MODEL BASED CONTROLLERS FOR BLOOD GLUCOSE REGULATION IN TYPE I DIABETICS

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SUMMARY

Diabetes is a chronic disease affecting millions of people in the world. Regular insulin injection therapy is now practiced for maintaining blood glucose level within normoglycemic range (70-100 mg/dl) in Type I diabetics having insulin dependent diabetes mellitus. Controllers for automatic monitoring and regulation of blood glucose in diabetics have been investigated. In this study, several model-based controllers including the ubiquitous proportional-integral-derivative (PID) controllers are designed for specifying insulin dosage in Type I diabetics. The study employs a recently reported and detailed physiological model of a diabetic along with a meal disturbance model. The performance and robustness of designed controllers are evaluated on 577 diabetic patient models generated by considering ±40% variation in the significant parameters of the physiological model.

The detailed physiological model of the diabetic is successfully implemented and validated for use in evaluating the designed controllers. An internal model controller (IMC) is designed based on a first order plus time delay (FOPTD) model approximation of the detailed physiological model of the nominal diabetic. Enhanced internal model controller (EIMC) is then developed due to its simple structure, better disturbance attenuation and uncertainty reduction. Both these controllers are assessed for their ability to track the normoglycemic set point of 81.1 mg/dl for blood glucose while rejecting meal disturbances both in the nominal patient case and 577 perturbed patient models. The results show that EIMC performs better than IMC as well as the robust H_∞ controller (Parker et al., 2000) for blood glucose regulation in Type I diabetics.

Noting that the ubiquitous PID controllers have not been tested on the detailed physiological model employed in this study, several PID controllers are designed using classical and recent tuning techniques. A secondary objective for this part of the study is to analyze the effectiveness of the recent tuning techniques for PID controllers for challenging biomedical applications such as diabetes control. Detailed results of testing the PID controllers designed on the perturbed patient models for meal disturbance rejection, show that the PID tuning by Shen (2002) is the best among the four tuning techniques tested. It is able to maintain the glucose concentration above the hypoglycemic range (hypoglycemia occurs when blood glucose concentration is less than 60 mg/dl) in 95% of all the 577 patient models considered while rejecting both single and multiple meal disturbances in a day.

A nonlinear internal model controller (NIMC) using input-output linearization is developed for a Type I diabetic. Although this controller showed promising results for rejecting meal disturbances in the case of nominal patient model, spikes in the controlled variable (i.e., insulin injected) made it impossible to test NIMC for all the 577 perturbed patient models. The reason for spikes seems to be numerical errors, and further investigation is needed to confirm this.

In summary, several model based controllers (namely, IMC, EIMC, PID and NIMC) are designed and evaluated for blood regulation in Type I diabetic. Among these, EIMC and PID controller tuned by Shen's technique have performed better than the robust H_∞ controller which itself was shown to be better than the computationally-intensive model predictive controller (Parker et al., 2000). Considering this and the

simplicity of EIMC and PID controller, it is concluded that these “simpler” controllers may be an attractive alternative over the more complex controllers for glucose regulation in Type I diabetics.

NOMENCLATURE

Abbreviations

AIDA	automated insulin dosage advisor
C	controller
C_1, C2	controllers in EIMC structure
C-C	cohen-coon
Ch_{crit}	critical value of carbohydrates intake where gastric emptying functions changes shape
DCCT	diabetes control and complications trial
DEE	differential equation editor
DMC	dynamic matrix control
e	error signal
EIMC	enhanced internal model control
ε	epsilon
FOPTD	first order plus time delay
g	gram
GA	genetic algorithm
G_H^C	arterial blood glucose concentration
i	suffix
IAE	integral absolute error
IMC	internal model control
IOL	input output linearization
ISE	integral squared error
ITAE	integral time averaged error
K_c	PID controller gain

τ_i	integral time
τ_d	derivative time
K_P	PID controller proportional gain coefficient
K_I	PID controller integral coefficient
K_D	PID controller derivative coefficient
$L_f h(x)$	lie derivative of h(x) with respect to f(x)
$L_g L_f h(x)$	lie derivative of h(x) with respect to g(x) and f(x)
M	model
MPC	model predictive control
MPCSE	model predictive control with state estimation
MPCSPE	model predictive control with state and parameter estimation
NIMC	nonlinear internal model control
ode15s	stiff differential equation solver
P	process or proportional
PD	proportional-derivative
PI	proportional-integral
PID	proportional-integral-derivative
r	set point
$Tasc_{ge}$	time of ascending part of gastric emptying function
$Tdes_{ge}$	time of descending part of gastric emptying funcition
$Tmax_{ge}$	time of plateau of gastric emptying function
x	state variable
$\tilde{x}$	estimated state variable
y	output
$Y_{sp}(t)$	set point of output variable as a function of time

Y(t)	output variable as a function of time
$\tilde{y}$	estimated output
γ	relative order
α	constant

Diabetic Patient Model Variables:

A	auxiliary equation state (dimensionless) or hepatic artery
B	fractional clearance (I, dimensionless; N, L/min) or Brain
BU	brain uptake
C	capillary space
FHIC	fractional hepatic insulin clearance
FKIC	fractional kidney insulin clearance
FPIC	fractional peripheral insulin clearance
G	glucose concentration (mg/dl)
G	glucose
H	heart and lungs
HGP	hepatic glucose production
HGU	hepatic glucose uptake
I	insulin concentration (mU/L)
IHGP	insulin effect on HGP
IHGU	insulin effect on HGU
IVI	intravenous insulin infusion
K	kidney
KC	kidney clearance
KE	kidney excretion

