ADAPTIVE CLARKE-GAWTHROP SELF-TUNING CONTROL OF BLOOD GLUCOSE CONCENTRATION IN PATIENTS WITH TYPE I DIABETES

by

Ceylan Çölmekçi

B.S. in Chemical Engineering, Boğaziçi University, 2006

Submitted to the Institute for Graduate Studies in
Science and Engineering in partial fulfillment of
the requirements for the degree of
Master of Science

Graduate Program in Chemical Engineering
Boğaziçi University

2008

dedicated to my parents,

my brother,

and Sinan

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor Prof. Mehmet C. Çamurdan for his everlasting support and patience throughout my study. He was the one that taught me to have faith in myself even at my most desperate moments. I am forever indebted to him for the insight into the graduate experience.

I wish to express my warm and sincere thanks to Prof. Ali Çınar of Illinois Institute of Technology (IIT) for introducing me to the field of Diabetes research and for his supplement of GlucoSim software and relevant literature. I am also greateful to Meriyan Eren Örüklü, PhD at IIT for her detailed and constructive comments besides her friendship.

My sincere gratitude is due to my thesis committee members, Assoc. Prof. Murat Dervişoğlu and Prof. Eşref Eşkinat for their comments and suggestions for my thesis.

Very special thanks goes to my beloved friend and housemate Seda Asan for her everlasting friendship and moral support. I want to thank to my sweet group member Dicle Hasdemir for her friendship and support. I wish to extend my gratitude to my dear friends Sevince Bayrak and Gizem Terzi for their presence whenever I needed. Life is easier with them.

I wish to thank my roomie Mustafa Karakaya for his special friendship and great patience for my endless questions and requests in the course of the thesis. I am also greateful to my roomie Erdem Günay for his assistance.

My special gratitude is due to my mother Özgül, my father Tuğrul, and my brother Özden İnan. It has always been comforting to know their existence and endless support, not only during my studies but also in a lifetime. I owe my loving thanks to my darling Sinan also. Words are insufficient to express my feelings for him. Without their encouragement and understanding it would have been impossible for me to finish this work. This thesis is dedicated to them.

ABSTRACT

ADAPTIVE CLARKE-GAWTHROP SELF-TUNING CONTROL OF BLOOD GLUCOSE CONCENTRATION IN PATIENTS WITH TYPE I DIABETES

Adaptive Clarke-Gawthrop type of self-tuning controller is used for regulating the blood glucose concentration in Type I diabetic patients. This control algorithm is proposed to be integrated into the automation pumps used by diabetic patients as a replacement for manual insulin injection. The controller is implemented on an educational software, GlucoSim which simulates the glucose-insulin dynamics in Type I diabetic patients with insulin infusion being the manipulated variable. The performance of the controller is investigated by changing some important parameters that should be specified at the beginning of the simulations. These parameters are the initial values of the controller parameters, the covariance matrix P, the setpoint of the blood glucose concentration, the constraint factor ζ, the clamp value of the manipulated variable, the forgetting factor λ, and the control interval. The simulations are carried out for two cases: when the process and disturbance model parameters are unknown and when they are approximately known. The best performance is obtained when the process model parameters are unknown. The optimum parameter settings found are then as follows: the setpoint of the blood glucose concentration is 100 mg dl^{-1}, the constraint factor is 1.5, the insulin infusion is clamped when it exceeds 50 000 mU min^{-1}, the forgetting factor is 0.5 and the control interval is 5 minutes.

ÖZET

KENDİNDEN AYARLANAN (SELF-TUNING) UYARLANIR CLARKE-GAWTHROP ALGORİTMASI İLE TİP I ŞEKER HASTALARININ KANINDAKİ GLİKOZ DERİŞİMİNİN DENETİMİ

Bu çalışmada, tip I şeker hastalarının kanındaki glikoz derişiminin düzenlenmesi için Clarke-Gawthrop kendinen ayarlanan (self-tuning) algoritmasının adaptif (uyarlanır) biçimi kullanılmıştır. Bu kontrol algoritmasının, insulinin şeker hastalarında şırınga ile vücuda zerki yerine uygulanabilecek otomatik pompalama sistemine entegre edilmesi düşünülmektedir. İşbu algoritma, GlucoSim adlı eğitim amaçlı geliştirilmiş yazılımda, insülin zerketme hızı ayarlan kontrol değişkeni olmak suretiyle, tip I şeker hastalarında glikoz-insülin dinamiğini incelemek üzere kullanılmıştır. Algoritmanın başarımı, değerleri benzetimlerin başında belirlenen bazı önemli parametrelerin değiştirilmesiyle ölçülmüştür. Bu parametreler, başlangıç değerleri, P covaryans matrisi, kandaki glikoz miktarının ayar noktası, ayarlanan kontrol değişkeninin kısıt faktörü ζ, insulin klemp değeri, unutma faktörü λ ve kontrol zaman aralığı olarak sıralanır. Benzetimler iki ayrı durum için yapılmıştır: süreç ve bozucu etkenlerin model parametrelerinin hiç bilinmediği birinci durum ve bu parametrelerin yaklaşık olarak bilindiği ikinci durum. Sonuçlar karşılaştırıldığında en iyi başarımın, süreç model parametreleri hiç bilinmediği durumda elde edildiği görülmektedir. Bu da şu parametre değerlerine tekabül etmektedir: kandaki glikoz miktarının ayar noktası 100 mg dl^{-1}, ayarlanan kontrol değişkeninin kısıt faktörü 1.5, insulin klemp değeri 50000 mU dak^{-1}, unutma faktörü 0.5 ve kontrol zaman aralığı 5 dakika olarak belirlenmiştir.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS/ABBREVIATIONS

a_t	White noise sequence
B	Backward shift operator
b	Total time delay in the process
c	Fractional period of process time delay
D	Differential operator
e	Prediction error
E	Expectation operator
f	Number of whole periods of process time delay
G_b	Blood glucose concentration
K_p	Process gain
N_t	Stochastic disturbance at time t
P_t	A matrix proportional to covariance of the parameter estimates
s	Laplace variable
T_s	Sampling time
$u(t)$	Deviations from the steady state value of input
$y(t)$	Deviations from the steady state value of output
z_t	Sequences of observation in time
∇	Backward difference operator
$\alpha(B)$	The numerator of the controller equation
$\beta(B)$	The denominator of the controller equation
γ	Autocovariances
$\delta(B)$	The denominator of discrete time process
ζ	Constraint factor
λ	Forgetting factor
μ	Mean
$\sigma_z^{\ 2}$	Variance
τ	Process time constant
τ_D	Time delay

$w(B)$	The numerator of discrete time process

ARI	Auto Regressive Integrated Models
ARIMA	Autoregressive Integrated Moving Average Models
ARMA	Autoregressive Moving Average Models
CHO	Carbohydrate
DCCT	The Diabetes Control and Complication Trial
GPC	Generalized Predictive Control
ISE	Integral Square Error
IV	Intravenous
LQC	Linear Quadratic Control
SC	Subcutaneous
STR	Self-Tuning Regulator

1. INTRODUCTION

Insulin is a hormone that is needed to convert sugar, starches and other food into energy needed for daily life. Diabetes mellitus which is simply called Diabetes is a disease in which the body does not produce or properly use insulin. Diabetes occurs when the body cannot make use of the glucose in blood for energy consumption, due to either a failure in insulin secretion from pancreas or secretion of ineffective insulin. According to the causing factors, diabetes is classified as Type I diabetes, Type II diabetes, Gestational diabetes and Pre-diabetes. Type I diabetes results from the body's failure to produce insulin which is used to allow glucose to enter the body cells and fuel them. Type II diabetes results from insulin resistance combined with relative insulin deficiency leading to improper usage of insulin. Furthermore, pregnant women who have never had diabetes before but who have high blood glucose levels during pregnancy are said to have Gestational diabetes. Gestational diabetes affects about four per cent of all pregnant women. Before people develop Type II diabetes, they almost always have "pre-diabetes" blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes (American Diabetes Association, 2005).

Therapies are diversified according to the type of diabetes. Insulin therapy is necessary to treat all patients with Type I diabetes and for others who do not produce enough of their own insulin to keep blood glucose in a secured interval. The current therapy for Type I diabetes is based on three to five daily insulin injections or insulin infusion by manual pump in which the insulin injection dose is arranged according to three to seven daily blood glucose measurement (Eren *et.al*., 2006). The Diabetes Control and Complication Trial study (DCCT, 1993) has stated that fixing the blood glucose levels in a secured interval reduces the possible complications of diabetes. However, patients frequently face with large variations in blood glucose concentration which may lead to hypo/hyperglycemia because of the open loop nature of the current therapy when combined with the unexpected daily life disturbances such as change in diet, exercise, stress or illness. To take precautions, strict regime and a very rigid and non-sedentary lifestyle are advised to the patients. Therefore, a novel therapy that gives the patient freedom in daily life is of great importance. Such therapy may be possible by totally

closing the loop with an automated artificial pancreas, consisting of a continuous blood glucose measuring device, an insulin infusion pump and a control algorithm (Eren *et al*., 2006).

The final element of an automated pump, which is the control algorithm, is a very popular research area for researchers with different majors. Up to the present, various control algorithms are applied to control blood glucose level. All the control algorithms can be classified according to the type of injection route, namely subcutaneous (SC) and intravenous (IV) injection route, each has different insulin absorption time which leads to different time delays in blood glucose control.

Shimoda *et al.* (1997) used the method for the controller design which is based on the pole-assignment strategy. Their work is an important example of a successful use of the SC route for the closed loop control of insulin-dependent diabetic patients. The reason is mainly due to the use of Lispro insulin, which is better suited for SC closed-loop control than regular insulin since it behaves like IV-injected insulin. However, the pole-assignment strategy used in the work of Shimoda and coworkers (1997) is not very robust; in addition, it requires a repeated assessment of the model parameters, which is usually difficult in clinical practice. To overcome these limitations, several authors have proposed and tested closed-loop strategies based on adaptive control (Candas *et al.,*1994). These strategies do not require periodical re-assessment of the patient parameters, and they have been shown to be at least as good, if not superior, to a pole-assignment strategy with repeated assessments (Fischer *et al*., 1987). Trajanoski, *et al*. (1997 and 1998), proposed a nonlinear predictive control strategy for closed-loop control with the subcutaneous route. The system has been assessed by simulation, using the SC route for both Lispro insulin delivery and glucose measurement. This study has some interesting aspects: first, the predictive control scheme seems flexible enough to deal with blood glucose control, even in presence of pathophysiological variations (i.e., variations in the system parameters such as time constants and gains of the system); second, the proposed controller may be easily modified to be used in real time. Unfortunately, the results are not completely satisfactory; in particular, in the presence of meals. Predictive control is emerging as an important control strategy in several applications. Its major advantages, which make it an appealing alternative to adaptive control approaches, are its capability of handling constraints in the

control space, and the possibility of ensuring stability to the controlled system. Recently, a predictive control strategy has been presented for controlling by infusing insulin via IV route (Parker *et al*. 1999), but one can easily see its possible extension to the SC route.

Eren *et al.* (2006) have developed low-order recursive linear time series models for the prediction of future blood glucose concentrations, using frequently sampled blood glucose measurements (at five minutes intervals). Such predicted glucose values are then integrated with model based control algorithms, such as generalized predictive control (GPC) and linear quadratic control (LQC), for adjusting the required insulin infusion rates with an automated insulin pump. Since the models are derived from patients' own glucose data, the proposed algorithm can dynamically adapt to inter- and intra-subject variability (Eren *et al.,* 2006).

In the regulation of blood glucose concentration, as the disturbances (e.g. change in diet, exercise, stress or illness) are highly stochastic, adaptive control algorithm would be a requirement for control mechanism. In an adaptive system it is assumed that the regulator parameters are adjusted on line continuously. This implies that the regulator parameters follow changes in the process. However, it is difficult to analyze the convergence and stability properties of such systems. To simplify the problem it can be assumed that the process has constant but unknown parameters. When the process is known, the design procedure specifies a set of desired controller parameters. The adaptive controller should converge to these parameter values even when the process is unknown. A regulator with this property is called self-tuning, since it automatically tunes the controller to obtain the desired performance (Astrom and Wittenmark, 1989).

It is proposed in this thesis that blood glucose concentration be regulated under adaptive Clarke-Gawthrop self tuning controller and blood glucose and insulin dynamics in patients with type I diabetes are simulated by GlucoSim which is an educational software package written by Agar *et al.* (2005)

In Section 2 necessary theoretical background for dynamical system and self-tuning regulation with an emphasis on Clarke-Gawthrop self-tuners are presented. In Section 3, discrete time dynamical-stochastic model of the virtual patient is obtained using impulse

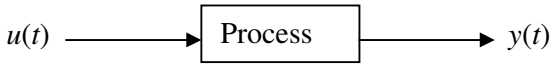
and step tests on the virtual patient. Section 4 discusses the self-tuning regulation results and finally Section 5 summarizes the conclusion reached and gives recommendation for future work.

2. THEORETICAL BACKGROUND

2.1. Discrete Process Transfer Function Models

2.1.1. Continuous Time Processes

Consider a continuous dynamical process in which an input $u(t)$ and an output $y(t)$ are related linearly.



The dynamic relationship can be represented via a first order linear ordinary differential equation as in Equation (2.1)

$$\tau \frac{dy(t)}{dt} + y(t) = K_p u(t) \tag{2.1}$$

where τ is the process time constant and K_p is the process gain. Equation (2.1) can be expressed as Equation (2.2) in operational form.

$$(\tau D + 1)\, y(t) = K_p u(t) \tag{2.2}$$

where D is the differential operator and $y(t)$ and $u(t)$ are deviations from the steady state values. One can get the first order transfer function model in Equation (2.3) by taking Laplace Transform with zero initial conditions.

$$\frac{y(s)}{u(s)} = \frac{K_p}{(\tau s + 1)} \tag{2.3}$$

Higher order systems can be expressed by the differential equation of order (r, s).

$$(1 + \tau_1 D + \tau_2 D^2 + ... + \tau_r D^r)\, y(t) = K_p (1 + G_1 D + G_2 D^2 + ... + G_s D^s) u(t - \tau_D) \tag{2.4}$$

where τ_D is the time delay in the process and $s \leq r$ for physical realizability.

2.1.2. Discrete Time Processes

If the output is measured at discrete specified time intervals (y_t; t = 0, 1, 2, ...) and the input is given at the same interval (u_t; t = 0, 1, 2, ... with u_t being constant during the time interval [t-1,t)) like in the case of digital computer control, the linear dynamic behaviour of y_t and u_t can be represented by a difference equation model, in Equation (2.5).

$$y_t - \delta_1 y_{t-1} - \delta_2 y_{t-2} - \ldots - \delta_r y_{t-r} = w_0 u_{t-b} - w_1 u_{t-b-1} - \ldots - w_s u_{t-b-s} \tag{2.5}$$

where b is the whole time delay of the process, i.e. the summation of time delay of process and a delay due to sampling. Equation (2.5) can also be expressed as Equation (2.6) by introducing the backward shift operator, B (i.e. $By(t) = y(t-1)$).

$$y_t = \frac{\left(w_0 - w_1 B - \ldots - w_s B^s\right) B^b}{\left(1 - \delta_1 B - \ldots - \delta_r B^r\right)} u_t = \frac{w_s(B)}{\delta_r(B)} B^b u_t \tag{2.6}$$

where $w(B)$ and $\delta(B)$ are polynomials of order s and r respectively and the order of the bacward shift operator B is b. Thus a model can be defined as the discrete transfer function model of order (r, s, b).

2.1.3. Relationship between Discrete and Continuous Time Processes

It is of great importance to look at the relationship between the discrete and continuous time models in order to convert one to another easily. The relationship between the continuous and discrete (sampled) system is based on the continuous behaviour of the input *u* between the sampling instants. An important case in digital computer control is that step-wise continuous input in which after taking a sample of output (y_t), the input (u_t) is adjusted to a new level and fixed at that value. This is called a zero order sample and hold.

Consider a first order system with a time delay presented by $(\tau D+1)\,y(t) = K_p u(t-\tau_D)$, where τ is the time constant, K_p is the process gain and τ_D is the time delay. Sampling a continuous process at a equispaced time interval of T_s units and assuming $u(t)$ is manipulated in the zero-order hold manner, the discrete model can be represented as a first order difference equation as follows:

$$(1-\delta B)\,y_t = \left(w_0 - w_1 B\right) u_{t-f-1} \tag{2.7}$$

by factoring the time delay into the form $\tau_D = (f+c)T_s$ where f is the number of whole periods of delay and c is a fractional period of delay. The discrete model parameters are defined as $\delta = e^{-T_s/\tau}$, $w_0 = K_p(1-\delta^{1-c})$ and $w_1 = K_p(\delta - \delta^{1-c})$. The parameter δ can be taken as the time constant of the discrete model whereas w_0 can be thought of the discrete model gain when T_s is an integer multiplier of τ_D.

2.2. Time Series Models for Stochastic Disturbances

The time dependent processes for which it is impossible to calculate the future behaviour can be defined as stochastic processes. They can be represented as time series, a sequences of observations in time $\{z_1, z_2, ..., z_N\}$. A stochastic process can be defined as stationary if its statistical properties such as its mean (μ), variance (σ_z^2) and autocovariances (γ_b) do not change with time.

$$\mu = E(z_t) \tag{2.8}$$

$$\sigma_z^2 = E(z_t - \mu)^2 \tag{2.9}$$

$$\gamma_b = \mathrm{cov}(z_t\ z_{t+b}) = E(z_t - \mu)(z_{t+b} - \mu) \tag{2.10}$$

The simplest stochastic disturbance is the white noise which is a sequence of independent identicallly distributed random variables $\{a_t,\ \ t = 1, 2, ...\}$. Assuming that a_t

is normally distributed with mean zero and variance σ_a^2, the autocovariance function is given by

$$\gamma_b = E\{a_t \ \ a_{t+b}\} = \sigma_a^2 \quad b = 0 \tag{2.11}$$
$$= 0 \quad b \neq 0$$

However, the disturbance processes are formed by highly correlated successive values.

2.2.1. Autoregressive Moving Average (ARMA) Models

The highly correlated successive series, N_t could be generated from a white noise sequence a_t by filtering through a linear dynamic filter.

$$N_t = \frac{1-\theta_1 B-\ldots-\theta_q B^q}{1-\phi_1 B-\ldots-\phi_p B^p} a_t = \frac{\theta_q(B)}{\phi_p(B)} a_t \tag{2.11}$$

or in the difference equation form

$$N_t = \phi_1 N_{t-1} + \ldots + \phi_p N_{t-p} + a_t - \theta_1 a_{t-1} - \ldots - \theta_q a_{t-q} \tag{2.12}$$

This is an autoregressive moving average (ARMA) model of order (p,q). If the $\theta(B)=1$, then the model is called autoregressive model (AR) with order of p whereas it is called moving average model (MA) with order q when $\phi(B)=1$.

2.2.2. Autoregressive Integrated Moving Average (ARIMA) Models

In most process control cases, the stochastic disturbances show a nonstationary trend and do not vary about a fixed mean. The mean level drifts, but the series in different

mean levels resemble each other. Non stationary models in charge of modeling this behaviour are obtained by one or at most two roots of $\varphi(B)$ on the unit circle. Calling the denominator of Equation (2.11) , $\varphi(B)$ and factoring as:

$$\varphi(B) = \underbrace{\phi(B)}_{stationary} \quad \underbrace{(1-B)^d}_{roots\ at\ unity} \qquad d = 1 \ \ or \ \ 2 \tag{2.13}$$

the general autoregressive-integrated-moving-average model (ARIMA) of order (p, d, q) can be obtained in Equation (2.14)

$$N_t = \frac{\theta_q(B)}{\phi_p(B)\nabla^d} a_t \tag{2.14}$$

where $\nabla = (1-B)$ is a backward difference operator. A comprehensive discussion of these models can be found in Box and Jenkins (1976).

