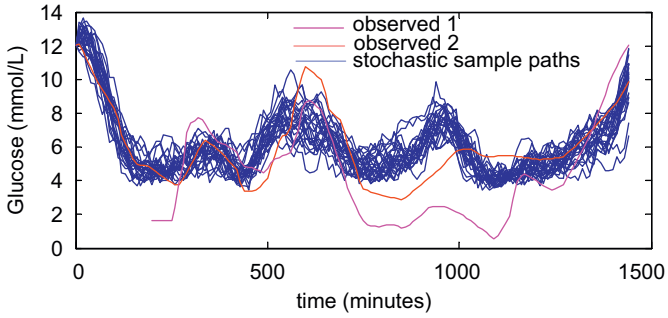

Fig. 6. The comparison between observed blood glucose values and stochastic sample paths generated using σ=0.25.

The optimal parameter estimates are given in Table 3. The determination of one set of parameters even for a single patient is a difficult task and as can be seen from Fig. 5, the deterministic model cannot account for the day to day variations in glucose due to a variety of reasons, which will be further elucidated in the Discussion section (Section 7).

If we introduce a stochastic model to represent the plasma glucose concentration, Eq. (22) can be modified as follows:

$$\frac{dx_1}{dt} = \frac{-x_1(p_2x_2+p_5)(K_M+G_X)}{G_X(K_M+x_1)V_G} + \frac{NHGB(p_1,x_3)}{V_G} + \frac{G_{in}}{V_G} - \frac{G_{ren}}{V_G} + \frac{\sigma\varepsilon}{\sqrt{dt}} \quad (26)$$

In this equation, blood glucose is modeled as a stochastic process of Ito type (an Ito process), where σ is the variance parameter and ε is a random number generated from a normal distribution with mean zero and a standard deviation of one ($N(0,1)$). In finance, σ refers to the volatility or the standard deviation of the change in the value of a financial instrument with a specific time horizon. In this case, we are trying to determine the standard deviation of changes in blood glucose over the course of 48 h. The results are shown for stochastic sample paths using σ=0.25 in Fig. 6. From this figure it can be seen that, the day to day variations in glucose concentration for a single patient can be modeled effectively. The trend of glucose concentration and intra-patient variability is captured accurately except for a brief time period between 750–1000 min. The error for this time period may be attributed to other factors that the model does not consider since there is a good agreement between the majority of the data and the model. The aim of this exercise is to show that the intrapatient variability can be captured using the Ito stochastic differential equations. The next step is to derive a stochastic optimal control profile to regulate blood glucose which will be discussed in Section 4.

4. Deterministic and stochastic optimal control: problem formulation

Optimal control problems in engineering have received considerable attention in the literature. In general, solutions to these problems involve finding the time-dependent profiles of the control variables so as to optimize a particular performance index. The dynamic nature of the decision variables makes these problems much more difficult to solve compared to optimization problems where the decision variables are scalar. In general mathematical methods to solve these problems involve calculus of variations, the maximum principle and the dynamic programming technique. Nonlinear programming (NLP) techniques can also be used to solve this problem provided all the system of differential equations is converted to nonlinear algebraic equations. For details of these methods, refer to Diwekar (2003). Calculus of variations considers the entire path of the function and optimizes the integral by minimizing the function by vanishing the first derivative, resulting in second-order differential equations that can be difficult to solve. Other two approaches keep the first order differential system as is but use transformation. In the maximum principle (Boltyanski et al., 1956; Pontryagin, 1957) the objective function is reformulated as a linear function in terms of final values of state variables and the values of a vector of constants (Mayer linear form). However, this maximum principle transformation needs to include additional variables and corresponding first order differential equations, referred to as adjoint variables and adjoint equations, respectively.