L	liver
LC	liver clearance
N	glucagons concentration (normalized)
NHGP	glucagons effect on HGP
P	periphery (muscle/adipose tissue)
PC	peripheral clearance
PGU	peripheral glucose uptake
PIR	pancreatic insulin release
PNC	pancreatic glucagons clearance
PNR	pancreatic glucagons release (normalized)
q	vascular blood flow rate (dL/min)
Q	vascular plasma flow rate (L/min)
RBCU	red blood cell uptake
S	gut (stomach/intestine)
SIA	insulin absorption into blood stream from subcutaneous depot
SU	gut uptake
T	tissue space or transcapillary diffusion time constant (min)
v	volume (dL)
V	volume (L)
$G_{empt,\, w_f}$	gastric emptying function
λ	lambda
λ_1, λ_2	filter constants in EIMC
Γ	metabolic source or sink rate (mg/min or mU/min)

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CHAPTER 1

Introduction

At the interface between biological sciences and engineering disciplines can be found an interesting set of problems most easily classified as biosystems. Further subdivision of these systems yields problems addressing biomedical and biotechnical issues. Biomedical is related to medicine or the human patient, whereas the biotechnical issues deal with non-human or exvivo organisms. These biosystems offer a challenging set of modeling and regulation problems to the biological, medical and engineering communities. Biomedical problem of glucose regulation using different control strategies in diabetes patients is the focus of this study.

Diabetes mellitus is a global, public health problem and a leading cause of morbidity and mortality in many parts of the world. Diabetes is of two types, Type I & Type II. **Type 1 diabetes**, formerly called juvenile diabetes or insulin dependent diabetes mellitus (IDDM), is usually diagnosed in children, teenagers, or young adults. In Type I diabetic, the glucose concentration is elevated beyond the normoglycemic range (70-100 mg/dl) due to the insufficient insulin secretion from the β-cells of islets of Langerhans present in the pancreas. **Type 2 diabetes**, formerly called adult-onset diabetes or non insulin dependent diabetes mellitus (NIDDM), is the most common form of diabetes. People can develop Type 2 diabetes at any age - even during childhood. This form of diabetes usually begins with insulin resistance, a condition in which fat, muscle and liver cells do not use insulin properly. The role of pancreas in the healthy person for the regulation of the blood glucose levels is depicted in Fig. 1.1.

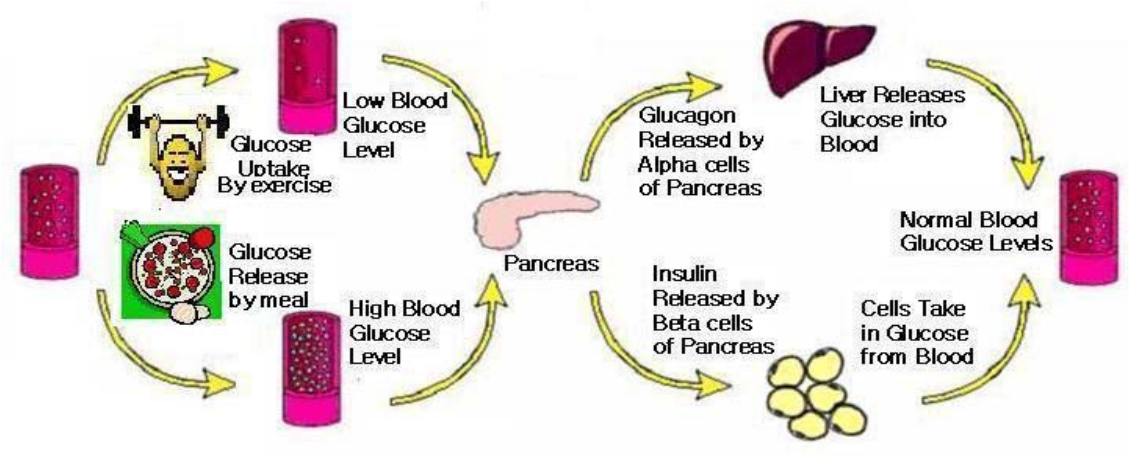

Fig. 1.1. Regulation of Blood Glucose by Insulin and Glucagon in a Healthy Person

As shown in Fig.1.1, the blood glucose level is regulated via two paths. Firstly when the glucose levels falls due to physical activity (e.g. exercise), it stimulates α-cells of pancreas which turn signals the liver to deliver the stored glucose (i.e. glucagon) into the blood stream to maintain the glucose concentration in the normoglycemic range (Glucose Concentration of 70-100 mg/dl). Secondly, when the blood glucose level rises by meal intake, it stimulates the β-cells of pancreas to release insulin. Insulin acts as a funnel for glucose to enter cells, and glucose is taken up by cells to return to normoglycemic range. Malfunctioning of pancreas is the cause for diabetes. Due to that, glucose level goes beyond the normoglycemic range in diabetics. In such patients, monitoring the glucose level and administering insulin are vital. Present study is to develop closed loop devices (referred as artificial β-cells) to mimic the action of pancreas.

1.1 Diabetes Mellitus

The medical name for diabetes, **diabetes mellitus**, comes from words with Greek and Latin roots. Diabetes comes from a Greek word that means to siphon. The most

obvious sign of diabetes is excessive urination. Water passes through the body of a person with diabetes as if it were being siphoned from the mouth through the urinary system out of the body. **Mellitus** comes from a Latin word that means **sweet like honey**. The urine of a person with diabetes contains extra sugar (glucose) and tastes as sweet like honey. **Insulin** is a hormone produced in the **pancreas** to regulate the amount of sugar in the blood. In persons with diabetes, the pancreas produces no insulin, too little insulin to control blood sugar or defective insulin.