2.2.3. Prediction of Stochastic Processes

Designing a controller requires an optimal prediction of the disturbance *b* times periods into the future. The value of an ARIMA disturbance model at a time *t+b* can be expressed in Equation (2.15).

$$\begin{aligned} N_{t+b} &= \frac{\theta_q(B)}{\phi_p(B)\nabla} a_{t+b} \\ &= (1+\psi_1 B+\psi_2 B^2+\psi_3 B^3+...)a_{t+b} \\ &= (a_{t+b}+\psi_1 a_{t+b-1}+...+\psi_{b-1}a_{t+1})+(\psi_b a_t+\psi_{b+1}a_{t-1}+...) \\ &= \psi_1(B)a_{t+b}+\psi_2(B)a_t \end{aligned} \tag{2.15}$$

The first term in the right hand side of the Equation (2.15) includes only future unknown random shocks $(a_{t+b},\ a_{t+b-1},\ ...,\ a_{t+1})$, leading the term to be unpredictable. On the other hand the second term is a function of only the known present and past shocks $(a_t,\ a_{t-1},\ a_{t-2},\ ...)$ which makes it predictable. Therefore, b-step ahead prediction $\hat{N}_{t+b/t}$

of N_t made at time t can be formed by the known part of the (t+b) head value of the disturbance in Equation (2.16)

$$\hat{N}_{t+b/t} = \psi_2(B)a_t \tag{2.16}$$

whereas the unpredictable part forms the prediction error:

$$e_{t+b/t} = \psi_1(B)a_{t+b} \tag{2.17}$$

The Equation (2.16) can also be expressed as a rational polynomial in Equation (2.18) since it is not easy to work with the form of infinite series of the prediction represented in (2.16).

$$N_{t+b} = \frac{\theta_q(B)}{\phi_p(B)\nabla^d} a_{t+b} \tag{2.18}$$

$$N_{t+b} = \psi_{b-1}(B)a_{t+b} + \frac{T(B)}{\phi_p(B)\nabla^d} a_t \tag{2.19}$$

where $\psi_{b-1}(B)$ is a polynomial of order (b-1) and $T(B)$ is a polynomial obtained from the relation below:

$$\frac{\theta_q(B)}{\phi_p(B)\nabla^d} = \psi_{b-1}(B) + \frac{T(B)}{\phi_p(B)\nabla^d} \tag{2.20}$$

or

$$\theta_q(B) = \psi_{b-1}(B)\phi_p(B)\nabla^d + T(B)B^b \tag{2.21}$$

where the subscripts denote the order of the polynomials and the order of $T(B) = \max\ (q-b, p+d-1)$.

2.2.4. Randomly Occuring Deterministic Disturbances

Although most processes have some stochastic disturbances, in many cases they are not the major disturbances in the system. In fact, the major disruptions in the process are resulting from the deterministic type disturbances such as sudden step changes, impulse changes, ramps, or exponential changes to new levels, occuring infrequently but at random intervals due to sudden unexpected loads on the system or due to unanticipated set point changes made by operators. It is shown by MacGregor *et. al.* (1980) that these processes can be represented by the structure of an ARIMA process differing only in the probability distribution of the shocks a_t which is zero most of the time and nonzero occasionally.

2.3. Optimal Controllers

The design of an optimal controller also requires a quantitative measure in order to judge the performance of the controller besides transfer function and the disturbance model of the process. Although each controller are judged via different performance indices, all indices are aimed to be minimized.

2.3.1. Minimum Variance Controller

In order to build minimum variance control, consider a model of the form

$$Y_t = \frac{w_s(B)}{\delta_r(B)} u_{t-f-1} + \frac{\theta_q(B)}{\phi_p(B)\nabla^d} a_t \tag{2.22}$$

The performance index is chosen to be the minimization of the expected value of Y_{t+b}^2 where $b = f + 1$.

$$\min_{U_t} \; E\left\{Y_{t+b}^2\right\} \tag{2.23}$$

where E is the expectation operator. The controller based on the criterion expressed in Equation (2.23) is called minimum variance controller. Using the forecasting factorization Equation (2.19), Equation (2.24) can be obtained.

$$\begin{aligned} E(Y_{t+f+1})^2 &= E\left\{\frac{w_s(B)}{\delta_r(B)}u_t + N_{t+f+1}\right\}^2 \\ &= E\left\{\frac{w_s(B)}{\delta_r(B)}u_t + \psi_f(B)a_{t+f+1} + \psi_2(B)a_t\right\}^2 \\ &= E\left\{\frac{w_s(B)}{\delta_r(B)}u_t + \psi_2(B)a_t\right\}^2 + E\left\{\psi_f(B)a_{t+f+1}\right\}^2 \\ &\quad + 2E\left\{\frac{w_s(B)}{\delta_r(B)}u_t + \psi_2(B)a_t\right\}\left\{\psi_f(B)a_{t+f+1}\right\} \end{aligned} \tag{2.24}$$

The last term on the right hand side of the Equation (2.24) will be zero because the future values of a_t in $\psi_f(B)a_{t+f+1}$ are independent of the present and past values. Besides that, the first two terms are positive. The only way to minimize the relation is equalize the term in the first parenthesis to zero. Hence one can obtain the controller equation for the manipulated variable, u_t.

$$\frac{w_s(B)}{\delta_r(B)}u_t + \psi_2(B)a_t = 0 \tag{2.25}$$

$$u_t = -\frac{\delta_r(B)}{w_s(B)}\psi_2(B)a_t = -\frac{\delta_r(B)}{w_s(B)}\hat{N}_{t+f+1/t} \tag{2.26}$$

The output deviation in response to the control action in terms of Y_t can be obtained by, eliminating a_t using the relation $a_t = 1/\psi_f(B)\, Y_t$. The controller equation can be rearranged as in the form of Equation (2.27) by inserting the Equations (2.16) and (2.19).

$$u_t = -\frac{\delta_r(B)}{w_s(B)} \cdot \frac{T(B)}{\phi_p(B)\nabla^d} \cdot \frac{1}{\psi_f(B)}Y_t \tag{2.27}$$

where $\psi_2(B) = \dfrac{T(B)}{\phi_p(B)\nabla^d}$. In differenced form the Equation (2.27) can be expressed as :

$$\nabla^d u_t = -\frac{\delta_r(B)}{w_s(B)} \cdot \frac{T(B)}{\phi_p(B)} \cdot \frac{1}{\psi_f(B)} Y_t \tag{2.28}$$

The first rational poynomial on the right hand side is inverse of the process dynamic model excluding the time delay term, the second one is the transfer function of the optimal disturbance predictor, and the last one is an optimal compensator for the f periods of time delay in the process.

2.3.2. Linear Quadratic Controller

As an alternative to minimum variance controller a different performance index in Equation (2.29) is taken.

$$\min_{U_t} \quad E\left\{Y_t^2 + \zeta'(\nabla U_t)^2\right\} \tag{2.29}$$

The performance index is aimed to minimize the output Y_t subject to a constraint on the difference of input U_t with the previous input U_{t-1}. The constraining parameter ζ' can be defined as the cost per unit control action. The controller synthesized by the criterion expressed in Equation (2.29) is called linear quadratic controller (LQC). The name comes from the linear process model and the quadratic performance index. A spectral factorization method (Wilson, 1970) is used to solve the problem. The important point of the solution is that as the constraint factor ζ' exists implicitly in the controller equation, spectral factorization should be performed for a range of values of ζ' until both the variance of the output Y_t and ∇U_t are acceptable. Furthermore, in LQC algorithm, the effect of the present control action on all future values of the variance of the output is considered which leads the controller also to be called "the infinite step controller".

2.3.3. One-step Optimal Controller

Clarke-Hasting James (1971) proposed a novelty in the LQC which eliminates the necessity of spectral factorization in the solution of minimizing the output Y_t subject to a constraint on the difference of input U_t with the previous input U_{t-1}. Their quadratic performance index can be summarized that at every control interval the controller drives the b-step ahead minimum mean squared forecast of the output to zero. This controller differs from the LQC in that it does not consider the effect of present control action on the variance of the output beyond the b time delay, just sets the instantenous b step ahead forecast of the output to zero.

One step optimal controller is obtained by minimizing an instantenous performance index given in Equation (2.30),

$$\min \ \left\{ Y_{t+b/t}^2 + \zeta''(\nabla U_t)^2 \right\} \tag{2.30}$$

where $Y_{t+b/t}$ is the b-step ahead forecast of the output Y_t.

To solve the minimization problem it is necessary to divide the disturbance part into two parts namely forecastable part and unforecastable part.

$$N_{t+b} = \psi(B)\, a_{t+b} + \frac{T(B)}{\phi_p(B)\nabla^d} a_t \tag{2.31}$$

In the Equation (2.31) the first term on the right hand side is the unforecastable part which is the forecast error and the second term is the forecastable one. After rearranging the Equation (2.30) by adding Equation (2.22) and Equation (2.31) and differentiating with respect to U_t and equating the derivative to zero, the controller equation can be obtained in which the constraint factor ζ appears explicitly,

$$\nabla U_t = -\frac{\delta(B)\ \ T(B)}{\psi_f(B)\ \ w(B)\ \ \phi(B)+\zeta\ \delta(B)\ \ \theta(B)} Y_t \tag{2.32}$$

where $\zeta = \frac{\zeta''}{w_0}$. When $\zeta = 0$ the controller reduces to minimum variance controller.

Note that the constraint factor appears explicitly in the control law. The constraint factor can be interpreted as the pole shifting parameter which gradually shifts the poles of $w(B)$ towards those of $\delta(B)\nabla$. For $\zeta \neq 0$ the "one-step" optimal controller can be viewed as cancelling some fraction of the minimum mean square forecast; therefore, for a given variance of the input, the variance of the output is slightly larger than the corresponding LQ design. Nevertheless the simplicity of the algorithm makes it popular.

2.4. Adaptive Control

In daily life, to adapt is used to change behavior in order to deal with new situations or purposes. Adaptive control is also found for the similar reasons. An adaptive controller is a controller which can change its behavior (i.e. its parameters) to fit changes in dynamics of the process or in disturbances. The primary reason for introducing adaptive control was to obtain controllers that could adapt to changes in process and disturbance parameters. Adaptive control can be classified as gain scheduling, model-reference adaptive control, and self-tuning regulators. In what follows self-tuning regulators are introduced as this is the controller implemented on a virtual patient with Type I diabetes.

2.4.1. Self-tuning Regulators

The theory of self-tuning regulator (STR) was originally proposed by Kalman (1958). Astrom and his coworkers have developed the self-tuning version of the controller proposed by Astrom and Wittenmark, (1973) and Astrom *et. al.* (1977). Self-tuning regulators, their design principles and applications can be found in the study of Astrom (1980). A guide of practical rules for applications can be found in the Ph.D. dissertation of Camurdan (1986). What follows in this section are excerpts from this work.

As was stated earlier, in designing an optimal controller the process and the disturbance model have to be known a priori, but for self-tuning regulators no such knowledge is necessary since the controller converges to the optimal controller that would have been obtained had the process and disturbance been known (the self-tuning property). STRs are based on an online combination of identification and control. Unknown contoller parameters are estimated through using a recursive parameter estimation routine. It is based on certainty equivalence i.e uncertainties associated with parameter estimates are not taken into account.

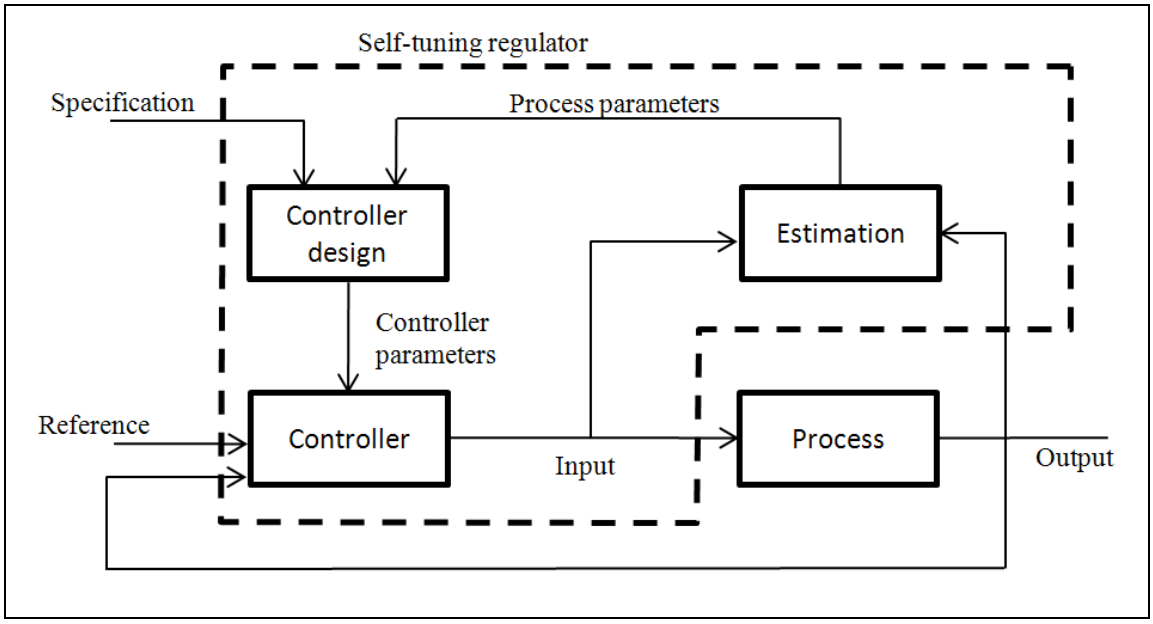


Figure 2.1 Block diagram of self-tuning regulator

There are many types of STRs resulting from different design procedures and different estimation routines. If the process dynamics is time varying then an adaptive version of STRs may be necessary to meet the model parameter variations since an adaptive controller can retune itself to changing dynamics. If the process has operating point dependent nonlinearity then this is handled by the STR as if it is time varying problem. STRs can be implemented as true self-tuning algorithms in that they use all the process information available to determine the optimal settings for the tuning parameters. They can also be implemented as an adaptive controllers, in that they only use a part of

the past process information to tune the parameters; they can re-tune as the process evolves because they forget very old process information.

A control loop operating under STR is composed of two parts; (i) the controller and the process and (ii) on line estimator and a controller design part as can be seen in Figure 2.1. The information that the estimator receives about the dynamics of the process and the disturbance are the present and the past values of the input (i.e. the manipulated variable) and the output (i.e. the controlled variable) deviations from their respective steady state values. The estimator uses this information to estimate the transfer function and the disturbance model and passes these estimates to the controller design block which operates on this data to carry out the controller parameter calculating such as a spectral factorization or pole placement and, in turn, feeds this information to the controller. Finally the controller calculates the present control action. This estimation form is being referred to as explicit identification because the process and the noise model are estimated explicitly. A simpler version of STR is the one whereby the controller parameters are updated directly bypassing the intermediate algorithmic computations. This STR algorithm is referred to as implicit. It must be emphasized that the rate at which the estimator adapts to varying process dynamics must be faster than the rate at which the process parameters change. Note that the parameters are estimated under closed loop conditions. This is possible since a closed loop system with STR is a nonlinear and time varying stochastic system.

2.4.1.1. Clarke-Gawthrop Self-tuning Regulator. Clarke-Gawthrop (1975), by using Clarke and Hasting-James (1971) performance index, developed the implicit self-tuning version of the “one-step” optimal controller as a straight forward extension of the stochastic minimum variance self-tuning controller proposed by Astrom and Wittenmark (1973). However, as pointed out by Macregor and Tidwell (1980) an assumption made regarding the expectation operator in the work of Clarke and Hasting-James (1971), and Clarke-Gawtrop (1975) is incorrect. A corrected version of the detailed derivation can be found in the study of Harris (1977). If the parameters of the Clarke-Gawthrop regulator converge then the controller will minimize

$$\hat{Y}_{t+b/t} + \zeta' (\nabla U_t)^2 \tag{2.33}$$

where $\hat{Y}_{t+b/t}$ is the b-step ahead forecast of Y_t made at time t. The self-tuning version of this constrained input controller can be obtained by showing that the same strategy will also minimize

$$E\left(\left(Y_{t+b/t} + \zeta \ \nabla^d U_t\right)^2\right) = E\left(\phi_{t+b}\right)^2 \tag{2.34}$$

where $\zeta = \zeta' / w_0$ and can be a negative or a positive number depending on the sign of w_0 such that ζ' is positive.

Defining a generalized output variable of the form:

$$\phi_{t+b} = Y_{t+b} + \zeta \ \nabla U_t \tag{2.35}$$

The unknown parameters of the numerator and the denominator polynomials in Equation (2.32), are estimated via the recursive least squares estimation algorithm, from the regression equation:

$$\phi_{t+b} = \alpha(B) \ \ Y_t + \beta(B) \ \ \nabla U_t + e_{t+b} \tag{2.36}$$

where e_{t+b} is the error term associated with the estimation, and is assumed to be uncorrelated with the regressors Y_t and ∇u_t. $\alpha(B)$ and $\beta(B)$ polynomials are the numerator and the denominator terms in Equation (2.32) The generalized loss function minimized by the estimation algorithm is :

$$J = \sum_{i=1}^{t} \lambda^{t-i} e_i^2(t) \tag{2.37}$$

In the equation above λ is the forgetting factor (exponentially discounting factor) whose domain is defined on the interval $0 < \lambda \leq 1$. This generalized form of recursive

least squares estimation, for λ less than 1, naturally leads to adaptive control whereby the controller parameters are adapted to changes in process transfer funstion parameters. If λ is equal to 1 then the estimation algorithm is reduced to ordinary least squares and when it is less then 1.0 then the algorithm will discount the information of the distant past by putting lesser weights on these past data points. A discounting factor between 0.99 and 0.95, provided that the disturbances are persistent and that the controller is not overparametrized, works well in practical applications. The number of past observations used in estimation is called the effective window length (Clarke-Gawthrop, 1975) and is given by:

$$\frac{1.0}{1-\lambda} \tag{2.38}$$

A large value of λ will lead to slow but smooth adaptation, whereas a small value of λ will lead to quick but noisy adaptation. λ equal to 1.0 corresponds to infinite memory length where all the present and past information are weighted equally.

The estimation routine is done in the following way: Define θ, X_t and X_{t-b} vectors as:

$$\theta = (\alpha_0, \alpha_1, ..., \alpha_{m+1}, \beta_0, \beta_1, ..., \beta_{l+1})' \tag{2.39}$$

$$X_t = (Y_t, Y_{t-1}, ..., Y_{t-m}, \nabla U_t, \nabla U_{t-1}, ...\nabla U_{t-l})' \tag{2.40}$$

$$X_{t-b} = (Y_{t-b}, Y_{t-b-1}, ..., Y_{t-b-m}, \nabla U_{t-b}, \nabla U_{t-b-1}, ...\nabla U_{t-b-l})' \tag{2.41}$$

where m is the order of the polynomial $\alpha(B)$, and l is the order of the polynomial $\beta(B)$ in the Equation (2.35). Note that the dimensions of the vectors defined in Equations (2.39) through (2.41) are equal to $m+l+2$.