Dynamic programming formulation (Dreyfus, 1965) results in first order system of partial differential equations (the Hamilton–Jacobi–Bellman, HJB equations) that may not be easy to solve. However, this dynamic programming method provides the basis for stochastic optimal control problems and real options theory. Although the mathematics of dynamic programming look different from the maximum principle formulation, in most cases they lead to the same results. This is not surprising and has been reported elsewhere (Diwekar, 1994; Diwekar, 2003) for the deterministic case. Financial literature reports an extension of the HJB equation for the stochastic case (Dixit and Pindyck, 1994; Merton and Samuelson, 1990; Thompson and Sethi, 1994) but an equivalent maximum principle is not reported. In this study, the mathematical equivalence between dynamic programming and the maximum principle is used to extend the maximum principle to the stochastic case. The main aspect of the derivation involves obtaining the expressions for the adjoint equations. The adjoint equations provide the dynamics of the adjoint variables in the maximum principle. For the deterministic case, it is shown that the adjoint variables in the maximum principle are equivalent to the derivatives of the objective function with respect to the state variables of the dynamic programming approach. Such equivalence is kept for the stochastic case and provides the basis of the reformulation. For more details on this

derivation and its application to a batch distillation column (stochastic optimal control policy), refer to Kirk, (1970), Rico-Ramirez et al. (2003), Rico-Ramirez and Diwekar (2004), Ulas and Diwekar (2004).

Let us consider the optimal control problem formulation for blood glucose control for the deterministic and stochastic cases.

4.1. Deterministic optimal control

The optimal control problem for blood glucose regulation is the following, which will be solved using the Pontryagin's maximum principle. The performance index for the optimal control problem is defined as

$$I = \int_0^T [(x_1 - G_b)^2 + \alpha(u_t - u_b)^2]\,dt \tag{27}$$

The optimal control problem formulation is provided below:

$$\underset{u(t)}{\text{Maximize}} - x_4(T) \tag{28}$$

subject to

$$\frac{dx_1}{dt} = \frac{G_m(t) + NHGB(t)}{V_G} - \frac{x_1(p_2x_2 + p_5)\cdot(K_M + G_X)}{G_X\cdot(K_M + x_1)\cdot V_G} - \frac{G_{rent}}{V_G}; x_1(0) = G_0 \tag{29}$$

$$\frac{dx_2}{dt} = p_3x_3 - p_4x_2; \quad x_2(0) = X_0 \tag{30}$$

$$\frac{dx_3}{dt} = -n\cdot x_3 + \frac{u_t}{V_I}; \quad x_3(0) = I_0 \tag{31}$$

$$\frac{dx_4}{dt} = (x_1 - G_b)^2 + \alpha(u_t - u_b)^2; \quad x_4(0) = (G_0 - G_b)^2 + \alpha(u_0 - u_b)^2 \tag{32}$$

The objective function consists of two parts; $(x_1 - G_b)^2$ where the variations of blood glucose from a preset level are minimized and $\alpha(u_t - u_b)^2$ which is the penalty function, in order to prevent the control action to result in hypoglycemic states by increasing the insulin level above a certain value for a predefined time period T.

Also for safety reasons, upper and lower bounds are exercised on the control variable:

$$u_{\min} \le u_t \le u_{\max} \tag{33}$$

The Hamiltonian function which should be maximized is

$$H = \mu_1\left[\frac{-G_{out} + NHGB + G_{in} - G_{ren}}{V_G}\right] + \mu_2(-p_4x_2 + p_3x_3) + \mu_3\left(\frac{u_t}{V_I} - nx_3\right) + \mu_4\left[(x_1 - G_b)^2 + \alpha(u_t - u_b)^2\right] \tag{34}$$

The maximum value of H is found by choosing the decision vector u_t, which satisfies the optimality condition:

$$\partial H/\partial u_t = 0 \tag{35}$$

The adjoint variables μ_i introduced in the Hamiltonian function are defined by these equations:

$$\frac{d\mu_i}{dt} = -\sum_{j=1}^{n}\mu_j\frac{\partial f_j}{\partial x_i} \tag{36}$$

where μ_i are the adjoint variables and x_i are the state variables.