The normal human body requires blood glucose concentrations of between 70 and 100 mg/dl (milligrams of glucose in 100 milliliters of blood), which is termed as normoglycemic region in the medical literature. The condition of blood glucose concentrations of below 60 mg/dl is termed 'hypoglycemia', and above 110 mg/dl after 2 to 3 hours from eating a meal, is considered abnormal. Hypergylcaemia is a condition when the blood glucose exceeds 180 mg/dl at any time. Blood sugar can occasionally fall below 60 mg/dl and even to below 50 mg/dl and still not indicate a serious abnormality or disease. Blood sugar levels below 45 mg/dl are almost always associated with a serious abnormality.

1.2 Modeling Literature

Various models developed for the human glucose-insulin system in whole or in part, are comprehensively reviewed by Parker (1999). Here, only the most relevant and important works are briefly described. The first modeling study of the diabetic is the work of Bolie (1961) who developed a two state linear model consisting of two differential equations, one for glucose and other for insulin. A model with similar structure was developed by Ackerman et al. (1965) for glucose-insulin dynamics in a

healthy person. Even though these models with two linear equations are oversimplification of the physiological glucose and insulin effects, the interaction effects of glucose and insulin were concluded from these studies. Primitive but detailed physiological (organ-derived model divisions) structures were developed for glucose dynamics (Tiran et al., 1975) and insulin dynamics (Tiran et al., 1979) including nonlinear effects in the glucose metabolism. These models accounted for the distribution of insulin and glucose throughout the body compared to the earlier approaches of Bolie (1961) and Ackerman et al. (1965), but they were unable to capture the threshold metabolic behavior of the physiological system.

Bergman et al. (1981) have developed a "minimal" model with three compartments as a lumped representation of the human body. The underlying dynamics of the glucose transport and distribution throughout the tissues were neglected by grouping these effects into a few parameters. The effects of glucagon, which raises the blood glucose concentration, were not accounted explicitly. Inadequacies of the "minimal" model were demonstrated in the literature (Quon et al., 1994; Weber et al., 1989).

Cobelli et al. (1982) have studied the glucose and insulin modeling extensively. These models utilized 5-compartment models for insulin, and glucose and glucagon effects, each lumped into its own whole-body blood pool. These nonlinear models included the use of threshold functions (hyperbolic tangents) to describe the saturation behavior seen in biological sensing (e.g. hepatic glucose production). Validation of these mathematical models with a case study on glucose regulation was performed (Cobelli and Mari, 1983). Comparison of the peripheral versus portal route for insulin administration in closed-loop glucose control was done by Cobelli and

Ruggeri (1983). In peripheral route, insulin is injected through subcutaneous tissue, where as in portal route, it is administered through the vein. They found portal vein insulin administration to diabetics accurately matches their glucose profiles to those of healthy persons. However, models of Cobelli and co-workers were unable to describe the glucose distribution throughout the body.

Puckett (1992) presented detailed modeling study of diabetes mellitus; the time scale of interest was much larger than that for the equilibration of glucose and insulin across the blood-tissue boundary, as determined from the blood perfusion data. In this work, the body was modeled as a two-blood-pool system representing insulin and glucose concentrations. The metabolic flux terms and exogenous signals directly affected the blood pool concentrations. Nonlinear metabolic behavior of the glucose insulin system was accounted, but the steady state compartmental representation neglects any high-frequency dynamics within the patient. Inclusion of carrier mechanism and diffusion pathways improved the accuracy of the glucose and insulin removal from the bloodstream. Puckett and Lightfoot (1995) have demonstrated both inter-and intrapatient variability (i.e. the differences in the dynamics of insulin and glucose profiles in different patients and the same patient over time) and steady state behavior by using their models. Variability is a challenging feature that needs to be addressed in both modeling and control of diabetics.

A physiologically based compartmental model of glucose and insulin dynamics was developed by Sorensen (1985), based on an earlier model by Guyton et al. (1978). In this model, glucose and insulin are treated separately, with coupling through metabolic effects utilizing threshold functions similar to those of Cobelli et al. (1982).

A lumped whole body representation for glucagon was included to complete the glucose-insulin system with counter regulation. Parker (1999) modified the Sorensen (1985) model to include meal disturbances as well as parameters for uncertainty analysis. This complete model is described in Chapter 2, and is used for the controller synthesis and analysis in the present study.

Lehmann and Deutsch (1992) developed a nonlinear model of glucose and insulin kinetics within the diabetic. The glucose sub-model was a single compartment extra cellular pool, from which glucose could be added or removed via metabolic processes and meal consumption. A two-compartment model of insulin representing plasma and "active" concentrations was developed. This "active" insulin compartment was responsible for regulating insulin-dependent glucose uptake. A generalized meal model was also developed by Lehmann and Deutsch (1992) as a trapezoidal waveform representative of a relatively constant glucose supply to the gut during carbohydrate absorption in series with a first order transfer function, which approximated the absorption kinetics of glucose by the blood stream. This allowed treatment of arbitrary meal sizes in disturbance rejection scenarios, which are highly relevant to the diabetic modeling and control. This generalized meal model is included in the diabetic model, as described in Chapter 2.