The equation (2.36) can then be written in compact vector notation as

$$\phi_{t+b} = X'_t \theta + e_{t+b} \tag{2.42}$$

or

$$\phi_t = X'_{t-b} \theta + e_t \tag{2.43}$$

Note that the controller equation is given by:

$$X'_t \theta = 0 \tag{2.44}$$

or

$$\beta_0 \nabla U_t + \beta_1 \nabla U_{t-1} + ... + \beta_l \nabla U_{t-l} + \alpha_0 Y_t + \alpha_1 Y_{t-1} + ... + \alpha_m Y_{t-m} = 0 \tag{2.45}$$

The elements of the θ vector that can be defined as the controller parameters are updated at every control interval from:

$$\theta_t = \theta_{t-1} + K_t (\phi_t - X'_{t-b} \theta_{t-1}) \tag{2.46}$$

The term in the paranthesis is an estimate of the one step ahead prediction error, and K_t is the gain vector for updating the parameters. The gain vector is related to the P_t matrix which is proportional to the variance covariance matrix of the parameter estimates i.e. the θ vector. The gain vector K_t and the P_t matrix are given by:

$$K_t = \frac{P_{t-1} X_{t-b}}{\lambda + X'_{t-b} P_{t-1} X_{t-b}} \tag{2.47}$$

$$P_t = \left[P_{t-1} - \frac{P_{t-1} X_{t-b} X'_{t-b} P_{t-1}}{\lambda + X'_{t-b} P_{t-1} X_{t-b}} \right] \Big/ \lambda \tag{2.48}$$

The diagonal elements of the P_t matrix are a measure of the uncertainty of the parameter estimates. A low value is an indication of the certainty and conversely a high value is an indication of the reduction in the parameter uncertainty attained from the last measurement. The second term in Equation (2.48) is a measure of the reduction in the parameter uncertainty attained from the last measurement. Therefore,

when the forgetting factor is equal to 1, the elements of the P_t matrix decrease monotonically as the parameters converge. This is because at every interval more information is obtained, consequently confidence over the parameter estimates is increased. The effect of the forgetting factor on the P_t matrix, for $\lambda < 1$, is that the elements of the P_t matrix and hence the gain of the estimator is kept larger; thereby the elements of the P_t matrix will not tend to zero and the algorithm will always be alert to track changing process dynamics.

Consider the case when the parameters of the process and the disturbance model are time invariant, and λ is 1.0. As more information is coming to the estimator the parameters converge to a constant value. This is reflected in the P_t matrix by the fact that the elements tend towards zero because of the increased confidence over the parameter estimates. This in turn causes the gain of the estimator to approach zero. At this point the estimator should be switched off to avoid numerical problems.

If the transfer function plus the noise model structural configurations can be conjectured without any knowledge as to the parameter values, then the orders of the $\alpha(B)$ and $\beta(B)$ polynomials can readily be obtained, from Equation (2.32). If, however, neither the structural configuration nor the parameters are known then the order of the $\alpha(B)$ and $\beta(B)$ polynomials can be guessed and then the optimality of the controller can be checked by means of the two theorems (Astrom and Wittenmark, 1973). According to one of these theorems, if the controller structure is optimal then certain cross and auto correlations of the generalized output variable ϕ_t with the input variable U_t will be statistically insignificant.

The parameters α_i and β_i are estimated at each control interval. A close look at Equation (2.45) shows that one parameter is redundant and hence can be fixed initially by zeroing out the corresponding rows and columns of the P_t matrix. Since a zero element of this matrix reflects an absolute certainty over this parameter it will not be updated. It is shown by Astrom and Wittenmark (1973) that the fixed

numerical value of β_0 must the satisfy the inequality $0.5w_0 < \beta_0 < \infty$ for the closed loop stability.

It should be emphasized that STRs are complex regulators. Contrary to what the name "self-tuning " might imply, a number of a priori estimates have to be provided so that a stable and optimal controller can be achieved. This requires system insight and engineering judgement to implement a self tuner in a control loop. Order of the $\alpha(B)$ and $\beta(B)$ polynomials, sampling period, number of periods of delay, discounting factor λ, and the initial estimates of the θ vector and the P_t matrix are required. A detailed discussion regarding the choice of the tuning parameters of the STR is given in the paper of Wellsted and Zanker (1982).

3. MODELING OF THE PROCESS-DISTURBANCE MODEL AND THE CONTROLLER

3.1. Modeling of the Process

In this study, adaptive Clarke-Gawthrop self-tuning regulator is tested on a virtual patient with type I diabetes. As a virtual patient a software GlucoSim is used. It is an educational software developed by Agar, *et. al.* (2005) for simulating glucose-insulin interaction in a type-I diabetic patient. Mathematical models with varying degrees of complexities are built on pharmacokinetic diagrams of insulin and glucose. Modeling the glucose-insulin interaction requires an understanding of the physiological and metabolic processes that determine the observable behavior. Chemical reactions and transport processes form an integrated network when modeling the glucose-insulin interaction in human body. A number of mathematical models of the insulin-dependent (type-I) diabetes mellitus have been previously reported in the literature (Puckett and Lightfoot, 1995; Cobelli *et. al.* , 1982; Bergman *et. al.*, 1973; Leaning and Boroujerdi, 1991). However, they extended and utilized two mathematical models of Puckett and Lightfoot (1995) based on pharmacokinetic diagrams of glucose and insulin which represent the transport of glucose and insulin through the major vessels to the capillaries.

In order to design the controller, a process model is required. This empirical model is obtained from the GlucoSim using a step test and approximating the process reaction curve by a first order plus time delay model from which a discrete pulse transfer function is obtained.

Consider a model given in the Equation (3.1)

$$Y_t = \frac{w_s(B)}{\delta_r(B)} u_{t-f-1} \tag{3.1}$$

where $w(B)$ and $\delta(B)$ are the polynomials of order r and s respectively and f is the process time delay. For a first order plus dead time model with a zero-order hold the Equation (3.2) has the form

$$Y_t = \frac{(w_0 - w_1 B)}{(1-\delta B)} B^f u_{t-1} \tag{3.2}$$

where $w_0 = K_p(1-\delta^{1-c})$, $w_1 = K_p(\delta - \delta^{1-c})$, $\delta = e^{-T_s/\tau}$, $f = \text{integer}\,(\tau_D/T_s)$ and $c = \text{fraction}\,(\tau_D/T_s)$

A process reaction curve obtained following a step change to insulin injection rate is given in Figure 3.1 in which the y axis denotes the blood glucose concentration G_B in a virtual patient. The identified process model transfer function is given by Equation (3.3).

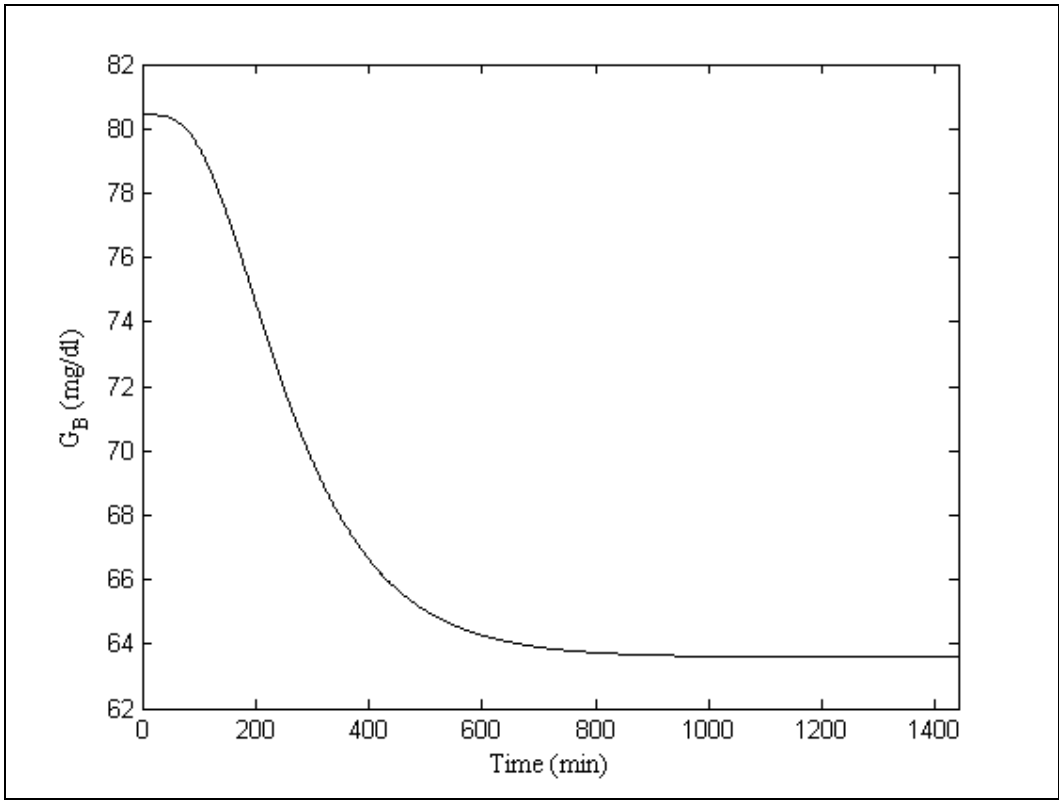


Figure 3.1. Open loop response of GlucoSim to a step change in insulin injection

Time delay is determined as 70 minutes and the process gain is found to be -0.0024.

$$G_P(s) = \frac{K_p e^{-\tau_D s}}{\tau_P s + 1} = \frac{-0.0024 e^{-70s}}{280s + 1} \tag{3.3}$$

This continuous model is then discretized for the sampling time of five minutes. Therefore the pulse transfer function for the GlucoSim process is

$$Y_t = \frac{-0.00004}{(1-0.98B)} B^{14} u_{t-1} = \frac{w_0}{(1-\delta B)} B^f u_{t-1} \tag{3.4}$$

3.2. Modeling of the Disturbance

The disturbances of a diabetic patient are generally formed by the meals taken at specified time intervals.

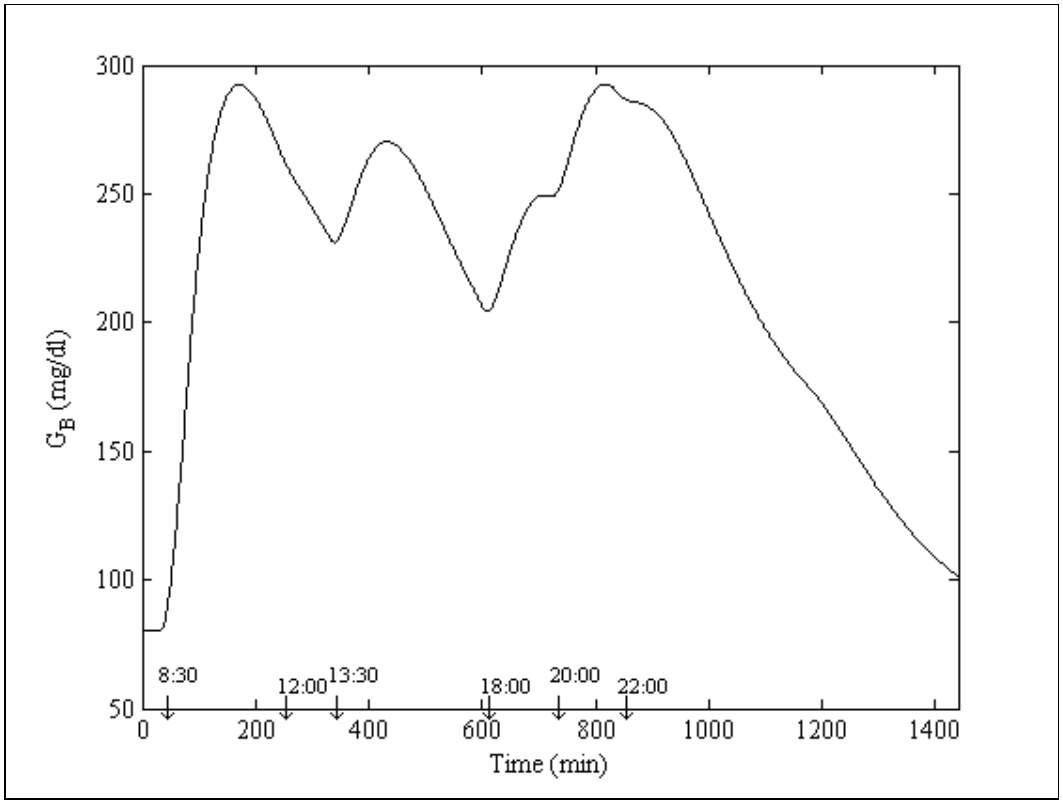


Figure 3.2. Open loop response of Glucosim to meals taken at specified times

By observing the open loop response of the GlucoSim to the meals taken at some specified times given in Figure 3.2, the disturbances are modeled as randomly occurring deterministic signals and expressed as :

$$N_t = \frac{1}{(1-\phi B)\nabla} a_t, \tag{3.5}$$

where a_t are random shocks which is most of the time zero and non zero occasionally. (Meal or snack times). The disturbance model given in the Equation (3.5) is an Auto Regressive Integrated (ARI) disturbance model, of order (1,1) with $d = 1$. The value of the parameter ϕ in the ARI (1,1) model is obtained as a step response from the impulse response in Figure 3.2 and determined approximately as 0.6.

Box-Jenkins type transfer function plus disturbance model is obtained upon combining Equation (3.4) and (3.5) which is hereafter referred to as discrete linear dynamic stochastic model

$$Y_t = \frac{w_s(z^{-1})}{\delta_r(z^{-1})} u_{t-b} + N_t \tag{3.6}$$

where $N_t = \frac{1}{\phi(z^{-1})\nabla^d} a_t$ and $b = f + 1$.

$$Y_t = \frac{-0.00004}{(1-0.98B)} B^{14} u_{t-1} + \frac{1}{(1-0.6B)\nabla} a_t \tag{3.7}$$

3.3. Design of the Controller

The Clarke-Gawthrop self tuning controller equation was given in Equation (2.32) previously in Section 2.3.3.

$$\nabla^d u_t = \frac{\delta_r(B)\ T(B)}{\psi_f(B)\ w_s(B)\ \phi_p(B) + \zeta\ \delta_r(B)\ \theta_q(B)} Y_t \tag{3.8}$$

$$\frac{\theta_q(B)}{\phi_p(B)\nabla^d} = \psi_f(B) + \frac{T(B)B^{-b}}{\phi_p(B)\nabla^d} \tag{3.9}$$

$$\theta(B) = \psi_f(B)\phi(B)\nabla^d + T(B)B^{-b} \tag{3.10}$$

To satisfy the above the order of $T(B)$ must be identified firstly.

$$\text{order of } T(B) = \text{maximum } (q - f - 1,\ p + d - 1) \tag{3.11}$$

As $q = 0, f = 14$, $p = 1$, and $d = 1$ the order of $T(B)$ is equal to 1 i.e. $T(B) = t_0 + t_1 B$. The $\psi_f(B)$ and $T(B)$ polynomials are obtained by long division of $\theta(B)$ into $\phi(B)\nabla^d$.

$$\begin{array}{l} \theta(B)\,\big|\,\underline{\phi(B)\nabla^d} \\ \qquad\qquad \psi_f(B) \\ \underline{-\quad\quad} \\ T(B)B^{-f-1} \end{array}$$

$$\begin{array}{l} 1 \quad \big|\,\underline{(1-\phi_1 B)(1-B)} \\ \qquad 1+(\phi_1+1)B+(\phi_1^{\,2}+\phi_1+1)B^{-2}+\ldots+(\phi_1^{\,f}+\phi_1^{\,f-1}+\ldots+1)B^{-f} \\ \underline{-\quad\quad} \\ \underbrace{\left[(1+\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})-(\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})B^{-1}\right]}_{T(B)}B^{-f-1} \end{array}$$

Controller parameters should converge to the values of the given expression below:

$$\begin{aligned} \underset{\beta_0}{1}\nabla u_t = & \underbrace{-\frac{(w_0-\zeta\delta_1)}{(w_0+\zeta)}}_{\beta_1}\nabla u_{t-1} \underbrace{-\frac{w_0}{(w_0+\zeta)}}_{\beta_2}\nabla u_{t-2} \underbrace{-\frac{w_0}{(w_0+\zeta)}}_{\beta_3}\nabla u_{t-3} -\ldots \underbrace{-\frac{w_0}{(w_0+\zeta)}}_{\beta_f}\nabla u_{t-f} \\ & \underbrace{+\frac{(\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})}{(w_0+\zeta)}}_{\beta_{f+1}}\nabla u_{t-f-1} \underbrace{+\frac{(1+\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})}{(w_0+\zeta)}}_{\alpha_0}Y_t \\ & \underbrace{-\frac{\left[\delta_1(1+\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})+(\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})\right]}{(w_0+\zeta)}}_{\alpha_1}Y_{t-1} \underbrace{+\frac{\delta_1(\phi_1+\phi_1^{\,2}+\ldots+\phi_1^{\,f+1})}{(w_0+\zeta)}}_{\alpha_2}Y_{t-2} \end{aligned} \tag{3.12}$$

The initial values of controller parameters are hence obtained using the discrete dynamic-stochastic model parameters given in Equation (2.32). In the Result and Discussion these parameter values are used as initial estimates for the case when the process-disturbance model parameters are approximately known.

4. RESULTS AND DISCUSSION

Prior to the regulation of blood glucose concentration, the Clarke-Gawthrop self-tuning regulator is firstly simulated on a simple first order system with different delay times. After ascertaining that the controller algorithm works properly for these simple systems used, it is then applied to GlucoSim which is an educational software that simulates the glucose-insulin interaction in Type I diabetic patients.

The maximum duration of simulation in GlucoSim is 24 hours. Times at which the meals are taken and the carbohydrate (CHO) content of the meals can be adjusted at the beginning of each run. The CHO content of the meals and the time of each meal are taken to be the same in each simulation. The patient is assumed to have three meals and three snacks in a day, i.e breakfast, snack, lunch, snack, dinner and snack. The carbohydrate content of the meals are 1000, 100, 500, 500, 500, 200 mg per kg body weight respectively and each of them is taken at 08:30, 12:00, 13:30, 18:00, 20:00 and 22:00.

Clarke-Gawthrop type self-tuning regulator is a sophisticated algorithm wherein many parameters need to be considered. In order to keep the blood sugar in a safe 80-110 mg dl^{-1} range, the parameters in the algorithm should be varied so that the optimum parameter settings can be found. As the whole glucose-insulin dynamics is very complex, the performance of the regulator is highly dependent on the initial parameters used. The parameters that should be specified at the beginning of control are the initial values of the controller parameters, (i.e. the $\theta = [\alpha_1, \alpha_2, \alpha_3, \beta_0, \beta_1, ..., \beta_{15}]$ at t=0), the covariance matrix P of the controller parameters, set point of blood glucose concentration, the maximum insulin infusion rate that a patient can take in a day, basal insulin infusion rate, the constraint factor ζ of the manipulated variable (insulin infusion), forgetting factor λ, and sampling time (control period) of continuous GlucoSim process.

Under open loop condition, if the patient simply has a breakfast of 1000 CHO mg per kg body weight and nothing for the next 24 hours then the blood glucose concentration level increases initially and then settles to the 147, 100, 92, 86 and 80 mg dl^{-1} if the basal rate of insulin infusion is set to 0, 2400, 3400, 4400, and 5400 mU min^{-1}

respectively. Therefore depending on the specified set point, the basal rate is specified accordingly (e.g. 5400 mU min^{-1} if the set point is 80 mg dl^{-1}). However, in the simulation studies carried out the optimum basal rate is found to be 5400 mU min^{-1} for all set points, and hence is fixed at this value.