According to this definition we can write

$$\frac{d\mu_1}{dt} = -\mu_1\left[-\frac{(p_2x_2 + p_5)\cdot(K_M + G_X)\cdot K_M}{G_X\cdot(K_M + x_1)^2\cdot V_G} + \frac{dNHGB}{V_G\cdot dx_1} - \frac{dG_{ren}}{dx_1\cdot V_G}\right]\mu_1(T) = 0 - 2\mu_4(x_1 - G_b); \tag{37}$$

$$\frac{d\mu_2}{dt} = -\mu_1\left(\frac{-x_1p_2\cdot(K_M + G_X)}{G_X\cdot(K_M + x_1)\cdot V_G}\right) + \mu_2p_4; \quad \mu_2(T) = 0 \tag{38}$$

$$\frac{d\mu_3}{dt} = -\mu_1\frac{dNHGB}{dx_3\cdot V_G} - \mu_2p_3 + \mu_3n; \quad \mu_1(T) = 0\mu_3(T) = 0 \tag{39}$$

$$\frac{d\mu_4}{dt} = 0; \quad \mu_4(T) = -1 \tag{40}$$

We can use the method of steepest ascent of Hamiltonian to reach a numerical solution to this optimal control problem using an iterative procedure (Diwekar, 2003; Kirk, 1970). The solution of this problem gives the optimal insulin infusion profile so as to minimize the variation of blood glucose from a preset level such as G_b (basal value) for a predefined time period T. The penalty function and lower and upper bounds on the insulin infusion profile ensures that the insulin levels stay within a safe range, so as to prevent hypoglycemic states.

4.2. Stochastic optimal control

If state variables are Ito processes of the form:

$$dx = f\,dt + g\,dz \tag{41}$$

Then the adjoint equations and Hamiltonian are modified as follows (Berger and Rodbard, 1989; Kirk, 1970):

$$\frac{d\mu}{dt} = -f_x\mu - \frac{1}{2}(g^2)_x\omega; \quad \mu(T) = c \tag{42}$$

$$\frac{d\omega}{dt} = -2\omega f_x - \mu f_{xx} - \frac{1}{2}(g^2)_{xx}\omega; \quad \omega(T) = 0 \tag{43}$$

$$H = \mu f + \frac{1}{2}g^2\omega \tag{44}$$

If the blood glucose profile is modeled as an Ito process:

$$dx_1 = \left(\frac{G_{in}(t) + NHGB(t)}{V_G} - \frac{x_1(p_2x_2 + p_5)\cdot(K_M + G_X)}{G_X\cdot(K_M + x_1)\cdot V_G} - \frac{G_{ren}(t)}{V_G}\right)dt + \sigma_1 dz; x_1(0) = G_0 \tag{45}$$

In this equation:

$$dz = \varepsilon_t\sqrt{dt} \tag{46}$$

where ε_t is a random number drawn from a normal distribution with a mean of zero and a standard deviation of one. Then Eqs. (29) and (30), (31) are the same, as well as the adjoint Eqs. (37), (38), (39) and (40). Another adjoint equation is added to our formulation.

$$\frac{d\omega}{dt} = -2\mu_4 - \mu_1\left(-\frac{d^2G_{out}}{dx_1^2\cdot V_G} + \frac{d^2NHGB}{dx_1^2\cdot V_G}\right) - 2\omega\left(\frac{-dG_{out}}{dx_1\cdot V_G} + \frac{dNHGB}{dx_1\cdot V_G} - \frac{dG_{ren}}{dx_1\cdot V_G}\right); \quad \omega(T) = 0 \tag{47}$$

The Hamiltonian is modified as follows:

$$H = \mu_1\left[\frac{-G_{out} + NHGB + G_{in} - G_{ren}}{V_G}\right] + \mu_2(-p_4x_2 + p_3x_3)$$

Table 4
Parameters of the optimal control problem.

Final time (T, min)	1440
Initial glucose concentration (G_0, mmol/L)	4.5
Initial insulin (remote) concentration (X_0, mU/L)	0.0
Initial insulin concentration (I_0, mU/L)	10.0
Penalty factor (α)	0.25
Penalty factor (u_b, mU)	10
Maximum value of insulin infusion (u_{max}, mU)	80
Minimum value of insulin infusion (u_{min}, mU)	10
Meal times (min)	[180 300 450 660 870 1020]
Carbohydrate content of each meal (g)	[47 16 63 31 63 31]

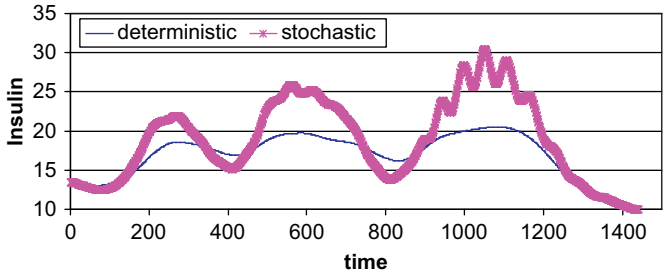

Fig. 7. Optimal insulin infusion profiles u_t for the stochastic and deterministic cases computed using the parameters estimated for Patient II and the ones represented in Table 4.