1.3 Control Literature

Several control algorithms were developed and studied for different models of diabetic in the literature. These are comprehensively reviewed by Parker (1999) and Parker et al. (2001). The earliest diabetes regulation work dates to the "BIOSTATOR" algorithm and device of Clemens (1979). This feedback controller utilized a low

volume continuous flow blood glucose sampling mechanism with a dual infusion system (insulin and dextrose) to maintain blood glucose concentration at a user-defined value. The multichannel nature of the algorithm could lead to interactions such as an increase in glucose stimulates the insulin release from its reservoir leading to lowering of glucose level which stimulates the dextrose release from its reservoir and continuation of this cycle. This system requires implantation of two reservoirs, and is difficult due to additional size of the second depot and patient specific requiring individualization prior to implementation. Sorenson (1985) tested an IMC strategy on his model for a particular set of patient parameters.

Optimal control theory was applied to the "minimal" model of Bergman et al. (1981) in two different studies (Ollerton, 1989; Fischer, 1991). Ollerton (1989) used an integral squared error cost function based on deviation from the desired glucose value. Sampling times of 10 and 180 min were studied. The longer sampling time had a longer rise time and was less sensitive to noise about the basal state, but could miss significant disturbances which occurred in the inter-sample window. With sampling time of 10 min, the controller was sensitive to oscillations of the glucose profiles about the basal state, and resulted in physiologically unrealistic insulin profiles characterized by high amplitude sustained oscillations (ringing). An insensitive model was introduced by Ollerton (1989), most likely based on a type of dead-band control, but no method for development of the insensitive model was discussed.

Fischer (1991) applied optimal control theory to "minimal" model by using integral squared error (ISE) based objective function. The deviations in the glucose concentration from the set point are minimized. As a second objective the amount of

insulin to perform the corrective action is minimized. The study examined three insulin infusion profiles, determining that an initial injection plus optimal hourly infusion minimizes the cost function for an initially hyperglycemic patient. This control design also suffered from long sampling time (180 min) problem of missing fast or inter-sample distribution and was not robust to patient uncertainty, as in Ollerton (1989).

Proportional Derivative (PD) and Proportional Integral (PI) type controllers (belonging to the Proportional-Integral-Derivative (PID) controller family) are employed by Fischer et al. (1990) and Chee et al. (2003) respectively for blood glucose control. Chee et al. (2003) have developed a PI controller to specify the amount of insulin to be injected based on glucose measurement in a real time manner by continuous glucose monitoring system (CGMS). This closed loop control was clinically tested on five patients and was able to control only one patient's glycaemia without manual intervention. Even though manual intervention is due to the real time sensor reading, refinement of the algorithm and sensor accuracy are needed.

Parker et al. (1999) have done an extensive study on blood glucose control and compared the performance of several model predictive controllers such as discrete IMC, Model Predictive Controller (MPC), Model Predictive Controller with State Estimation (MPCSE), Nonlinear Quadratic Dynamic Matrix Control with State Estimation (NLQDMCSE). Camelia and Doyle (2001) used IMC framework to maintain the blood glucose concentration in diabetics simulated by Bergman and Automated Insulin Dosage Advisor (AIDA) of Lehmann and Deutsch (1992) models. In the synthesis and/or evaluation of these controllers, however, the inherent

uncertainty in the model has not been addressed. Such control strategies could lead to significant performance degradation in the presence of inevitable patient-model mismatch.

Significant inter- and intra-patient variability has been documented in the literature (Simon et al., 1987; Steil et al., 1994; Puckett and Lightfoot, 1995; Bremer and Gough, 1999). The control algorithm employed for blood glucose regulation must be able to compensate for the uncertainty that exists between the model used in the controller design and the actual patient. Keinitz and Yoneyama (1993) used the H_∞ framework to treat the model uncertainty on a slightly extended version of metabolic equations of glucose and insulin in Fischer and Teo (1989). Parker et al. (2000) too employed the H_∞ framework to explicitly treat the model uncertainty but they employed a detailed and fairly complex physiological patient model (a 19-state nonlinear dynamic model) because it allows uncertainty characterization on particular tissues or effects that are responsible for the insulin or glucose variability. They assessed the resulting H_∞ controller based on the disturbance rejection capability on 577 patients by considering the parametric uncertainty, and concluded that it has comparable performance to the computationally-intensive MPC.

Recently, Ruiz-Velazquez et al. (2004) have addressed blood glucose control for diabetics as a set point tracking problem using H_∞ controller strategy. In this study, blood glucose regulation problem was reformulated as a tracking problem. The amount of insulin to be injected was specified by H_∞ controller strategy to track the glucose profile of the healthy patient subjected to meal disturbances. Even though maximum tracking error for nominal and worst case condition reported are 15 mg/dl,

there is a possibility for prevalence of hyperglycaemia for quite some time, which could result in retinopathy and nephropathy over a long run.

1.4 Motivation and Scope of this Work

The reason why diabetes mellitus is of such concern is that, on a worldwide scale, it was estimated that the disease affected 4% of all adults in 1995 and is expected to rise to 5.4% by 2025. Compared to other parts of the world, Singapore has a higher prevalence rate, with 9% of Singaporeans being diabetic in 1998. In 1999, it accounted for 2.2% of annual total mortality in Singapore, and is the sixth most common cause of death (Wee et al., 2002).

In addition to the significant mortality, diabetes-related morbidities such as diabetic retinopathy, neuropathy and cardiovascular disease have also placed a heavy financial burden on society. According to American Diabetes Association (2003), the economic costs of diabetes in 1997 was estimated to be US$98 billion, with US$44 billion direct medical and treatment costs and US$54 billion for indirect costs. The economic costs of diabetes have further increased to US$132 billion, with US$90 billion direct medical and treatment costs and US$42 billion for indirect costs. In total U.S. health expenditure of US$865 billion, US$160 billion was incurred by people with diabetes. In addition, the prevalence of diabetes is increasing drastically in all parts of the world. A few recent news paper articles describing the increase in the prevalence of diabetes are summarized below in chronological order.