This part is divided into six subsections wherein each of the aforementioned parameters are varied and the manipulated and the controlled variables are recorded. Furthermore, all the subsections are also subdivided into two parts according as whether only the structure of the controller is assumed to be known but the parameters are not, and both the structure of the controller and its approximate parameter values are known. This means that in the first case both the structures of process dynamic stochastic model and the disturbance dynamic stochastic model are known but the parameter values are unknown (hereafter referred to as unknown dynamic stochastic model parameters case) whereas in the second part both the transfer function and the disturbance dynamic stochastic model are approximately known (hereafter referred to as approximately known dynamic stochastic model parameters case).

In all the simulations presented in this section some parameters are specified as follows: Basal rate of the insulin infusion rate is set to 5400 mU min^{-1}, the constraint factor of insulin infusion rate is 1.5 and the forgetting factor is 0.5. Unless otherwise stated the values of the parameters given above are kept constant all through the simulations. The initial diagonal elements of covariance P matrix are set to appropriate values given while the off diagonal elements are set to zero, i.e. $P = a\ I$ where a is an appropriate scalar and I is the unit matrix with appropriate dimensions. Every time a change is made in a parameter e.g. initial values of controller parameters, the constraint factor, etc. This change is simulated for both unknown and approximately known dynamic stochastic model parameter cases. In all figures that follow, the controlled variable, the blood glucose concentration G_b versus time is presented in the (a) part of figures in mg dl^{-1} unit, whereas the control action, insulin infusion rate is given in mU min^{-1} unit in the (b) part.

Controller performance is measured quantitatively by Integral Square Error (ISE) and defined as sum of squares of the difference between the set point and the controlled variable.

4.1. Changes in the Initial Values of Controller Parameters (θ Vector) and Their Covariance P Matrix Estimates

In this part, the effects of the changes in initial values of controller parameters and covariance matrix of these parameters on the regulation of blood glucose concentration are investigated. In each run presented in this part, the other parameters, i.e. set point of blood glucose concentration, the maximum insulin infusion rate, basal insulin infusion rate, the constraint factor ζ of insulin infusion, forgetting factor λ and sampling time of continuous GlucoSim process are kept constant at the values of 100 mg dl^{-1}, 50000 mU min^{-1}, 5400 mU min^{-1}, 1.5, 0.5, and 5 minutes respectively.

4.1.1. Changes in the Initial Values of θ Vector and P matrix with Unknown Process-Disturbance Model Parameters

Since in the adaptive self-tuning controller algorithm, it is not necessary to know the process and disturbance dynamic stochastic model, at the onset of the control all the controller parameters θ_i are set to "1", and the diagonal elements of covariance P matrix is set to large values since large diagonal values of P indicates little information about the parameters, this in turn renders the parameter estimator with a large gain.

The closed loop responses of GlucoSim process to the changes in the initial values of the controller parameters are presented in Figures 4.1 to 4.3. The initial values of the controller parameters are taken as (1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) in Figure 4.1, (1, 1, 1, 1, 1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1) in Figure 4.2, and (1, 1, 1, 1, 1, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01) in Figure 4.3. The choice of initial parameters is a consequence of the fact that β_is for $i > 3$ converges to very small values. In these runs variances of the controller parameters are initially set to 1000.

For the responses presented in Figure 4.1, all the values of controller parameters α_is and β_is (θ_is) are initialiazed at 1. At the end of 24 hour period, the glucose concentration decreases below to 50 mg dl^{-1} which is a real threat for hypoglycemia. Therefore a change in initial guesses of θ vector is made and the values of β_is (i=3,4,...,n) are reduced to 0.1 in Figure 4.2.

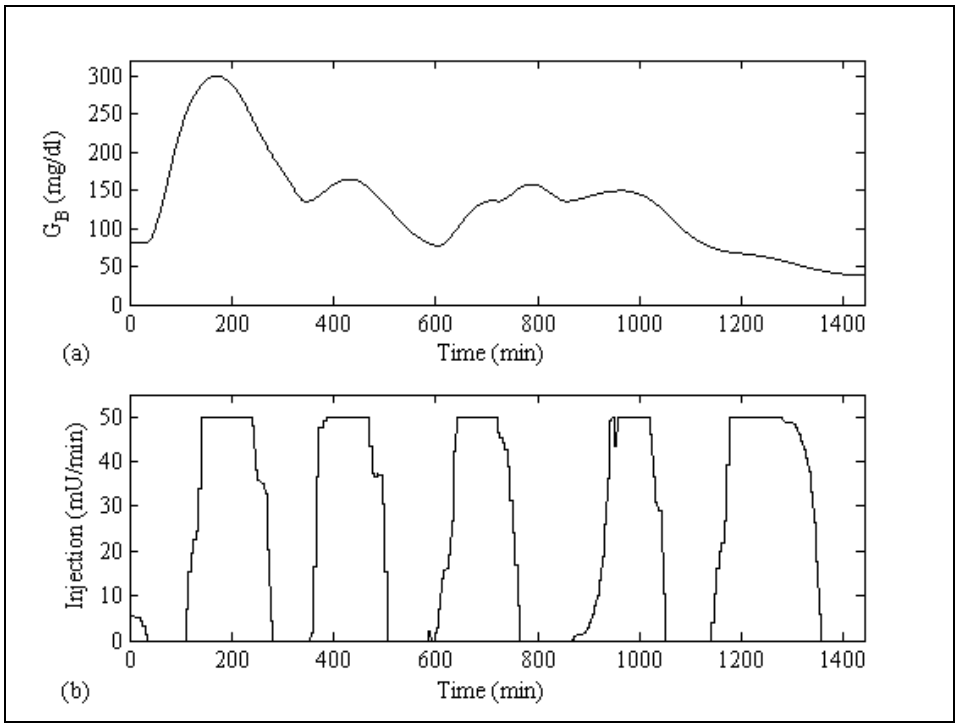


Figure 4.1. The response when all the controller parameters α_is and β_is are initialized at 1 and dynamic stochastic model parameters are unknown.

The response of blood glucose concentration is more acceptable than the one in Figure 4.1 until the early morning hours. But in the hours closer to wake up, the patient is again exposed to hypoglycemia. ($G_B < 50$ mg dl^{-1})

Later the initial values of β_is (i=3,4,..n) are further decreased to 0.01 in Figure 4.3.

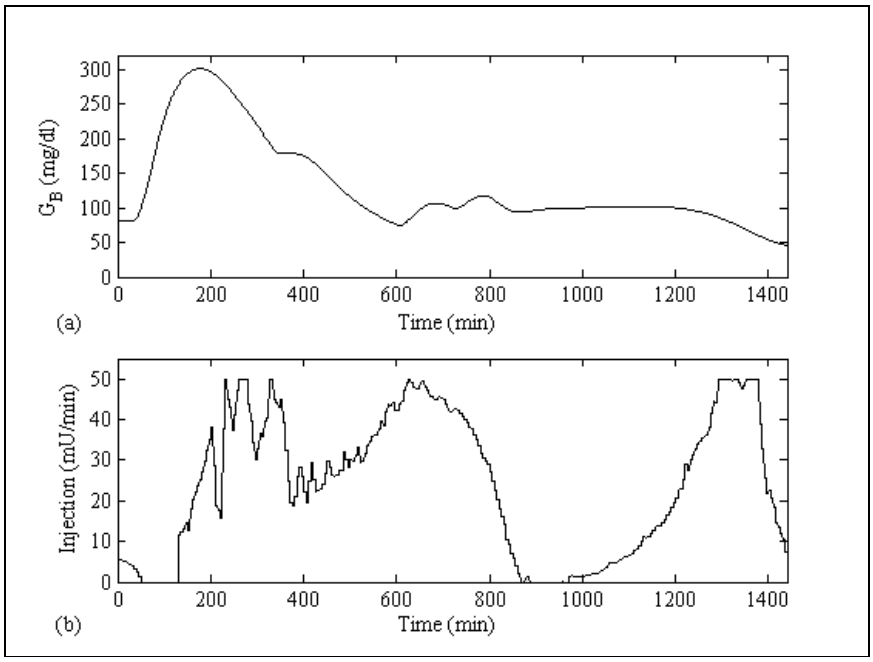


Figure 4.2. The response when the controller parameters α_is are initialized at 1, β_is are initialized at 0.1 and dynamic stochastic model parameters are unknown.

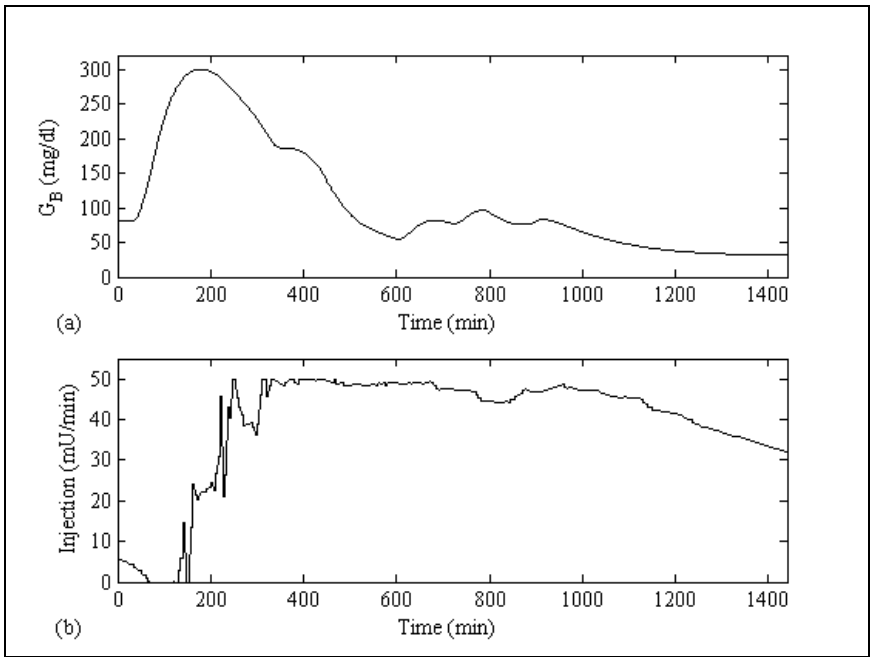


Figure 4.3. The response when the controller parameters α_is are initialized at 1, β_is are initialized at 0.01 and dynamic stochastic model parameters are unknown.

When the responses in Figures 4.1 to 4.3 are compared, the most appropriate guess for the θ vector seems to be the one with β_is =0.1 (i=3,4,..n) and the rest is equal to 1, which is presented in Figure 4.2. As G_B falls just below 50 mg dl^{-1} at the very end of 24 hour period whereas other two cases G_B to go below 50 mg dl^{-1} for much larger periods of time after midnight (1000 minutes in Figures 4.1 and 4.3). Since the response corresponding to Figure 4.2 has the lowest ISE (Table 1) the parameter values used for this case are also used to check the effect of the initial P matrix.

Table 4.1. ISE values of all simulations presented in Figures 4.1-4.34

ISE = Integral Square Error			
	ISE ($x10^{-6}$)		ISE ($x10^{-6}$)
Figure 4.1	3366	Figure 4.18	12738
Figure 4.2	2488	Figure 4.19	7498
Figure 4.3	3130	Figure 4.20	9186
Figure 4.4	2540	Figure 4.21	6235
Figure 4.5	2853	Figure 4.22	6196
Figure 4.6	3025	Figure 4.23	2631
Figure 4.7	2125	Figure 4.24	2019
Figure 4.8	9188	Figure 4.25	4414
Figure 4.9	8572	Figure 4.26	4090
Figure 4.10	12698	Figure 4.27	5264
Figure 4.11	2861	Figure 4.28	3738
Figure 4.12	5378	Figure 4.29	2530
Figure 4.13	7624	Figure 4.30	4891
Figure 4.14	3373	Figure 4.31	4147
Figure 4.15	14864	Figure 4.32	5072
Figure 4.16	4163	Figure 4.33	3690
Figure 4.17	5067	Figure 4.34	3574

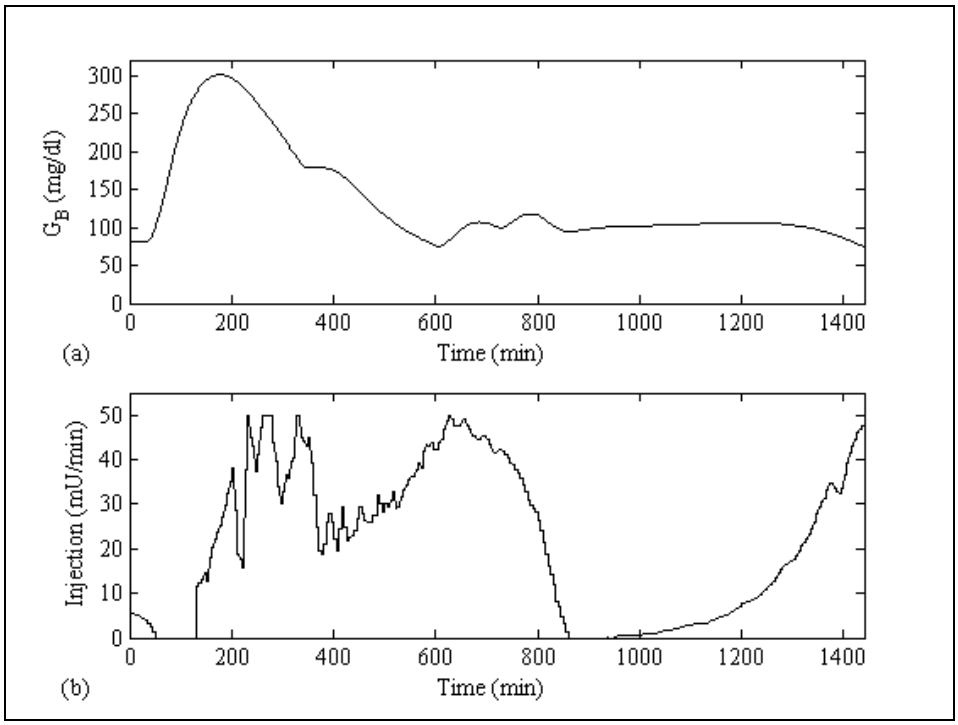


Figure 4.4. The response when diagonal elements of *P* matrix are initialized at 100 and dynamic stochastic model parameters are unknown.

On the other hand, the effect of initial values of covariance *P* matrix when regulating the blood glucose concentration is investigated by setting the variances of the controller parameters to 100, 1000, 10000 and 100000 in Figures 4.4, 4.2, 4.5, and 4.6 respectively.

As the P matrix values become larger, a better control of glucose concentration in the blood is obtained (lower ISE values), since larger variances allows more freedom to controller parameter variations to converge to the initially unknown true values.

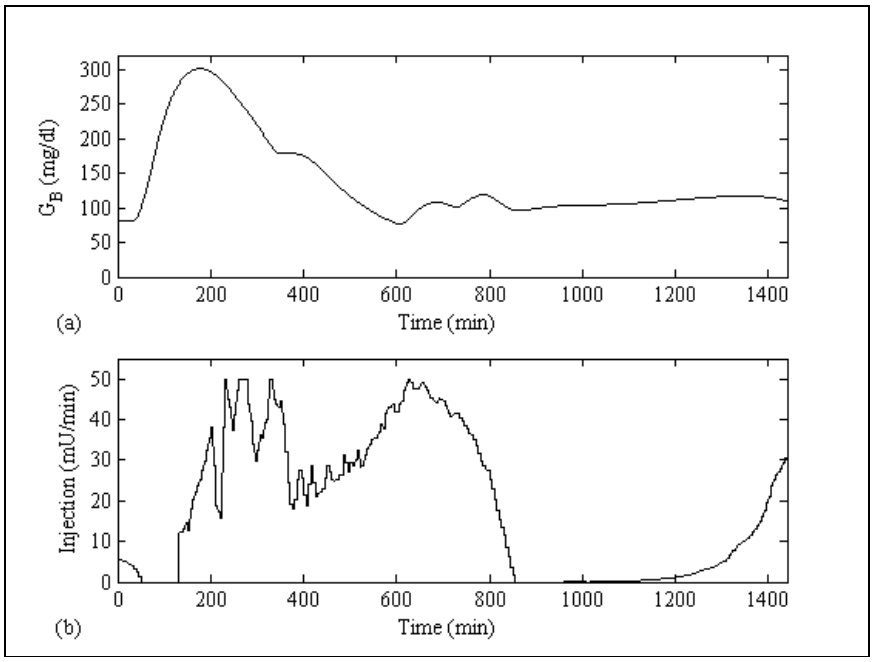


Figure 4.5. The response when diagonal elements of *P* matrix are initialized at 10000 and dynamic stochastic model parameters are unknown.

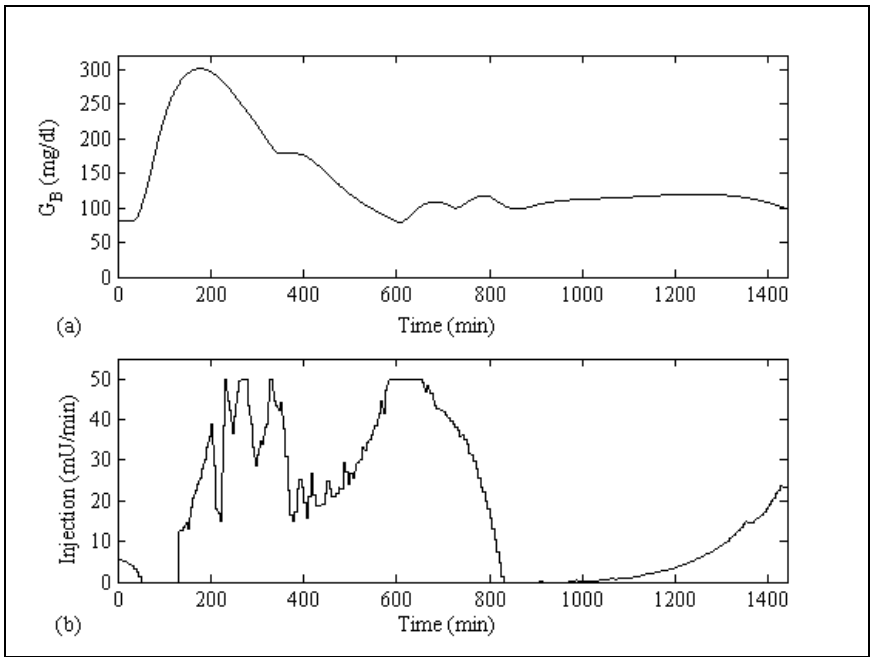


Figure 4.6. The response when diagonal elements of *P* matrix are initialized at 100000 and dynamic stochastic model parameters are unknown.

4.1.2. Changes in the Initial Values of θ Vector and P matrix with Approximately Known Process-Disturbance Model Parameters

Finally in Figures 4.7 to 4.9, the controller parameters that can be approximately obtained if the discrete linear dynamic-stochastic dynamic stochastic model parameters are known (from impulse tests), are used with low initial covariance matrix in the GlucoSim. In these simulations, P matrix are initialized at 1, 0.1, and 0.01 respectively.