$$+\mu_3\left(\frac{u_t}{V_I}-nx_3\right)+\mu_4[(x_1-G_b)^2+\alpha(u_t-u_b)^2]+\frac{\omega\sigma_1^2}{2} \quad (48)$$

The stochastic optimal control problem is solved using the stochastic maximum principle by choosing a decision vector u_t, which satisfies the optimality condition given in Eq. (35).

The next section compares the results for the numerical solution of this problem for the stochastic and deterministic cases.

5. Deterministic and stochastic optimal control: numerical results

The optimal control problems for the deterministic and the stochastic cases are solved using the method of steepest ascent of Hamiltonian. The optimal parameter estimates obtained from experimental data for Patient II are used. Other parameters used in these simulations are represented in Table 4.

The penalty factor is determined such that it prevents hypoglycemic states and keeps the glucose levels within a safe range.

The optimal insulin infusion profiles for the course of 24 h are shown in Fig. 7 for the deterministic and stochastic cases.

6. Performance comparison in the presence of parametric uncertainty

In order to achieve a realistic comparison of the performance of stochastic and deterministic optimal control profiles in the presence of parametric uncertainty, an analysis is performed using a more detailed compartmental model representing glucose–insulin system consisting of 19 differential equations

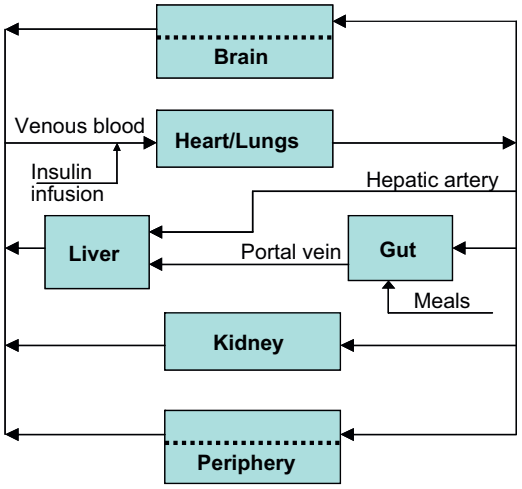

Fig. 8. Compartmental diagram of glucose–insulin system.

and algebraic equations to represent the metabolic source and sink rates. This model was initially developed by Guyton et al. (1978) and updated by Sorensen (1985) and Parker et al. (2000).

This model, which we use as a proxy for real experiments, uses a six compartment representation for the internal organs that are the brain, heart/lungs, liver, gut, kidney and periphery. The combined effects of muscle and adipose tissue are represented by the periphery and the stomach and intestine effects are lumped into the gut compartment. The compartmental diagram for the glucose–insulin system is shown in Fig. 8 for this model.

A sensitivity analysis performed by Parker et al. (2000) identified that the glucose and insulin dynamics were found to be more sensitive to variations in three metabolic parameters. In this model, threshold functions are used to describe glucose metabolism.

These threshold functions are of the form:

$$\Gamma_e = E_\Gamma\{A_\Gamma - B_\Gamma \tan h[C_\Gamma(x_i+D_\Gamma)]\} \quad (49)$$

Inter or intra-patient variability is classified physiologically as either a receptor parameter (D_Γ) or post-receptor (E_Γ) parameter. The threshold functions used to describe the effect of insulin on peripheral glucose uptake (Γ_{EIPGU}) and effect of glucose on hepatic glucose uptake (Γ_{EGHGU}) are given below:

$$\Gamma_{EIPGU} = 1.0\left\{7.035+6.51623\tanh\left[0.33827\left(\frac{I_P^T}{5.304}-5.82113\right)\right]\right\} \quad (50)$$

$$\Gamma_{EGHGU} = 1.0\left\{5.6648+5.6589\tanh\left[2.4375\left(\frac{G_L^C}{101}-1.48\right)\right]\right\} \quad (51)$$