Diabetes prevalence cause for concern, The Hindu - NEW DELHI, 12 March 2003

Madras Diabetes Research Foundation (MDRS), has conducted a survey in five major cities -- Mumbai, Chennai, Kolkata, Bangalore and Hyderabad -- where samples of 2,000 people from each city were taken and "glucose tolerance test" (GTT) conducted. In the survey, we found that Hyderabad has the maximum number of diabetes patients (where 16 per cent of the respondents tested positive) followed by Chennai (13 per cent), Bangalore (12 per cent), Kolkata (11 per cent), Delhi (10 per cent) and Mumbai (9 per cent), and World Health Organization (WHO) has already declared India as the world's "diabetic Capital" WHO estimates an alarming 250 percent increase in diabetics in Indians from 19 millions in 1995 to 57 millions by 2025.

Diabetes up by an alarming 40 percent in Oman, Times of Oman, MUSCAT, 5 June 2003

Oman has seen nearly 40 per cent increase of diabetics since the last 10 years, top experts here told the Times of Oman yesterday. In Oman, those afflicted with diabetes has increased from 8.3 per cent in 1991 to 11.6 per cent in 2000, posting almost 40 per cent increase in the last decade. Worldwide the problem was getting worse. The World Health Organization (WHO) estimates that 135 million people in the world suffer from diabetes and it is expected to increase by 170 per cent to 300 million in 2025, mainly in developing countries. In the second survey, conducted in 2000, but published recently, the highest prevalence of diabetes was found in males over 80 years (26.2 per cent) and in females between 60-69 years (28.3 per cent). Diabetes mellitus is a global, public health problem and a leading cause of morbidity and mortality. Projections for the year 2025 estimate that the global burden of the disease

to increase by 122 per cent, affecting around 300 million people worldwide. The problem seems to be very acute in developing countries where a 170 per cent surge in diabetes mellitus is forecast, compared to 40 per cent in developed countries. According to the annual statistical report, patient morbidity for diabetes mellitus has risen steadily from 1,528 cases in 1986 to 3,695 in 2000.

Diabetes Carnival in conjunction with World Diabetes Day November 2003, Alexandra Hospital, 15 November 2003

Almost one in 10 Singaporeans has diabetes and may not even know it. In the next 25 years the number of people in the world with diabetes will double - from 140 to 300 millions.

Current clinical treatment methods:

The current treatment method for diabetes is diet therapy and insulin injection therapy with physical activity (i.e. exercise). In diet therapy, the patient is asked to take prescribed meal pattern. In insulin injection therapy, prescribed insulin doses will be given to the patient at regular intervals, all these are “open loop” in nature. Insulin injection therapies, with minor changes in the diet and physical activity have failed to maintain the glucose concentration within the allowable ranges leading to abnormalities (Parker et al. 2001). So there is a need for new treatment methods to assist diabetics to maintain their glucose concentration within the allowable ranges. For diabetics, continuous monitoring of blood glucose level with user intervention in insulin dosage is thought to be an ideal solution.

As current clinical treatment methods being "open-loop nature", it is thought that "closed loop" control approaches can result in good glycaemia control over extended periods of time, and also mimic the glucose control in healthy persons. Such closed loop control strategy consists of three major components – *in-vivo* sensor for blood glucose concentration, a control algorithm to set appropriate insulin dosage based on sensor measurement and a suitable insulin delivery device.

Significant improvements in two major components glucose sensing and insulin pumps have led the practical feasibility of artificial β-cells in diabetics. The developments in sensor technology have resulted in fast (i.e. within 4 min) and reliable glucose concentration measurements, approved by Food and Drug Administration (FDA) USA. The implantable insulin pumps are developed and are able to deliver insulin accurately and safely; these are also approved by FDA. With the significant improvements in the sensing, insulin delivery devices, the development of control algorithm is vital.

An algorithm to specify the insulin dosage plays a significant role in maintaining the glucose concentration within normoglycemic range in presence of daily activities such as meal and exercise. The present study is on the development of simple and effective controllers to specify the insulin dosage given the blood glucose measurement. Due to the cost and complexity involved in testing the control algorithm on a patient, we plan to use a compartmental first principles model of a patient. As significant inter- and intra patient variability is reported in the literature, the designed controllers are tested on a wide range of patient models in order to evaluate their robustness.

The specific objectives of the study are:

- Synthesis and evaluation of model based controllers such as IMC and EIMC
- Synthesis and evaluation of fundamental PID controller, comparison of various tuning methods of PID for diabetics
- Synthesis and evaluation of nonlinear controller for diabetics using input output linearization technique

1.5 Outline of the Thesis

This work deals the regulation of blood glucose levels in Type I diabetics. Thesis consists of modeling and control aspects of diabetics. Chapter 2 deals with the modeling issues and Chapters 3-5 deal with the control aspects. Chapter 2 describes the modeling of Type I diabetic, dynamics of meal disturbance(s), uncertainty characterization followed by development of test bed to assess the designed controller(s) performance. Chapter 3 deals with the synthesis and evaluation of model based control strategies such as Internal Model Controller (IMC) and Enhanced Internal Model Controller (EIMC) in the presence of meal disturbance(s) and parametric uncertainty. Chapter 4 discusses the design of fundamental Proportional-Integral-Derivative (PID) controller for the diabetics with several tuning rules, followed by the assessment of the resulting controllers to track the set point in the presence of meal disturbance(s) and parametric uncertainty. Chapter 5 deals with the synthesis and evaluation of nonlinear controller using Input Output Linearization (IOL) technique. Findings of the present work are summarized in Chapter 6 along with some recommendations for further research in this area.