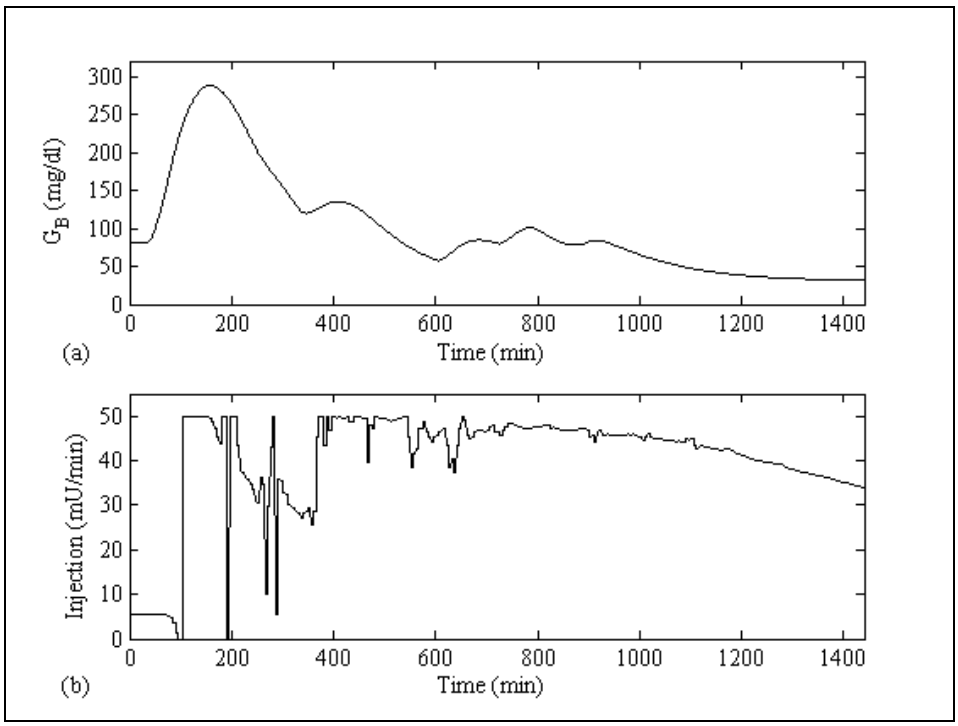


Figure 4.7. The response when diagonal elements of P matrix are initialized at 1 and dynamic stochastic model parameters are approximately known.

The benefit of initially giving close to the true values of parameters is limited to the first few hours when faster response to the breakfast is obtained because of rapid insulin infusion. Glucose concentration level which exceeds of 300 mg dl^{-1} is prevented. However, due to the nonlinearity of the process a low gain estimator (because of low P matrix) cannot keep track of changing controller parameters and hence the control deteriorates. After about 10 hours (600 minutes), the unknown parameter case gives better results.

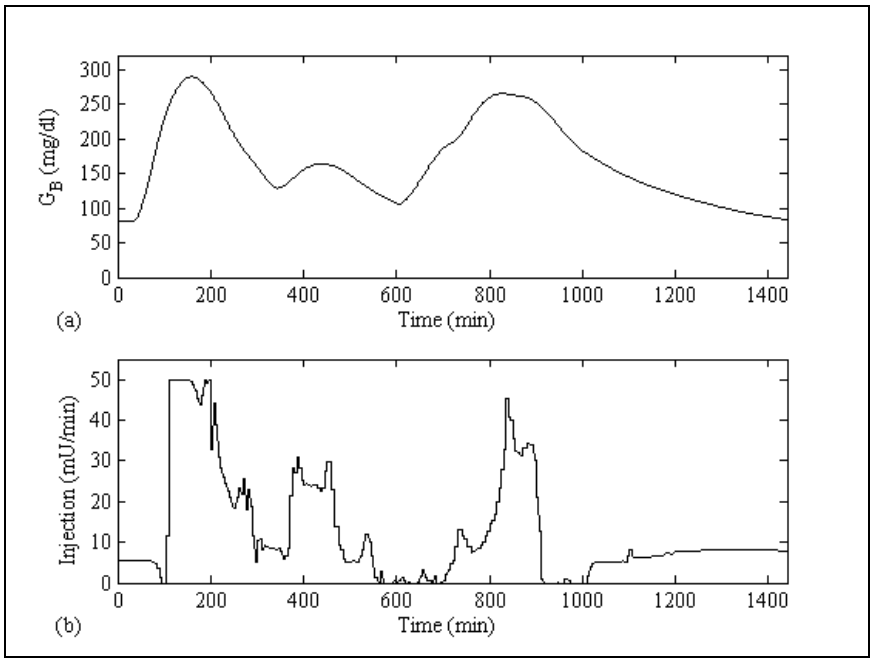


Figure 4.8. The response when diagonal elements of *P* matrix are initialized at 0.1 and dynamic stochastic model parameters are approximately known.

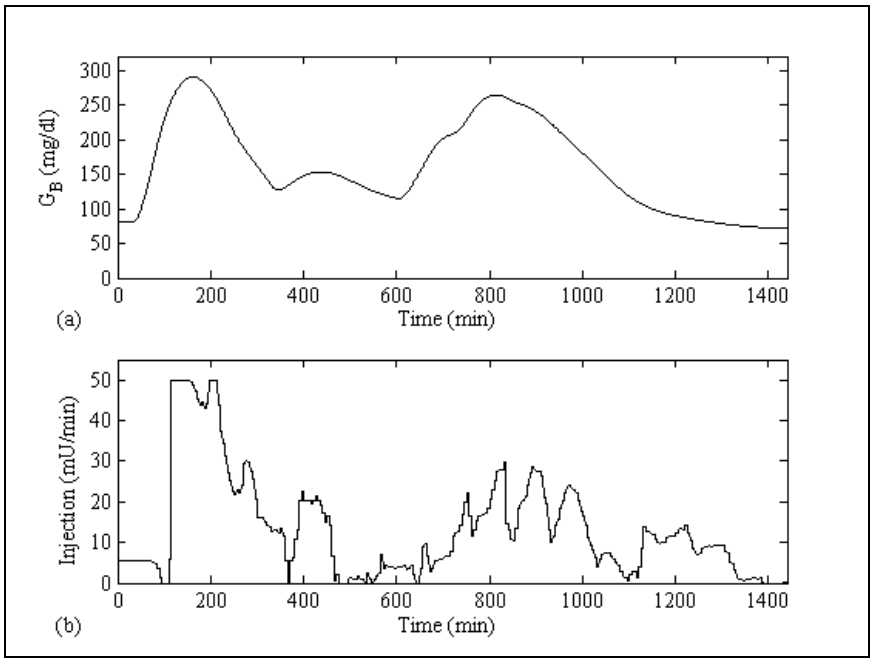


Figure 4.9. The response when diagonal elements of *P* matrix are initialized at 0.01 and dynamic stochastic model parameters are approximately known.

4.2. Changes in the Set Point of the Blood Glucose Concentration

Fasting blood glucose level in a healthy person should be in between 80-110 mg dl^{-1} (American Diabetes Association, 2005) in order to prevent the hypo and hyperglycemia. Set point of the blood glucose concentration is also one of the important parameters in the controller algorithm. A number of different set points (i.e 90, 95, 100, 105 mg dl^{-1}) which are in the safe range (80-110 mg dl^{-1}) are used both when linear dynamic-stochastic dynamic stochastic model parameters are unknown and approximately known in Figures 4.10 to 4.15.

4.2.1. Changes in the Set Point of the Blood Glucose Concentration with Unknown Process-Disturbance Model Parameters

In Figures 4.10 to 4.12, the only change is the set points of blood glucose concentration (90, 95, 105 mg dl^{-1}), and the other parameters are kept constant. The variances of the controller parameters are taken as 100000 while the controller parameters (α_i's) are initialized at 1, (β_i's) are initialized at 0.1 and the variances of the controller parameters are initialized at 1000. The constraint factor of insulin infusion rate is 1.5, and the forgetting factor is 0.5. The closed loop response of GlucoSim when the set point of the blood glucose concentration equals to 100 mg dl^{-1} is already given in Figure 4.6.

When the set point of blood glucose concentration is set to a value closer to the base limit of the fasting glucose concentration, i.e 80 mg dl^{-1}, at the end of the day the patient faces hypoglycemia as the concentration falls below the base limit of hypoglycemia, i.e. 50 mg dl^{-1}.

Increasing the set point to 95 mg dl^{-1} leads blood glucose concentration to settle in a safer range as can be seen in Figure 4.11 and the blood glucose concentration reaches the set point.

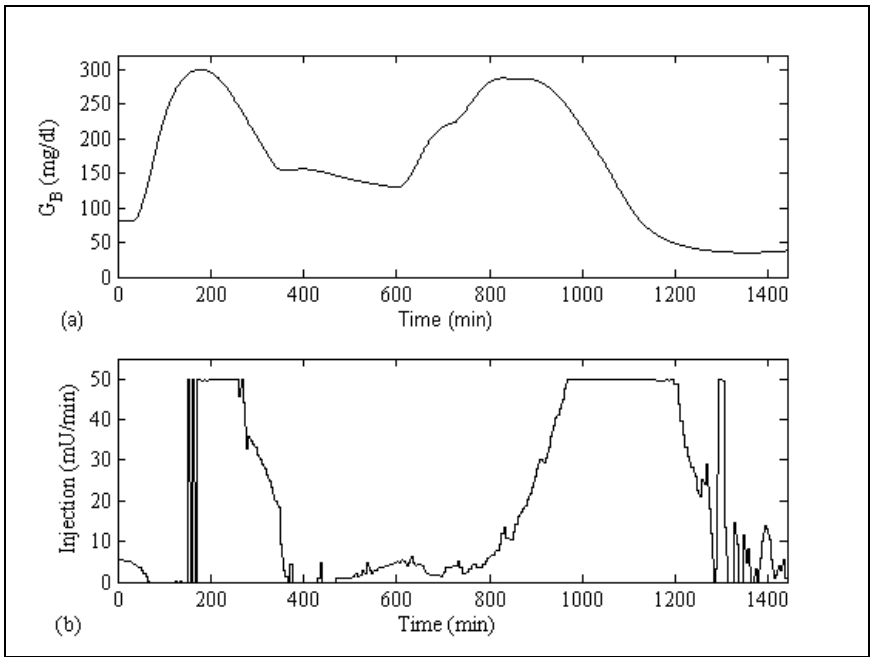


Figure 4.10. The response when the set point of blood glucose concentration is 90 mg dl^{-1} and dynamic stochastic model parameters are unknown.

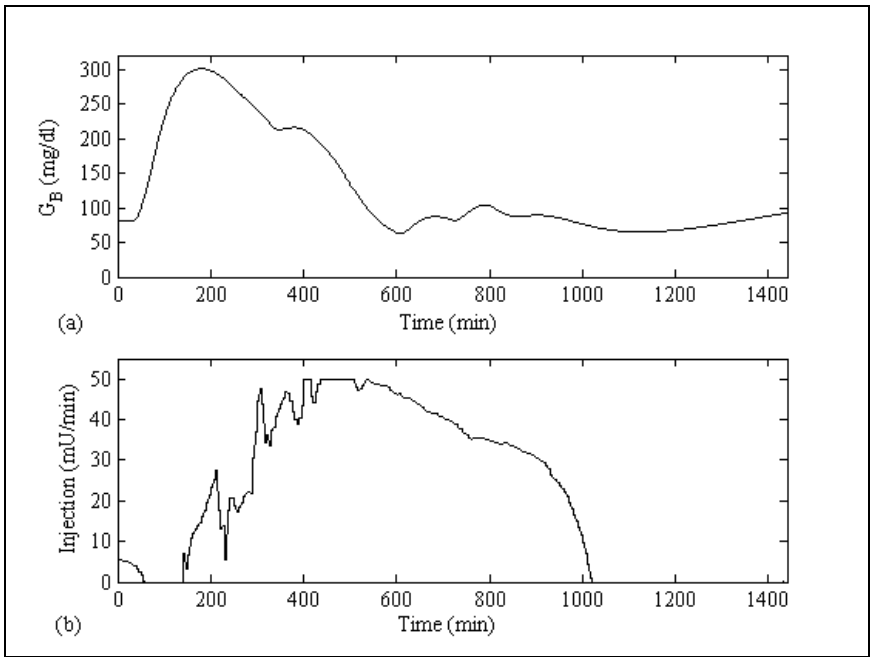


Figure 4.11. The response when the set point of blood glucose concentration is 95 mg dl^{-1} and dynamic stochastic model parameters are unknown.

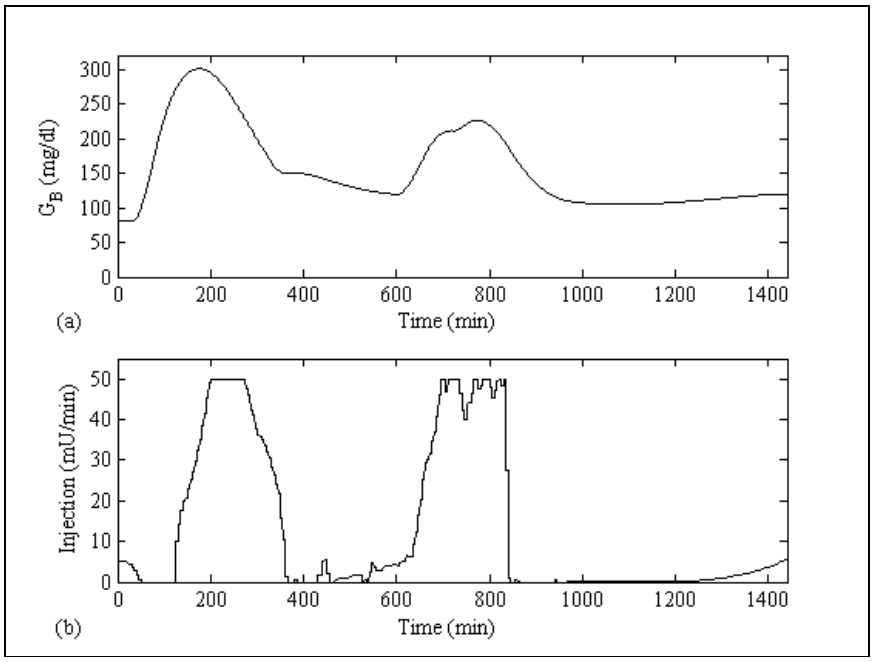


Figure 4.12. The response when the set point of blood glucose concentration is 105 mg dl^{-1} and dynamic stochastic model parameters are unknown.

When the set point is chosen closer to the upper limit of the fasting glucose concentration, the blood glucose concentration varies at high values for long periods of time as might be expected. The case for set point equals to 100 mg dl^{-1} is already given in Figure 4.6. Hence among all the set points (90, 95, 100, 105 mg dl^{-1}), 95 mg dl^{-1} seems to be the most appropriate choice for the proposed algorithm as this set point has the lowest ISE value. (2860E06)

4.2.2. Changes in the Set Point of the Blood Glucose Concentration with Approximately Known Process-Disturbance Model Parameters

In the responses presented in Figures 4.13 to 4.15, only the set point of blood glucose concentration is varied as 90, 95, and 105 mg dl^{-1} respectively whereas the other parameters are kept constant. The controller parameters which are approximately obtained from impulse and step tests are initially used with low initial covariance P matrix in the GlucoSim. The closed loop response of GlucoSim in which the set point is 100 mg dl^{-1} is already given in Figure 4.8.

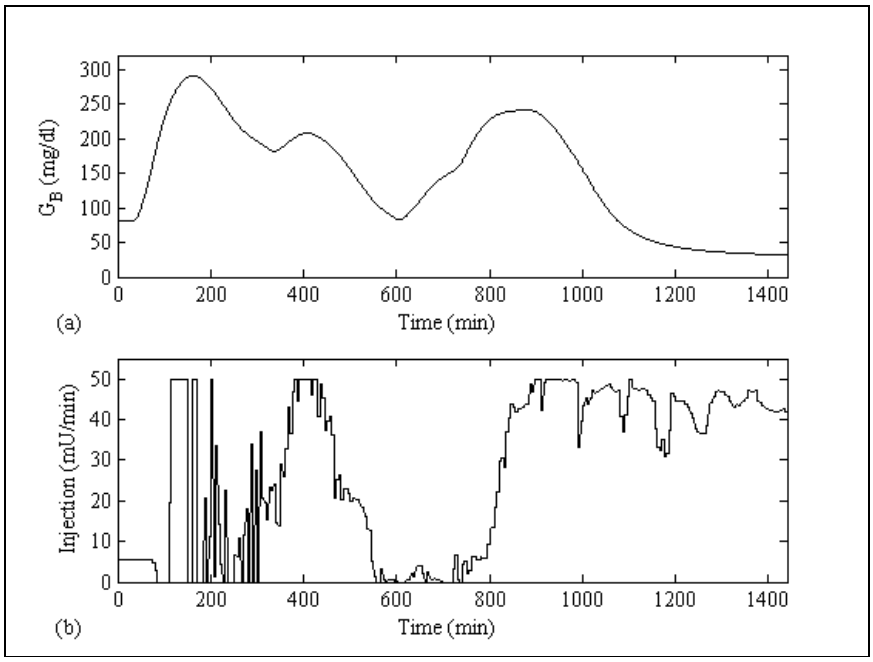


Figure 4.13. The response when the set point of blood glucose concentration is 90 mg dl^{-1} and dynamic stochastic model parameters are approximately known.

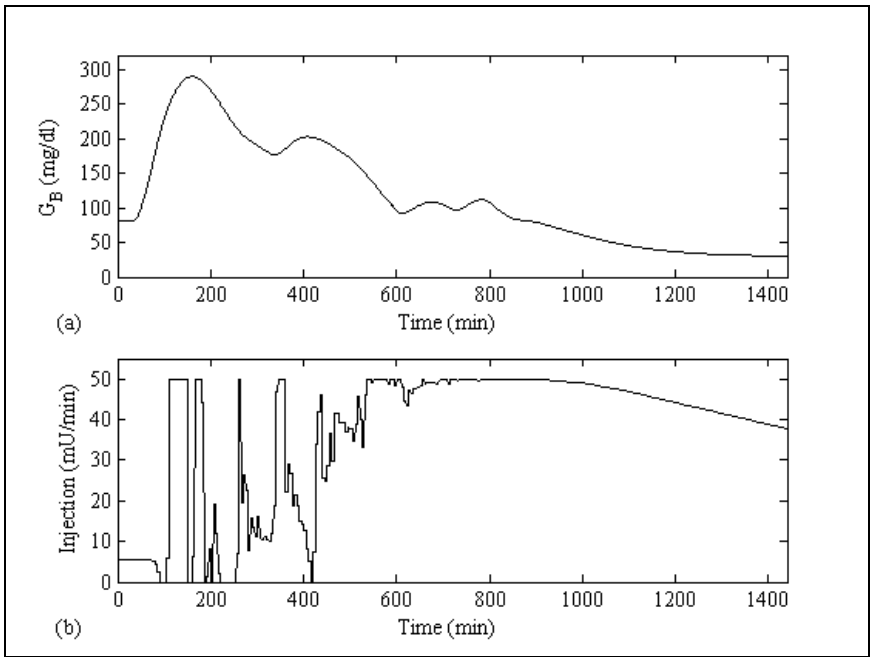


Figure 4.14. The response when the set point of blood glucose concentration is 95 mg dl^{-1} and dynamic stochastic model parameters are approximately known.