In these equations, I_P^T is the state variable describing the insulin concentration in the peripheral tissue space and G_L^C is the state variable describing the glucose concentration in the liver capillaries. Another important threshold function is one that is used to describe the liver clearance:

$$\Gamma_{LC} = F_{LC}(I_H^C Q_A + I_S^C Q_S + \Gamma_{PIR}) \quad (52)$$

where F_{LC} is the fraction of hepatic insulin clearance, I_H^C is the insulin concentration in heart capillaries, I_S^C is the insulin concentration in gut capillaries, Γ_{PIR} is the rate of pancreatic insulin release, Q_S and Q_A are vascular plasma flow rates for the gut and hepatic artery respectively.

The three parameters which have the most significant effect on the glucose–insulin dynamics were identified as Γ_{EIPGU}-D_Γ (nominal = −5.82113), Γ_{EGHGU}-D_Γ (nominal = −1.48) and F_{LC} (nominal = 0.40) (Parker et al., 2000).

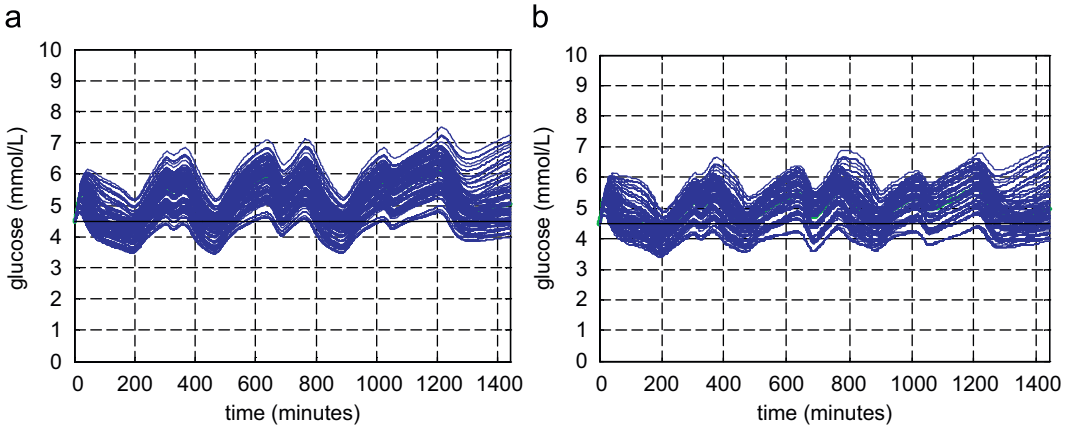

Fig. 9. (a) The glucose profiles for 125 perturbed models generated by parametric variations and using the *deterministic* insulin infusion profile; (b) The glucose profiles for 125 perturbed models generated by parametric variations and using the *stochastic* insulin infusion profile.

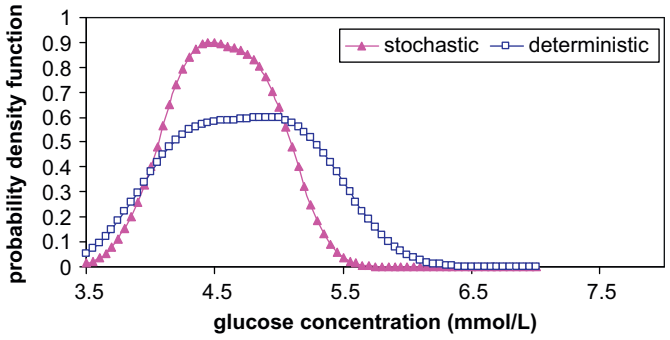

Fig. 10. The results of kernel density estimation for the blood glucose profiles generated by the 125 perturbed models and stochastic and deterministic optimal control profiles.

The performance of stochastic and deterministic optimal control profiles were compared in the presence of $\pm 40\%$ variation in Γ_{EIPGU}-D_Γ and Γ_{EGHGU}-D_Γ and $\pm 20\%$ variation in F_{LC}. For this purpose, Γ_{EIPGU}-D_Γ and Γ_{EGHGU}-D_Γ were varied by 20% increments and F_{LC} was varied by 10% increments which resulted in 125 perturbed patient models. Then the glucose concentration was plotted against time for these 125 perturbed models, using the stochastic and deterministic insulin infusion profiles. The results are shown in Fig. 9(a) and (b). The meal times and carbohydrate contents of each meal was considered to be the same as the optimal control problem in Section 5.