CHAPTER 2

Physiological Modeling of Diabetic

2.1 Introduction

Due to the cost and complexity involved in testing the control algorithm on a diabetic patient, model of a diabetic is vital. Performance of the control algorithm in the regulation of blood glucose levels for a diabetic is dependant on the accuracy of diabetic model. Mismatch in the model to patient dynamics is directly proportional to the designed controller performance degradation. So model development is a crucial step in designing the controller.

Modeling strategies can be divided into three general categories: first-principles based, data-driven and hybrid models. First-principles based models are developed by considering the mass, energy and momentum balances for the given physical system. Data-driven models are developed based on the input-output data. In this modeling strategy, an empirical model employs a user-defined functional form and contains coefficients which are identified by fitting the input-output data. Hybrid models are the combination of both first-principles and data-driven models. In this strategy, the functional form of the system is obtained from mass, energy and momentum balances, and the unknown parameters in the functional form are estimated by fitting the input-output data.

2.2 Physiological Modeling

Several models in literature addressed the interaction of glucose-insulin in the human body using different modeling strategies, starting from the early modeling work of Bolie (1961). Brief review of modeling literature is available in Section 1.2.

2.2.1 Compartmental Model

In this study, the detailed physiological model of the human glucose-insulin system developed by Parker et al. (2000) based on models developed earlier by Guyton et al. (1978) and Sorensen (1985), is used. In this model, human body is divided into 6 compartments (brain, heart/lungs, gut, liver, kidney, and periphery) as depicted in Fig. 2.1. Mass balance equations for both glucose and insulin around each compartment are considered. General representation of a compartment (Fig. 2.2) includes capillary blood space, interstitial fluid space and intracellular space, throughout each of which the glucose/insulin concentration is assumed to be uniform. The capillary blood space is fed by arterial blood inflow and drained by venous blood outflow. The interstitial fluid space may exchange mass with the capillary blood space by diffusion of solute through the capillary wall. The intracellular space may exchange mass with the interstitial fluid space through transport of solute across the cell membrane. Based on the cell membrane permeability, capillary wall permeability each compartment consists of at most two spaces. For modeling glucose and insulin dynamics, all compartments are assumed to have only one space; the exceptions are brain (for glucose) and periphery (for both glucose and insulin) having two spaces (namely, capillary and tissue).

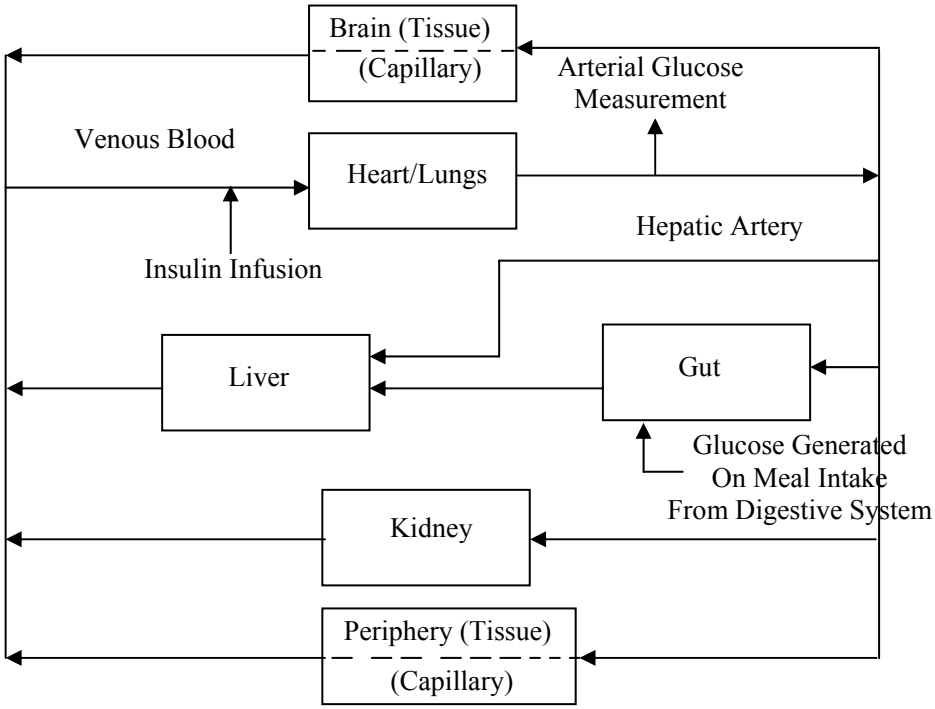

Fig. 2.1. Compartmental diagram of the glucose and insulin systems in a diabetic. The arrow indicates the direction of blood circulation.