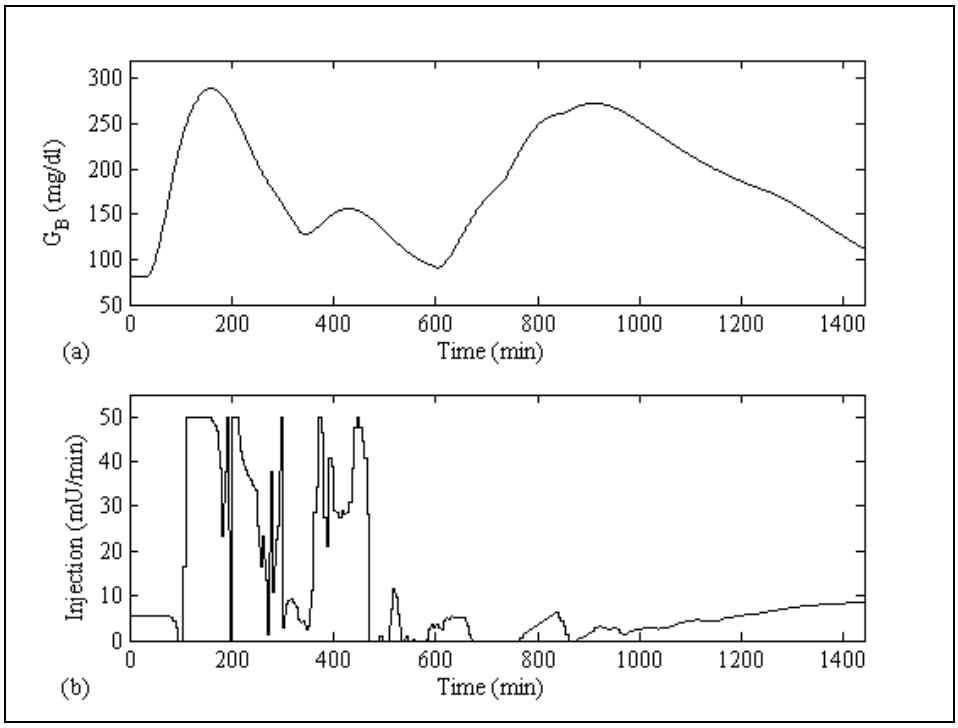


Figure 4.15. The response when the set point of blood glucose concentration is 105 mg dl^{-1} and dynamic stochastic model parameters are approximately known.

4.3. Changes in the Upper Clamp Value of Insulin Infusion Rate

There is a limitation on the amount of insulin that is given to diabetic patients (American Diabetes Association, 2005). When the controller is implemented without any clamp on the manipulated variable then the process becomes unstable. When the upper clamp is set to 100 000 mU min^{-1} with lower being 0 then the controller becomes on-off (bang-bang) controller. By trial and error an optimum clamp is found to be 50 000 mU min^{-1}. The other two upper limits tested are 40 000 mU min^{-1} and 60 000 mU min^{-1} and are discussed below.

4.3.1. Changes in the Maximum Insulin Infusion Rate with Unknown Process-Disturbance Model Parameters

In Figures 4.16 and 4.17, only the maximum insulin infusion rate is varied as 60 000 and 40 000 mU min^{-1} respectively, whereas the other parameters kept constant. The initial

diagonal elements of covariance P matrix are taken as 100000 while the controller parameters α_is are initialized at 1, β_is are initialized at 0.1, basal rate of the insulin infusion rate is set to 5400 mU min^{-1}, the constraint factor of insulin infusion rate ζ is set to 1.5 and the forgetting factor λ is set to 0.5. The closed loop response of GlucoSim in which the maximum insulin infusion rate is 50 000 mU min^{-1}, can be seen in Figure 4.6. As G_b falls below 50 mg dl^{-1} in Figures 4.16 and 4.17, the virtual patient faces glycemia at the end of 24 hours.

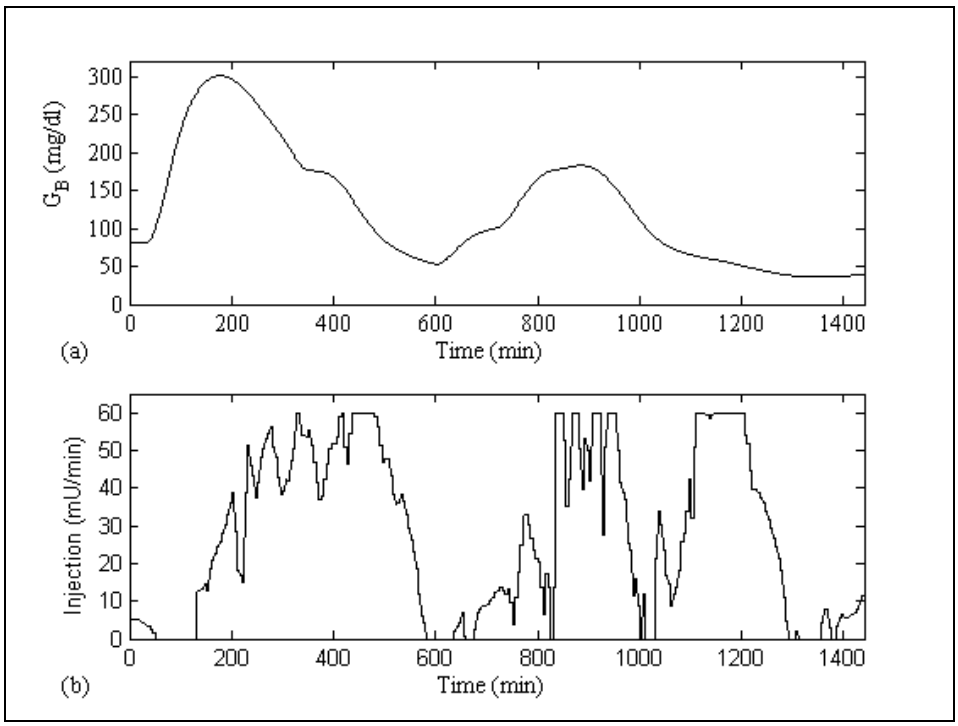


Figure 4.16. The response when the maximum insulin infusion is 60 000 mU min^{-1} and dynamic stochastic model parameters are unknown.

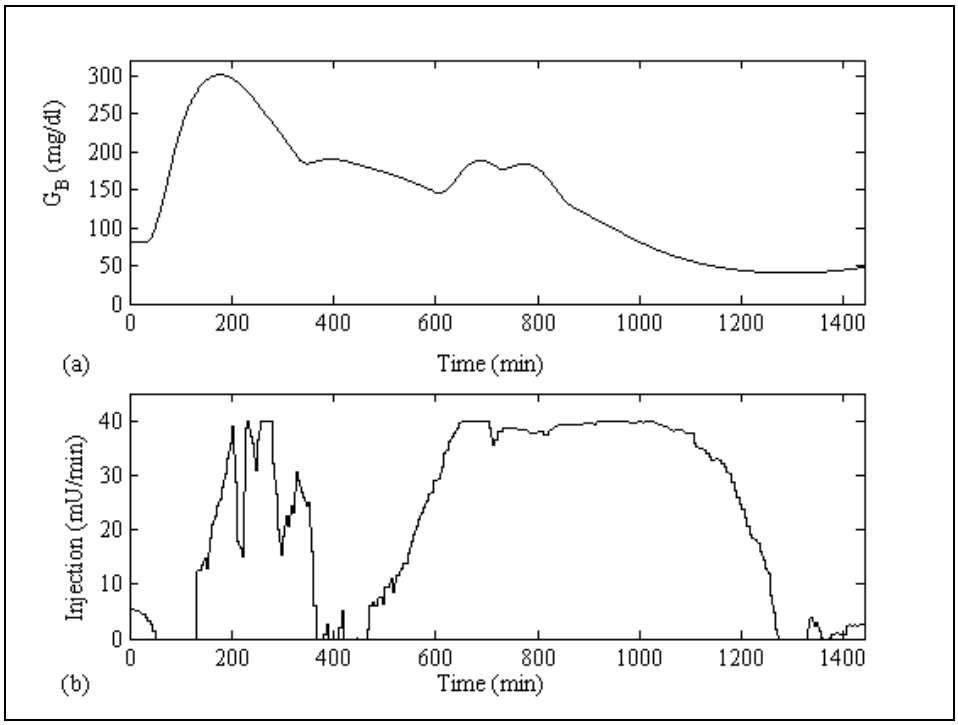


Figure 4.17. The response when the maximum insulin infusion is 40 000 mU min^{-1} and dynamic stochastic model parameters are unknown.

4.3.2. Changes in the Maximum Insulin infusion Rate with Approximately Known Process-Disturbance Model Parameters

Here responses are obtained for two different upper level clamp values 60 000 and 40 000 mU min^{-1}. Only the maximum insulin infusion rate is varied as 60 000 and 40 000 mU min^{-1} while keeping the other parameters constant. The responses obtained are given in Figures 4.16 and 4.17 respectively. The P matrix is initialized at 0.1, basal rate of the insulin infusion rate is set to 5400 mU min^{-1}, the constraint factor ζ of insulin infusion rate is 1.5 and the forgetting factor λ is 0.5. The closed loop response of GlucoSim in which the maximum insulin infusion rate is 50 000 mU min^{-1}, can be seen in Figure 4.8.

The responses in Figures 4.18 and 4.19 are similar to the case of the dynamic stochastic model parameters are unknown presented in Figures 4.16 and 4.17.

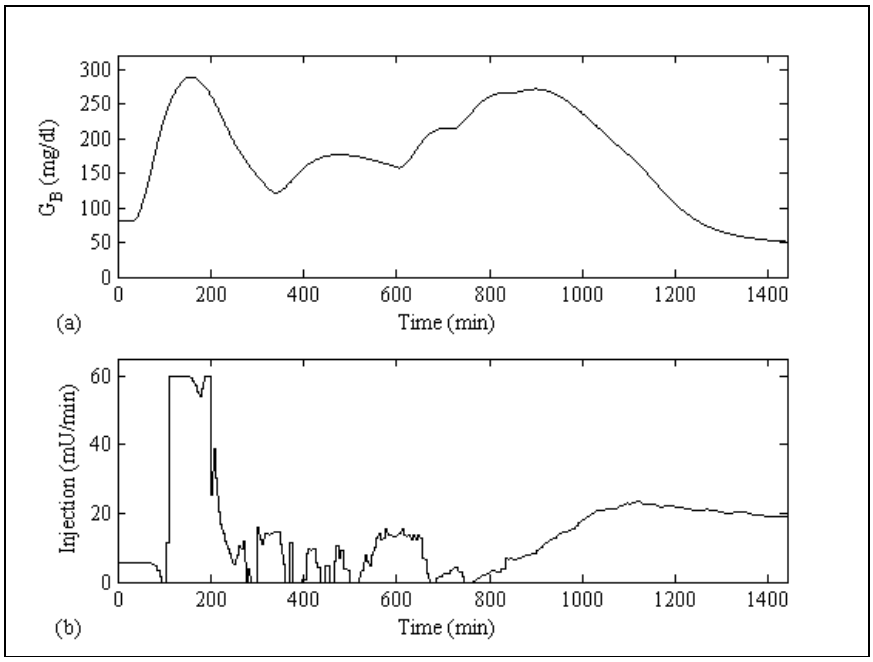


Figure 4.18. The response when the maximum insulin infusion is 60 000 mU min^{-1} and dynamic stochastic model parameters are approximately known.

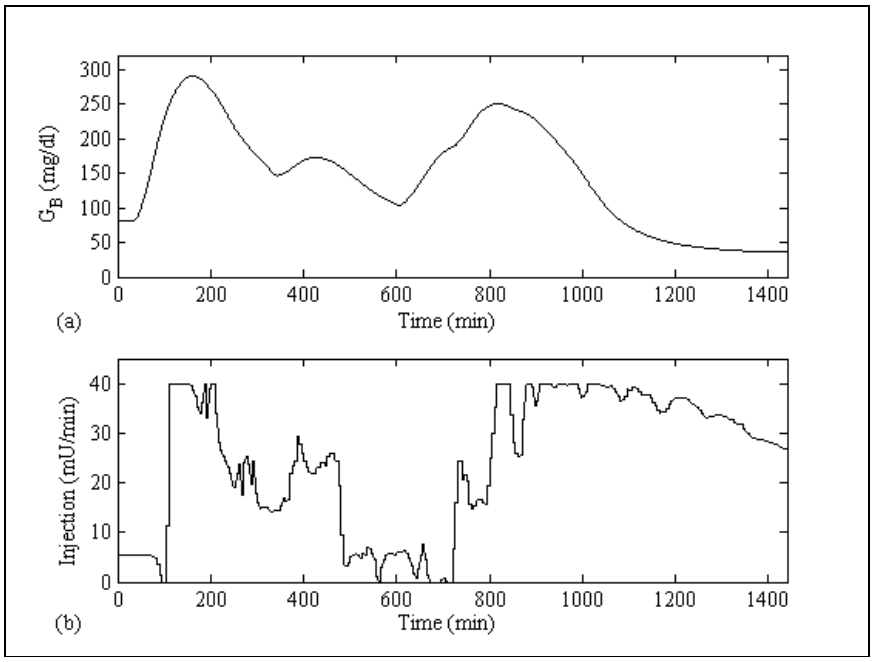


Figure 4.19. The response when the maximum insulin infusion is set to 40 000 mU min^{-1} and dynamic stochastic model parameters are approximately known.

4.4. Changes in the Constraint Factor of Manipulated Variable

The constraint factor ζ constrains the change in the manipulated variable and hence prevents large variations. When ζ is reduced to 0, a minimum variance control is obtained where the manipulated variable can change without any contraints. The variation of constraint factor ζ with a clamp on the manipulated variable is investigated in this part by setting ζ to 0, 1, 1.5 and 2. Figures 4.20 to 4.22 and 4.6 refer to the variations of ζ for both when the process dynamic stochastic model is unknown and approximately known. The variation of constraint factor ζ is investigated in this part when it is equal to 0, 1, 1.5, and 2 for the cases when the process dynamic stochastic model is unknown and known.

4.4.1. Changes in the Constraint Factor with Unknown Process-Disturbance Model Parameters

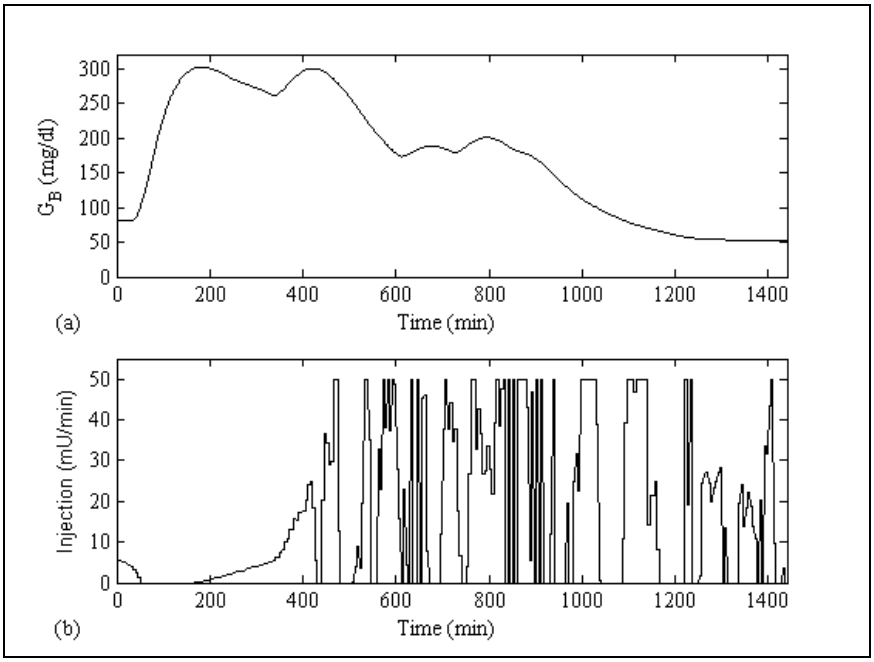


Figure 4.20. The response of minimum variance control ($\zeta = 0$) when dynamic stochastic model parameters are unknown.

In Figures 4.20 to 4.22, only the constraint factor of insulin infusion rate is varied as 0 (corresponding to minimum variance self-tuner), 1 and 2 respectively, whereas the other

parameters are kept constant. The diagonal elements of P-matrix are initially taken as 100000 while the controller parameters α_is are initialized at 1, β_is are initialized at 0.1 and the variances of the controller parameters are initialized at 1000 when the process dynamic stochastic model is unknown. The closed loop response of GlucoSim in which the constraint factor ζ is set to 1.5, can be seen in Figure 4.6.

The response given in Figure 4.20 is when the constraint factor is set to 0. The variations in the manipulated variable is unacceptable as it changes between upper and lower clamp value. Figure 4.22 illustrates an interesting response where too high a constraint factor ζ (ζ = 2) does yield very oscillatory variations in the manipulated variable similar to the case when ζ is zero.

In order to prevent large variations in insulin infusion rate and to form a smooth pattern non-zero constraint factor is used which results in the Clarke-Gawthrop self-tuning controller algorithm.

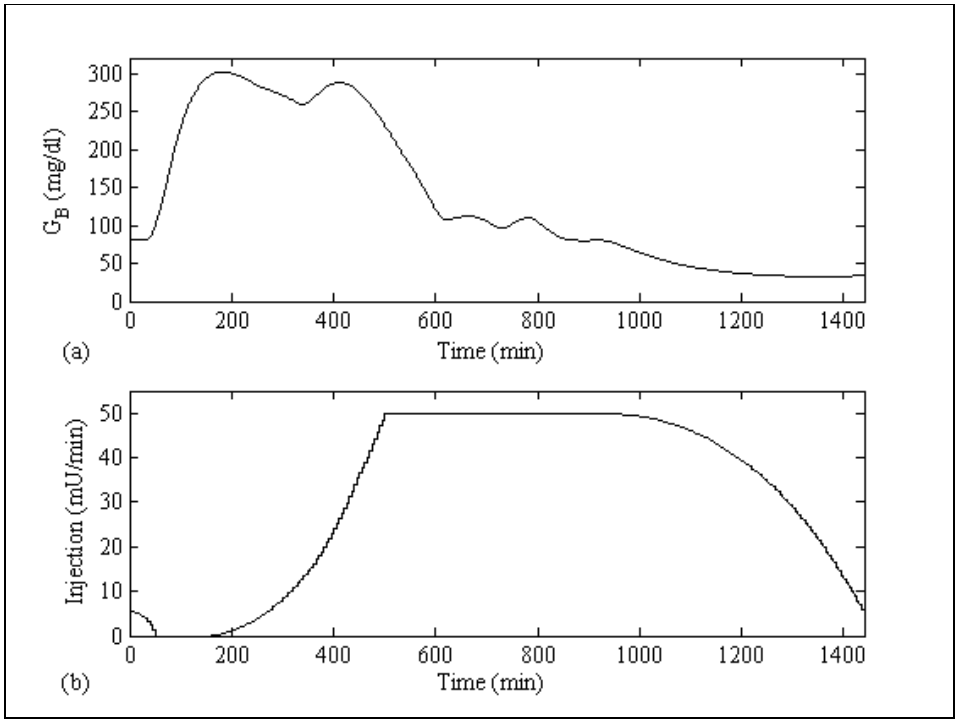


Figure 4.21. The response when the constraint factor ζ is 1 and dynamic stochastic model parameters are unknown.