From Fig. 7, it can be observed that the stochastic control trajectory employs more insulin over the time period T then the deterministic case and ultimately results in lower blood glucose levels and less variations from the reference blood glucose value of 4.5 mmol/L as shown in Fig. 9. This can also be observed in the probability distribution plots provided in Fig. 10. These plots were generated using the blood glucose data from the simulations given in Fig. 9. The probability density function for the time dependent blood glucose data from Fig. 9 was estimated using kernel density estimation technique to observe the distribution of blood glucose values for deterministic and stochastic cases. From Fig. 10, it can be seen that the blood glucose values for deterministic and stochastic cases are similar to a normal distribution. The most likely value for glucose concentration for the stochastic case is 4.5 mmol/L, which was the target value for the control problem and the variance is lower as compared to the deterministic case. The standard deviation for the deterministic and stochastic cases are 0.39 and 0.35 respectively. For the deterministic case, both the variance is higher and the most likely value is about 4.7, which is higher than the target value. It means that with the deterministic case, the probability of having a blood glucose level that is above the normal levels is higher than the stochastic case. As mentioned earlier, clinical trials have shown that keeping blood glucose levels as close to normal as possible slows the onset and progression of the eye, kidney, and nerve damage caused by diabetes (The Diabetes Control and Complications Trial Research Group, 1993). Also any sustained lowering of blood glucose reduces the risk of long term complications, evenif the patient has a history of poor control. Therefore, the stochastic approach has the potential to reduce the occurrence of long term complications of diabetes and improving the quality of life for diabetic patients by keeping the blood glucose levels within the target range.

7. Discussion

The results presented in Section 6 show that the stochastic optimal insulin infusion profile results in blood glucose values within the normoglycemic range of 70–120 mg/dL (3.89–6.67 mmol/L) and less variations from the reference value of 4.5 mmol/L (80 mg/dL) in the presence of parametric uncertainty.

There are various factors involved in obtaining an optimal insulin infusion profile and one of these factors is to find a model which would account for the day to day variations in blood glucose in response to insulin injections or infusion using an insulin pump. The stochastic model where the blood glucose profile is represented using an Ito process accomplishes this as shown in Fig. 6. However it should be noted that the parameter estimates obtained for the AIDA model which were used in the optimal control problem were based on the experimental data given in Section 3 for a 48 h monitoring period. Longer monitoring periods could be beneficial in modeling the day to day variability and variability within a given day in blood glucose values in response to insulin. For each patient, an individual set of parameters should be estimated based on this blood glucose monitoring for optimal glycemic control.

It should also be noted that the AIDA model also does not include the effects of exercise on insulin–glucose dynamics. Additional differential equations are needed to account for the glucose uptake, hepatic glucose production and insulin clearance

induced by elevated exercise intensity (Roy and Parker, 2006). Another approach is to introduce additional parameters to model these effects during physical activity (Derouich and Boutayeb, 2002). In order to estimate the model parameters and validate these models, diabetic patient data is needed during physical exercise. If the effect of exercise could be modeled accurately, an optimal insulin infusion profile in the presence of physical activity can be computed.

8. Conclusion ANF future work

This work develops a novel methodology based on stochastic processes called Ito processes originally used in finance literature to model time dependent uncertainties in a biological system to compute optimal control trajectories. The biological system being considered is the glucose–insulin system in a diabetic patient.

The results show that the hourly and daily variations of blood glucose in response to meals and insulin action can be modeled using this methodology and using stochastic maximum principle; optimal insulin infusion profiles can be computed. The stochastic optimal control profile results in fewer variations from the reference blood glucose value of 4.5 mmol/L as compared to the deterministic profile and could potentially be useful in preventing the complications of diabetes.

The success of optimal control trajectory in achieving a normoglycemic range with minimal variations from the reference blood glucose level critically depends on the model parameters being estimated. Therefore patients could be monitored for longer periods than 48 h to increase the quality of estimated parameters and achieve better glycemic control. Furthermore, the mathematical model used in computing the optimal control trajectories can be further improved to include the effects of physical exercise, which is considered as future work.

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