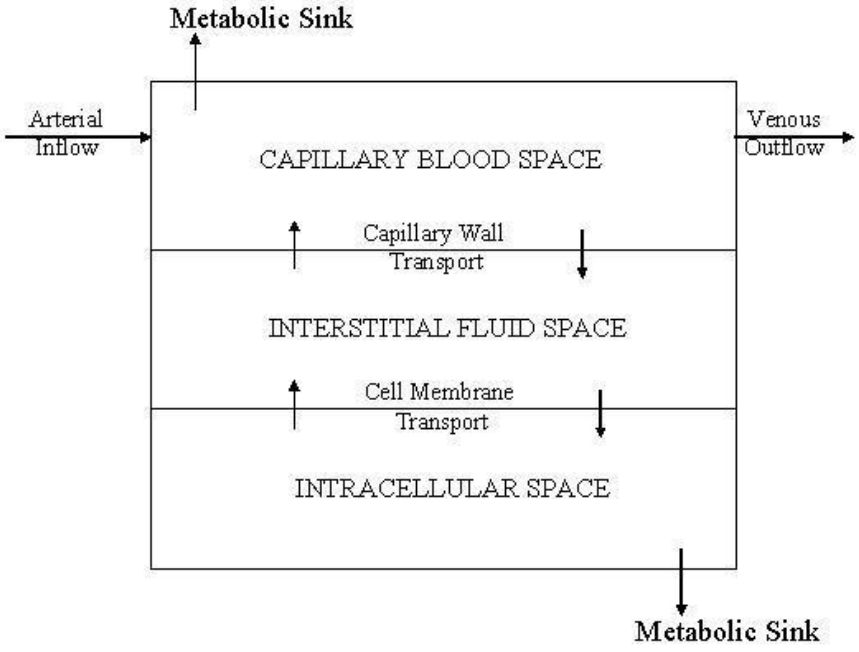

Fig. 2.2. General Representation of a Physiological Organ

The glucose sub-model differential mass balance equations are as follows:

$$\dot{G}_B^C = (G_H^C - G_B^C)\frac{q_B}{v_B^c} - (G_B^C - G_B^T)\frac{v_B^T}{T_B v_B^c} \tag{2.1}$$

$$\dot{G}_B^T = (G_B^C - G_B^T)\frac{1}{T_B} - \frac{\Gamma_{BU}}{v_B^T} \tag{2.2}$$

$$\dot{G}_H^C = (G_B^C q_B + G_L^C q_L + G_K^C q_K + G_P^C q_P + G_H^C q_H - \Gamma_{RBCU})\frac{1}{v_H^c} \tag{2.3}$$

$$\dot{G}_S^C = (G_H^C - G_S^C)\frac{q_s}{v_S^C} + \frac{\Gamma_{meal}}{v_S^C} - \frac{\Gamma_{SU}}{v_S^C} \tag{2.4}$$

$$\dot{G}_L^C = (G_H^C q_A + G_S^C q_s - G_L^C q_L)\frac{1}{v_L^C} + \frac{\Gamma_{HGP}}{v_L^C} - \frac{\Gamma_{HGU}}{v_L^C} \tag{2.5}$$

$$\dot{G}_K^C = (G_H^C - G_K^C)\frac{q_K}{v_K^C} - \frac{\Gamma_{KE}}{v_K^C} \tag{2.6}$$

$$\dot{G}_P^C = (G_H^C - G_P^C)\frac{q_P}{v_P^C} - (G_P^T - G_P^C)\frac{v_P^T}{T_P^G v_P^C} \tag{2.7}$$

$$\dot{G}_P^T = (G_P^C - G_P^T)\frac{1}{T_P^G} - \frac{\Gamma_{PGU}}{v_P^T} \tag{2.8}$$

where

$$k_B^C = G_B^C \frac{v_B^T}{T_B}$$

$$k_B^T = G_B^T \frac{v_B^T}{T_B}$$

The metabolic source and sink terms (Γ_I mg/min) in the above equations are defined by

$$\Gamma_{BU} = 70 \tag{2.9}$$

$$\Gamma_{RBCU} = 10 \tag{2.10}$$

$$\Gamma_{SU} = 20 \tag{2.11}$$

$$\Gamma_{HGP} = 155 A_{IHGP} [2.7 \tanh(0.388N) - A_{NHGP}][1.425 - 1.406 \tanh\{0.6199(\frac{G_L^C}{101} - 0.4969)\}] \quad (2.12)$$

$$\dot{A}_{IHGP} = \frac{1}{25}\left[1.2088 - 1.138 \tanh\{1.669(\frac{I_L^C}{21.43} - 0.8885)\} - A_{IHGP}\right] \quad (2.13)$$

$$\dot{A}_{NHGP} = \frac{1}{65}[\frac{2.7 \tanh(0.388N) - 1}{2} - A_{NHGP}] \quad (2.14)$$

$$\Gamma_{HGU} = 20 A_{IHGU} [5.6648 + 5.6589 \tanh\{2.4375(\frac{G_L^C}{101} - 1.48)\}] \quad (2.15)$$

$$\dot{A}_{IHGU} = \frac{1}{25}[2 \tanh(0.549 \frac{I_L^C}{21.43}) - A_{IHGU}] \quad (2.16)$$

$$\Gamma_{KE} = 71 + 71 \tanh[0.011(G_K^C - 460)], \quad \text{for } G_K^C < 460$$

$$= 0.872 G_K^C - 330, \quad \text{for } G_K^C \geq 460 \quad (2.17)$$

$$\Gamma_{PGU} = \frac{35 G_P^T}{86.81}[7.035 + 6.51623 \tanh\{0.33827(\frac{I_P^T}{5.304} - 5.82113)\}] \quad (2.18)$$