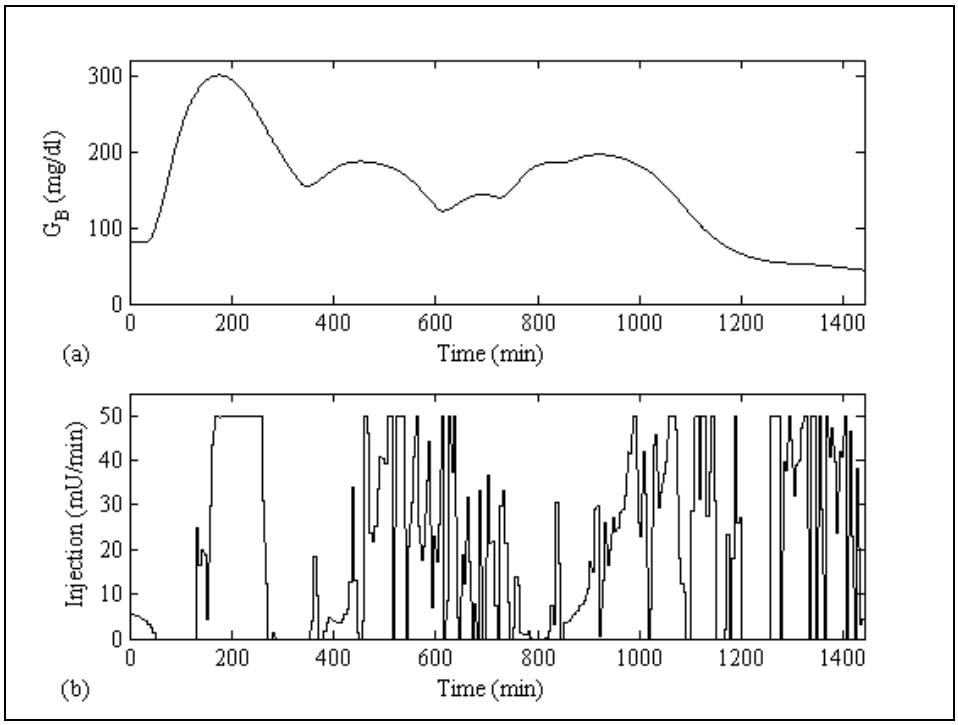


Figure 4.22. The response when the constraint factor ζ is 2 and dynamic stochastic model parameters are unknown.

4.4.2. Changes in the Constraint Factor with Approximately Known Process-Disturbance Model Parameters

In Figures 4.23 to 4.25, are given the responses of the controlled and the manipulated variables for ζ equals to 0, 1, and 2 respectively while the other parameters are kept constant. The response when the constraint factor ζ is set to 1.5 is already presented in Figure 4.8.

Again, as in the process dynamic stochastic model unknown case the manipulated variable variations become unacceptable when ζ equals to 0, 1, and 2 as can be seen in Figures 4.23 to 4.25.

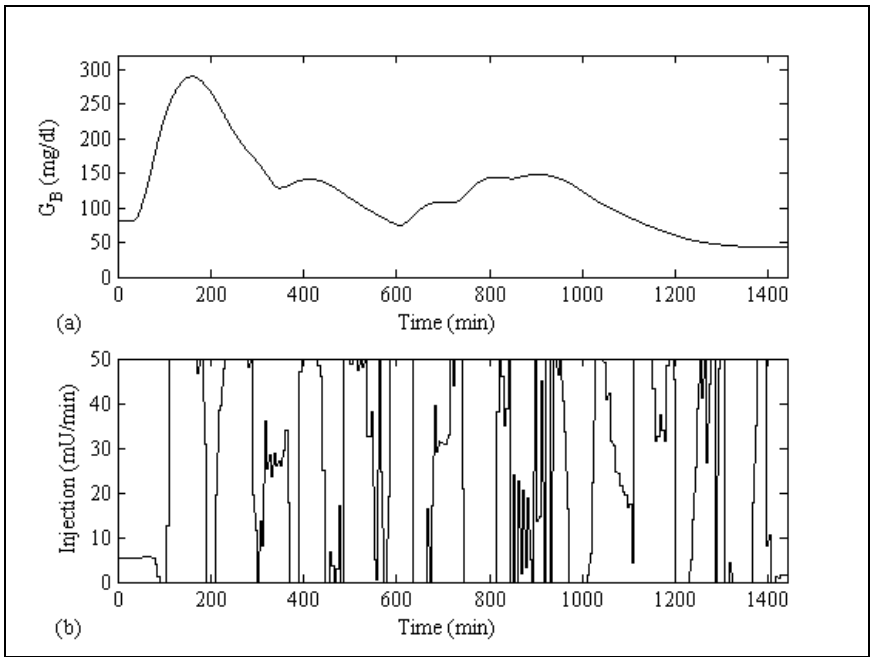


Figure 4.23. The response of minimum variance control (ζ =0) when dynamic stochastic model parameters are approximately known.

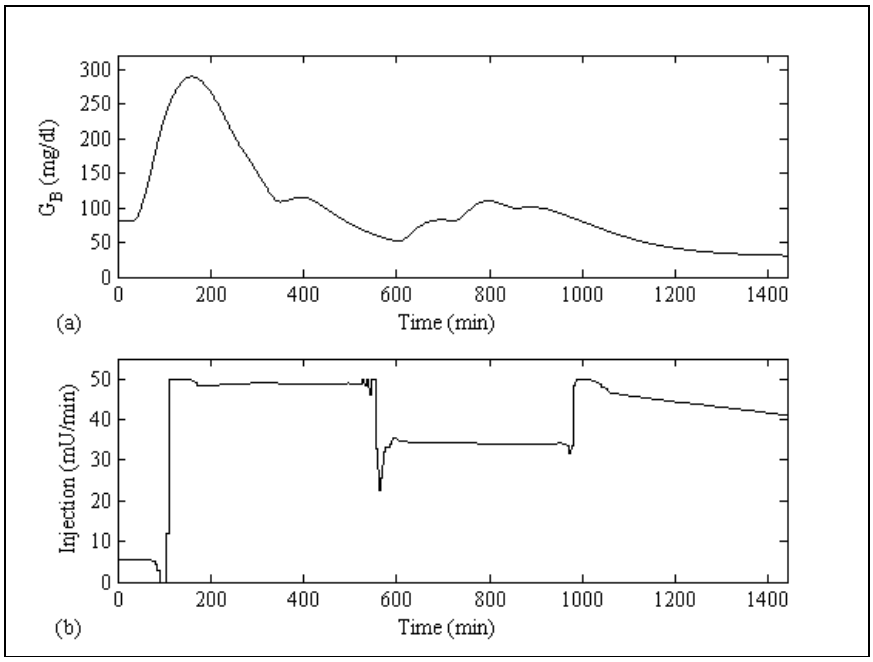


Figure 4.24. The response when the constraint factor ζ is 1 and dynamic stochastic model parameters are approximately known.

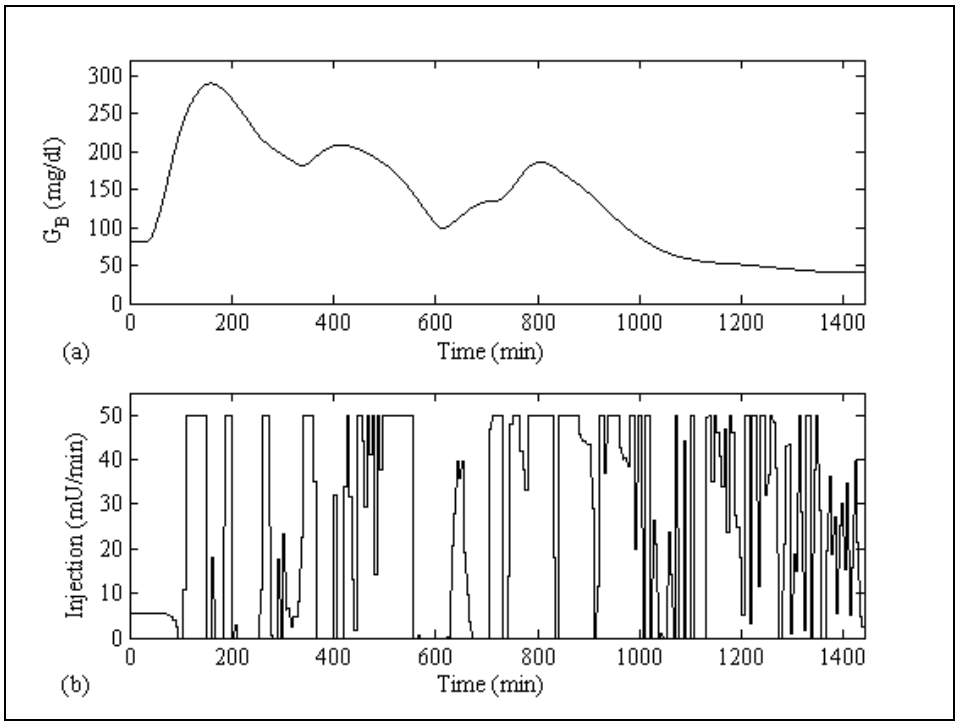


Figure 4.25. The response when the constraint factor ζ is 2 and dynamic stochastic model parameters are approximately known.

4.5. Changes in the Forgetting Factor

The forgetting factor λ which can be defined also as exponentially discounting factor, has a domain defined on the interval $0 < \lambda \leq 1$. The generalized form of recursive least squares estimation, for λ less than 1, naturally leads to adaptive control whereby the controller parameters are adapted to changes in process and disturbance transfer function parameters. If λ is equal to 1 then the estimation algorithm is reduced to ordinary least squares and when it is less then 1.0 then the algorithm will discount the information of the distant past by putting lesser weights on these past data points.

4.5.1. Changes in the Forgetting Factor with Unknown Process-Disturbance Model Parameters

In Figures 4.26 to 4.28, only the forgetting factor is varied as 1, 0.75, 0.25 respectively, whereas the other parameters are kept constant. The variances of the controller parameters are taken as 100000 while the controller parameters (α_i's) are initialized at 1, (β_i's) are initialized at 0.1, the maximum insulin infusion rate is 50 000 mU min^{-1}, the basal rate of the insulin infusion rate is set to 5400 mU min^{-1}, and the constraint factor of insulin infusion rate is set to 1.5. The closed loop response of GlucoSim in which the forgetting factor is set to 0.5, can be seen in Figure 4.6.

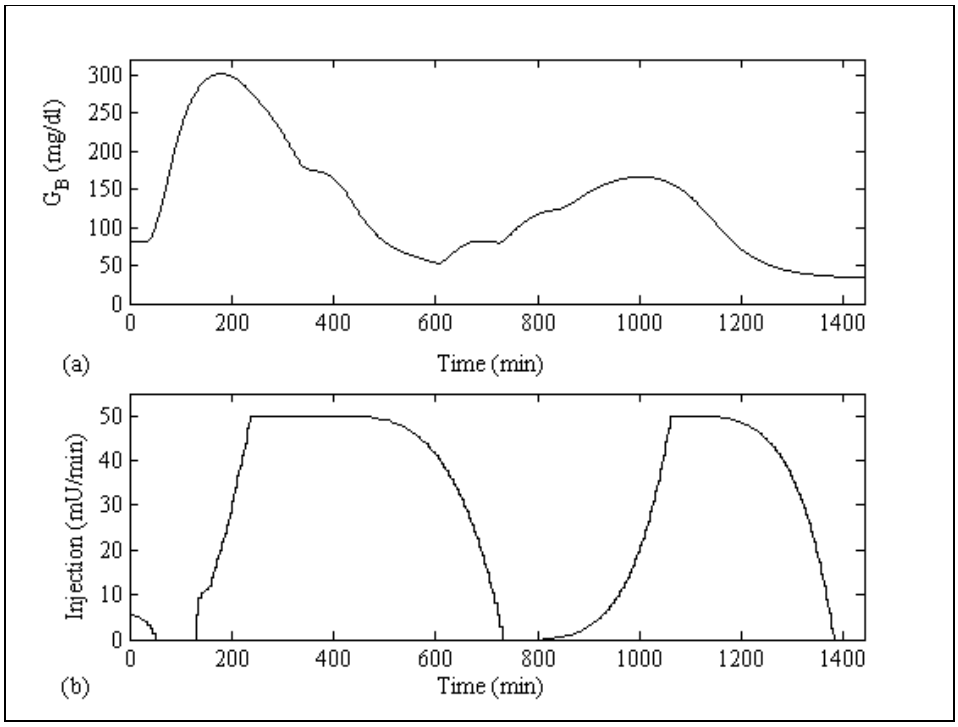


Figure 4.26. The response when the forgetting factor λ is 1 and dynamic stochastic model parameters are unknown.

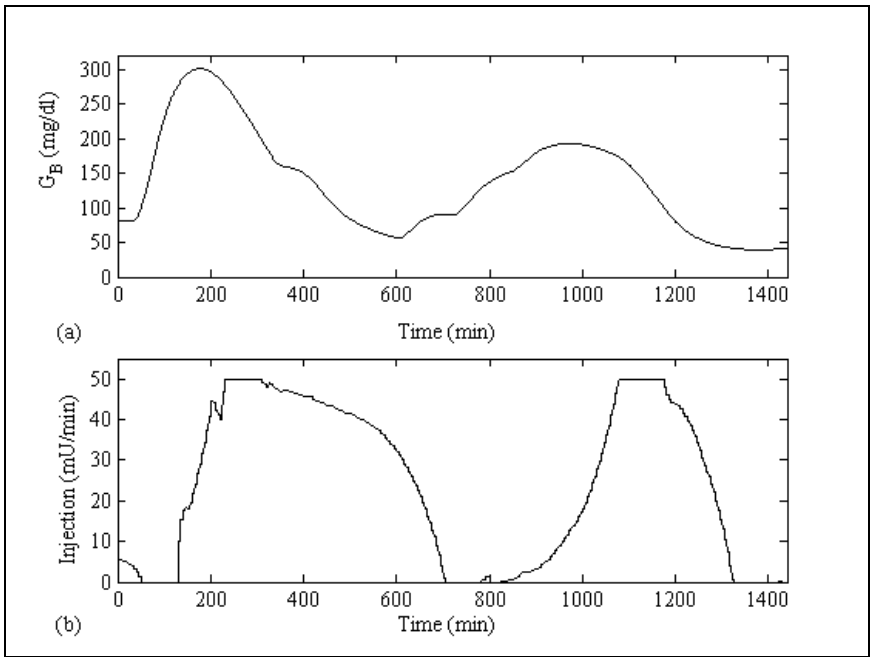


Figure 4.27. The response when the forgetting factor λ is 0.75 and dynamic stochastic model parameters are unknown.

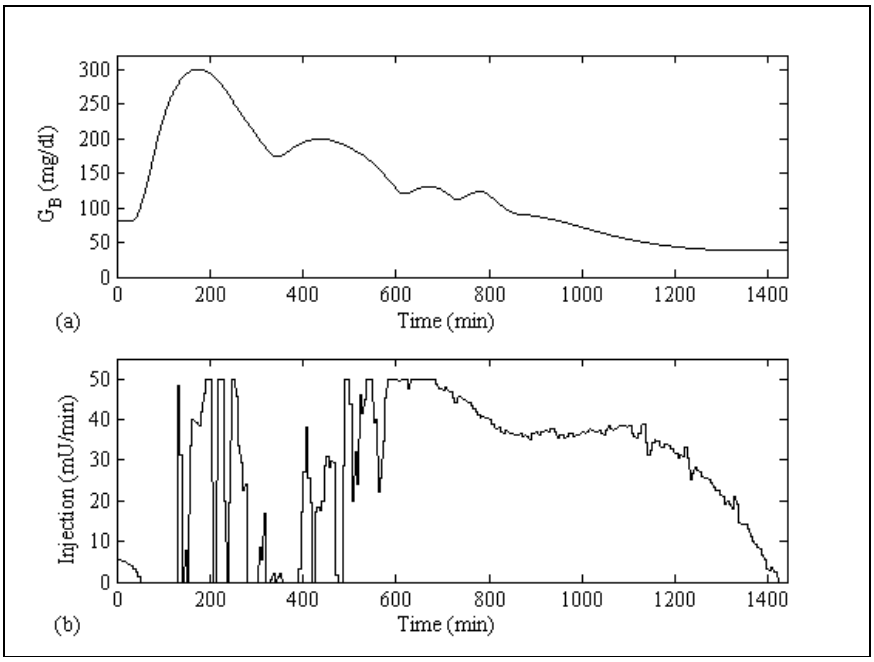


Figure 4.28. The response when the forgetting factor λ is 0.25 and dynamic stochastic model parameters are unknown.

4.5.2. Changes in the Forgetting Factor with Approximately Known Process-Disturbance Model Parameters

In Figures 4.29 and 4.30, only the forgetting factor is varied as 0.75, 0.25 respectively, whereas the other parameters are kept constant. P-matrix is initially set to 0.1, the maximum insulin infusion rate to 50 000 mU min^{-1}, basal rate of the insulin infusion rate is to 5400 mU min^{-1}, and the constraint factor of insulin infusion rate to 1.5. The closed loop response of GlucoSim in which the forgetting factor is set to 0.5, can be seen in Figure 4.8.

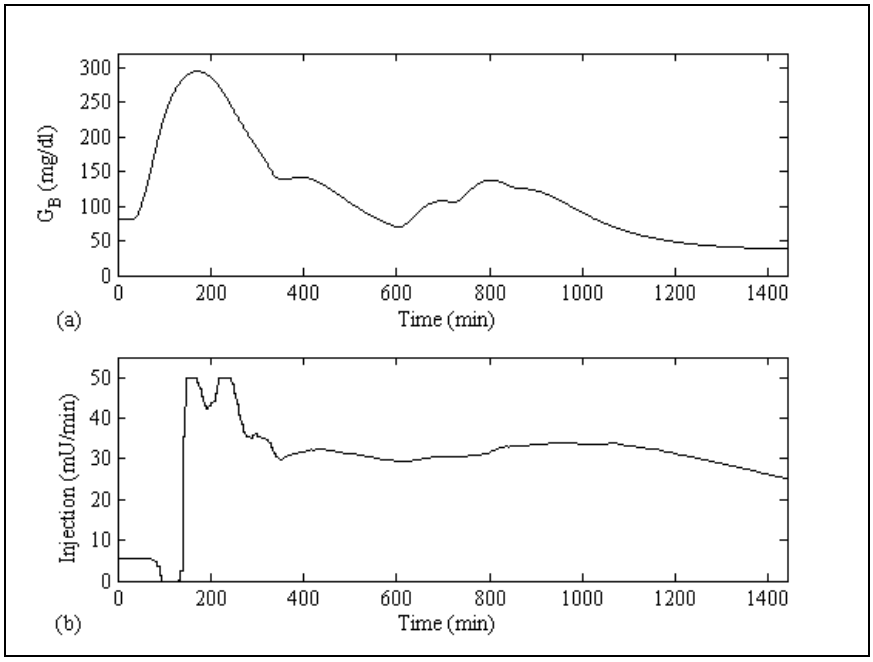


Figure 4.29. The response when the forgetting factor λ is 0.75 and dynamic stochastic model parameters are approximately known.

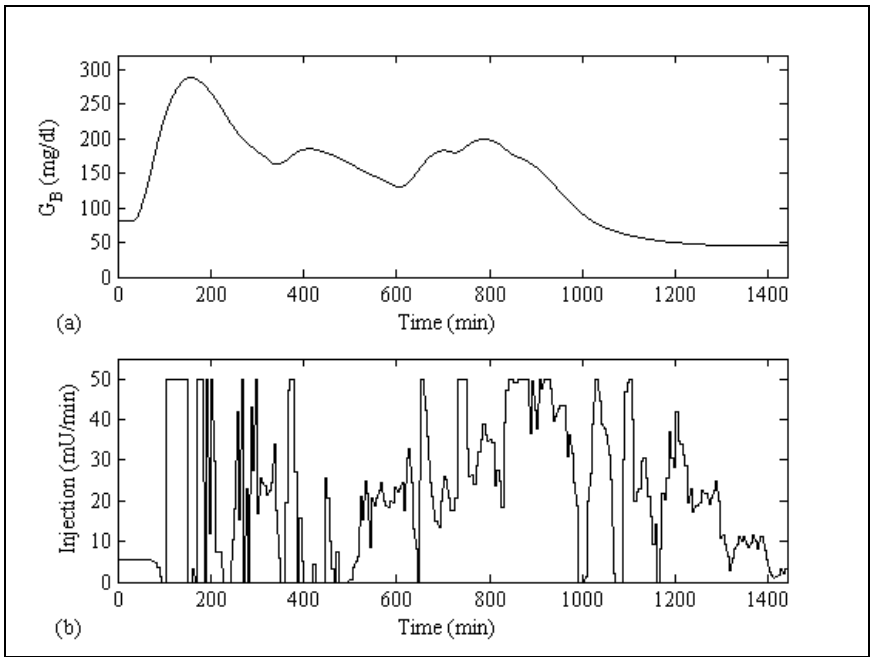


Figure 4.30. The response when the forgetting factor λ is 0.25 and dynamic stochastic model parameters are approximately known.

4.6. Changes in the Sampling Time of the GlucoSim Process

In order to reduce the time delay which complicates the control algorithm when it is high, the sampling time of the process can be increased which will reduce the whole periods of delay *b* in the transfer function. Previously used sampling time is 5 minutes in GlucoSim is increased to 10 minutes and 14 minutes since they are integer multiples of 70 minutes of the dead time in GlucoSim. So that when the process is discretized the process time delay of the Box- Jenkins type dynamic stochastic model without one period of delay imposed by sampling is decreased to 7 and 5 respectively. The closed loop response of GlucoSim process to a decrease in time delay can be seen in Figures 4.31 to 4.34.

4.6.1. Changes in the Sampling Time of the GlucoSim Process with Unknown Process-Disturbance Model Parameters

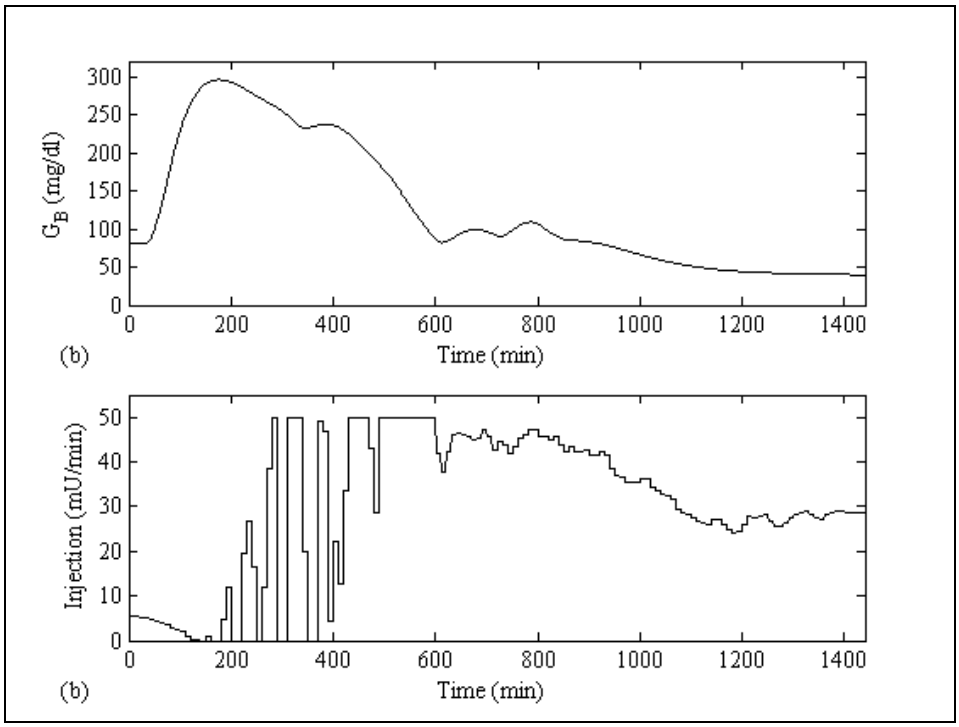


Figure 4.31. The response when the sampling time is set to 10 minutes and dynamic stochastic model parameters are unknown.

As far as the final value of the controlled variable is concerned the patient suffers from hypoglycemia since G_B value falls below 50 mg dl^{-1}. Reducing the control interval does not seem to improve the regulatory response.

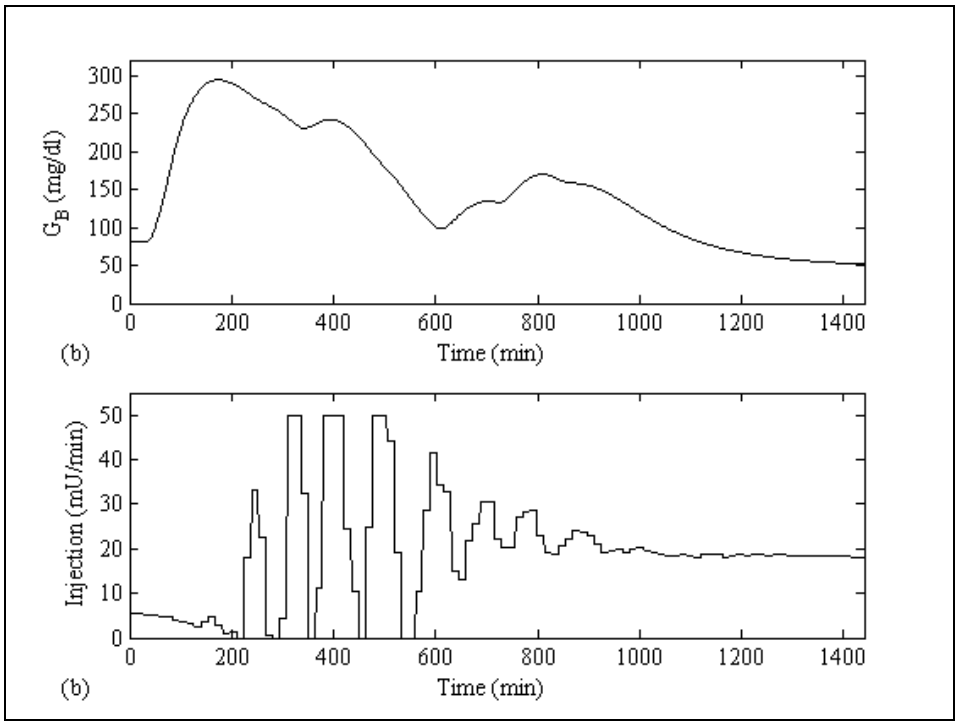


Figure 4.32. The response when the sampling time is set to 14 minutes and dynamic stochastic model parameters are unknown.

By decreasing the time delay via increasing sampling time was, to simplify the controller algorithm which may lead to a superior control. However, this expectation is not realized. At the end of the day the blood glucose concentration decreases to below 50 mg dl^{-1} in Figure 4.35 and closer to 50 mg dl^{-1} in Figure 4.36 which is an undesirable result.

4.6.2. Changes in the Sampling Time of the GlucoSim Process with Approximately Known Process-Disturbance Model Parameters

As can be seen in Figures 4.33 and 4.34, the regulator performance is also not acceptable in this case too as hypoglycemia limits are reached.

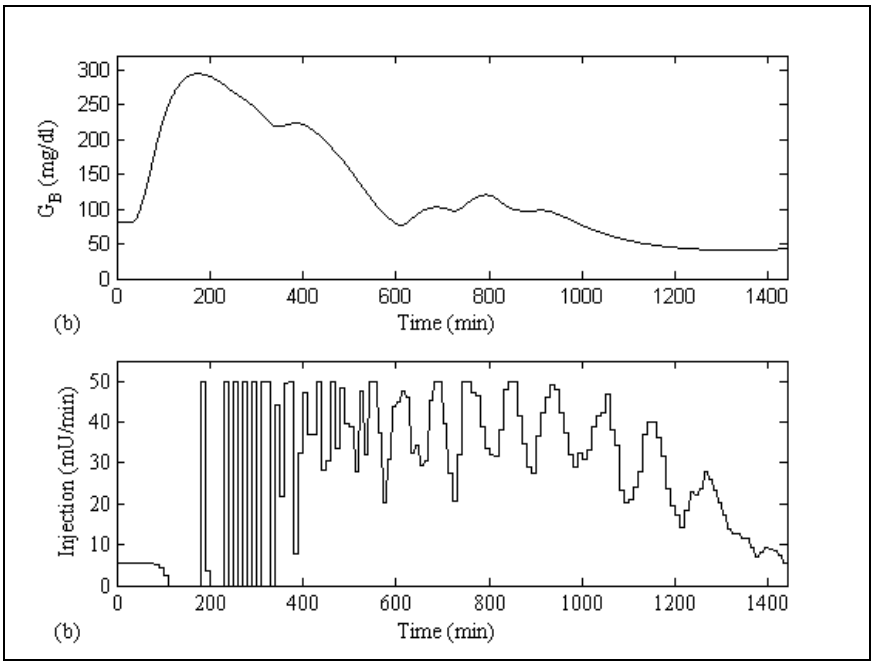


Figure 4.33. The response when the sampling time is set to 10 minutes and dynamic stochastic model parameters are approximately known.

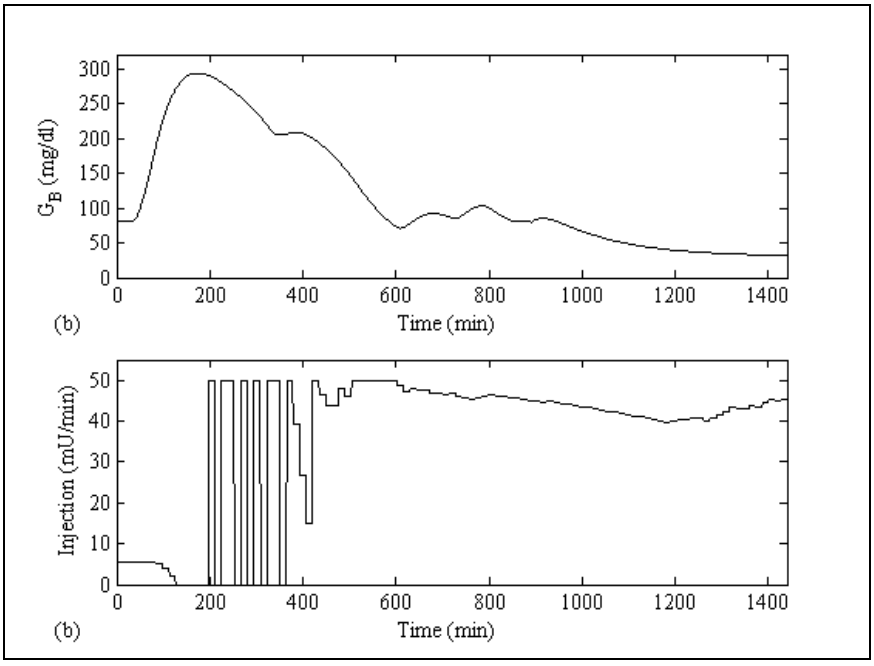


Figure 4.34. The response when the sampling time is set to 14 minutes and dynamic stochastic model parameters are approximately known.

5. CONCLUSION AND RECOMMENDATION

5.1. Conclusion

In the regulation of blood glucose concentration, as the disturbances are highly stochastic, adaptive control algorithm is a requirement for control mechanism. In an adaptive system, the regulator parameters are adjusted on line continuously. This implies that the regulator parameters follow changes in the process. However, it is difficult to analyze the convergence and stability properties of such systems. To simplify the problem it can be assumed that the process has constant but unknown parameters. When the process is known, the design procedure specifies a set of desired controller parameters. The adaptive controller should converge to these parameter values even when the process is unknown. A regulator with this property is called *self-tuning*, since it automatically tunes the controller to obtain the desired performance (Astrom and Wittenmark, 1989).

The blood glucose concentration in Type I diabetic patients is regulated by adaptive Clarke-Gawthrop self tuning controller on a virtual patient simulated by GlucoSim which is an educational software package written by Agar *et. al*. (2005). In order to obtain the desired performance of self tuning regulator, some parameters (i.e. initial values of the controller parameters θ vector, the covariance matrix P, the set point of blood glucose concentration, the maximum allowable insulin infusion rate, the constraint factor ζ, the forgetting factor λ, the sampling time mentioned in Section 4 are changed for two different cases: the process-disturbance model parameters are known and approximately known. When the regulation of blood glucose concentration is carried out in Type I diabetic patients using Clarke-Gawthrop self tuning controller a better performance is obtained for the case with unkown process-disturbance model parameters. The best control performance is selected among those which has the lowest ISE value, does not allow too high an increase in the blood glucose concentration and prevent hypoglycemia at the end of 24 hours period. The optimum settings found are as follows: for the set point of the blood glucose concentration 100 mg dl^{-1} concentration is chosen among the set of 90, 95, and 105 mg dl^{-1}, the forgetting factor is determined to be 0.5 among the set of (0.25, 0.5, 0.75, 1), the constraint factor of manipulated variable is 1.5, the initial values

of controller parameters are (1, 1, 1, 1, 1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1) and the diagonal elements of the *P* matrix are initialized at 100000. By using these parameter settings a safe blood glucose level is determined for the virtual patient with Type I diabetes in a 24 hours period. The risk of hypo and hyperglycemia is prevented. Adaptive control achievement is that a freedom in daily life can be given to the patients to change their diets, exercises, change in diet, exercise and stress levels.

5.2. Recommendation

In Clarke-Gawthrop type self tuning regulator the fact that there is no need to estimate the process-disturbance model parameters and design a controller at each control period, it simplifies the regulation algorithm when compared to other controller algorithms such as LQC, and MPC. However, in this case the GlucoSim process formed by the glucose-insulin interaction in Type I diabetic patients, is a nonlinear process and the performance of the regulator is highly dependent on the initial parameters. This makes it hard to find the optimum parameters set that should be specified in the beginning of the simulation. In this work, one variable at a time is used to obtain the best settings of the initial conditions. Response surface methodology (with the response being ISE) using factorial design can be used to find the optimum settings for the initial parameter settings as described in Section 4.

As an alternative to controlling the blood glucose level manipulating insulin infusion rate in a single loop, a cascade control arrangement can be carried out wherein the inner loop controlled variable is the insulin concentration in the blood and the outer loop is the blood glucose concentration. A simple PI controller can be used as the slave and an adaptive STR as the master controller.

REFERENCES

Agar B. U., M. Eren, and A. Cinar, 2005, "GLUCOSIM: Educational Software for Virtual Experiments with Patients with Type I Diabetes", Conf. Proc. IEEE Eng. Med. Biol. Soc. Vol. 1, pp. 845-848.

American Diabetes Association, 2005, *Complete Guide to Diabetes*, 4th Edition, U.S.A..

Astrom K. J. and B. Wittenmark, 1973, "On self-tuning Regulators", *Automatica*, Vol. 9, pp. 457-476.

Astrom K. J., U. Borrison, L. Ljung and B. Wittenmark, 1977, "Theory and Applications of Adaptive Regulators", *Automatica*, Vol.9, pp.185-199.

Astrom K. J., 1980, *Self-tuning Regulators-Design Principles and Applications, in K. S. Narendra an R. V: Monopoli (Eds.), Applications of Adaptive Control*, Acedemic Press, New York.

Astrom K. J. and B. Wittenmark, 1989, *Adaptive Control*, Addison-Wesley, U.S.A..

Bergman R. N., Y. Z. Ider, C. R. Bowden, C. Cobelli, 1979, "Quantitative estimation of insulin sensitivity", *Am J* Physiol., Vol. 236, pp. E667-77.

Box G. E. P., and G. M. Jenkins, 1976, *Time Series Analysis forecasting and control*, Holden-Day, San Francisco.

Camurdan, M. C., 1986, *Application of Adaptive Control to a Reciprocating Plate Liquid-Liquid Solvent Extraction Column*, PhD. Dissertation, McMaster University, Canada.

Candas B. and J. Radziuk**,** 1994, **"**An Adaptive Plasma Glucose Controller Based on a Nonlinear Insulin/Glucose Model.", *IEEE Trans. Biomed.* Eng., Vol. 41, pp. 116-123.

Clarke, D. W. and R. Hasting-James, 1971, "Design of Digital Controllers for Randomly Disturbed Systems", *Proc. IEEE*, Vol. 118, pp. 1503-1506.

Clarke, D. W. and R. Gawthrop, 1975, "Self-tuning Controller", *Proc. IEEE*, Vol. 122, pp. 929-934.

Cobelli, C., G. Federspil, G. Pacini, A. Salvan and C. Scandellari ,1982, "An integrated Mathematical Model of the Dynamics of Blood Glucose and its Hormonal Control", *Math* Biosc, Vol. 58, pp. 27-60.

DCCT, 1993, "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus". *N. Engl. J. Med.* pp. 977-1086.

Eren M., A. Cinar, L. Quinn, and D. Smith, 2007, "Adaptive Control Strategy for Glucose Regulation Using Recursive Linear Models", *10th Int. IFAC Symp. Comp. Appl. Biotech.*,Vol. 1, pp.153-158.

Fisher U., W. Schenk, E. Salzsieder, G. Albrecht, P. Abel, and E. J. Freyse, 1987, "Does Physiological Blood Glucose Control Require an Adaptive Strategy?", *IEEE Trans. Biomed. Eng*., Vol. 34, pp. 575-582.

Harris, T. J., 1977, "Theory and Application of Self-tuning Regulators", M. End. Thesis, McMaster University, Canada.

Kalman, R. E., 1958, "Design of a Self Optimizing Control System",*Trans. ASME*, Vol. 80, pp. 468-478.

Leaning M. S. and M. A. Boroujerdi, 1991, "A System for Compartmental Modelling and Simulation", *Comp Meth Prog Biomed*, Vol. 35, pp. 71-92.

MacGregor, J. F. and P. Tidwell, 1977, “Discrete Stochastic Control with Input Constraints”, *Proc IEE*, Vol. 124, pp. 732-734.

MacGregor J. F., T. J. Harris, and J. D. Wright, 1980, "Self-tuning and Adaptive Controllers: An Application to Catalytic Reactor Control", *Technometrics*, Vol. 22, No: 2.

Parker R. S., F. J. III Doyle, and N. Peppas, 1999, “A Model-Based Algorithm for Blood Glucose Control in Type I Diabetic Patients.”, *IEEE Trans Biomed Eng*, Vol. 46, pp. 148-157.

Puckett, W. R. and E. N. Lightfoot, 1995, "A model for multiple subcutaneous insulin injections developed from individual diabetic patient data", *American Journal of Physiology*, Vol. 269, pp. E1115–E1124.

Shichiri M., M. Sakakida, K. Nishida, and S. Shimoda, 1998, “Enhanced, Simplified Glucose Sensors: Long-term Clinical Application of Wearable Artificial Pancreas”, *Artif Organs*, Vol. 22, pp. 32-42.

Shimoda S., K. Nishida, M. Sakakida, Y. Konno, K. Ichinoshi, M. Urkhara, T. Nowak, and M. Shichiri, 1997, "Closed-loop Subcutaneous Insulin Infusion Algorithm with a Short Acting Insulin Analog for Long-term Clinical Application of a Wearable Artificial Endocrine Pancreas", *Frontiers Med Biol Eng.*, Vol. 8, pp. 197-211.

Trajanoski Z., G. Brunner, L. Schaupp, M. Ellmerer, P. Wach, T. R. Pieber, P. Kotanko, and F. Skrabal, 1997, "Open-flow Microperfusion of Subcutaneous Adipose Tissue for On-line Continuous ex Vivo Measurement of Glucose Concentration", *Diabetes Care*, Vol. 20, pp. 1114-1121.

Trajanoski Z. and P. Wach, 1998, "Neural Predictive Controller for Insulin Delivery Using the Subcutaneous Route", *IEEE Trans Biomed Eng*, Vol. 45, pp. 1122-1134.

Wellstead P. E. and P. Zanker, 1982, “Techniques of Self-tuning”, *Opt. Cont. Appl. Methods*, Vol. 3, pp. 305-322.

Wilson, G. T., 1970, *Modeling Linear Systems For Multivariable Control*, PhD. Dissertation, University of Lancaster, England.