The insulin sub-model mass balances are given by

$$\dot{I}_B^C = (I_H^C - I_B^C)\frac{Q_B}{V_B^C} \quad (2.19)$$

$$\dot{I}_H^C = (I_B^C Q_B + I_L^C Q_L + I_K^C Q_K + I_P^C Q_P - I_H^C Q_H + \Gamma_{IVI})\frac{1}{V_H^C} \quad (2.20)$$

$$\dot{I}_S^C = (I_H^C - I_S^C)\frac{Q_S}{V_S^C} \quad (2.21)$$

$$\dot{I}_L^C = (I_H^C Q_A + I_S^C Q_S - I_L^C Q_L)\frac{1}{V_L^C} + \frac{\Gamma_{PIR} - \Gamma_{LC}}{V_L^C} \quad (2.22)$$

$$\dot{I}_K^C = (I_H^C - I_K^C)\frac{Q_K}{V_K^C} - \frac{\Gamma_{KC}}{V_K^C} \quad (2.23)$$

$$\dot{I}_P^C = (I_H^C - I_P^C)\frac{Q_P}{V_P^C} - (I_P^C - I_P^T)\frac{V_P^T}{T_P^I V_P^C} \quad (2.24)$$

$$\dot{I}_P^T = (I_P^C - I_P^T)\frac{1}{T_P^I} + \frac{\Gamma_{SIA} - \Gamma_{PC}}{V_P^T} \tag{2.25}$$

The related metabolic sink terms (Γ_I mU/min) are

$$\Gamma_{LC} = F_{LC}(I_H^C Q_A + I_S^C Q_S + \Gamma_{PIR}) \tag{2.26}$$

$\Gamma_{PIR} = 0$, as there is no pancreatic insulin release (2.27)

$$\Gamma_{KC} = F_{KC} I_K^C Q_K \tag{2.28}$$

$$\Gamma_{PC} = \frac{I_P^T}{\frac{1 - F_{PC}}{F_{PC}}\frac{1}{Q_P} - \frac{1}{V_P^T / T_P^I}} \tag{2.29}$$

The mass balance of glucagon is modeled as follows:

$$\dot{N} = (\Gamma_{PNR} - N)\frac{F_{PNC}}{V_N} \tag{2.30}$$

The equation used to describe glucagon release from the α-cells of pancreas is:

$$\begin{aligned}\Gamma_{PNR} = &[1.3102 - 0.61016\tanh\{1.0571(\frac{I_H^C}{15.15} - 0.46981)\}]\times \\ &[2.9285 - 2.095\tanh\{4.18(\frac{\Gamma_{KC}}{91.89} - 0.6191)\}]\end{aligned} \tag{2.31}$$

The mass balances for glucose and insulin over 6 compartments along with metabolic terms resulted in 19 nonlinear coupled differential equations with eleven describing glucose dynamics, seven for insulin dynamics and one for glucagon. This model consists of 47 physiological parameters: values of 35 parameters are in Table 2.1, those of 8 other parameters in Table 2.2 and the remaining 4 parameters are $\Gamma_{BU} = 70$; $\Gamma_{RBCU} = 10$; $\Gamma_{SU} = 20$ and $\Gamma_{PIR} = 0$.

Table 2.1 Values of the Parameter in the Diabetic Model

v_B^C=3.5 dL	q_B=5.9 L/min	T_B=2.1 min
v_B^T=4.5 dL		
v_H^C=13.8 dL	q_H=43.7 L/min	
v_S^C=11.2 dL	q_S=10.1 L/min	
v_L^C=25.1 dL	q_L=12.6 L/min	
	q_A=2.5 L/min	
v_K^C=6.6 dL	q_K=10.1 L/min	
v_P^C=10.4 dL	q_P=15.1 L/min	T_P^G=5.0 min
v_P^T=63.0 L		
V_B^C=0.265 L	Q_B=0.45 L/min	
V_H^C=0.985 L	Q_H=3.12 L/min	
V_S^C=0.945 L	Q_S=0.72 L/min	
V_L^C=1.14 L	Q_L=0.9 L/min	
	Q_A=0.18 L/min	
V_K^C=0.505 L	Q_K=0.72 L/min	
V_P^C=0.735 L	Q_P=1.05 L/min	T_P^I=20 min
V_P^T=6.3 L		
V_N=9.93 L	F_{PNC}=0.910 L/min	F_{KC}=0.3

The diabetic model has two inputs - insulin delivery and meal disturbance, and one measured output, namely, blood glucose concentration. Insulin delivery rate, represented as deviation from its 22.3 mU/min nominal delivery, is the manipulated variable (represented as $\bar{u}$). The meal disturbance had a nominal value of 0 mg/min (absorption into blood stream), and its signal denoted as $\overline{m}_d$. The output variable, $\overline{Y}$ represents the deviation in blood glucose concentration from the nominal value of 81.1 mg/dl. All these three variables are scaled as mentioned in Parker et al. (2000).

$$m_d = \frac{1}{360}\overline{m}_d, u = \frac{1}{33.125}\bar{u}, Y = \frac{1}{20}\overline{Y} \tag{2.32}$$

Here, the disturbance scaling was determined by its maximum value, scaling for the manipulated variable, u is based on its expected range and the output scaling by maximum allowable deviation in glucose concentration. Note that the measured value, Y is the (blood) plasma glucose concentration, obtained by multiplying the arterial glucose concentration (3rd state in the model of Parker et al., 2000) by a factor of 0.925. A few typographical errors in the differential equations provided in Parker et al. (2000) are confirmed, corrected and listed in the Appendix A (Parker, 2002). These corrected differential equations (2.1 to 2.31) are reported in this Section 2.2.1.

2.2.2 Uncertainty Description

Uncertainties exist due to the inevitable patient-model mismatch; the uncertainties between the actual patient and the model could be translated to variations in the model parameters. The glucose and insulin dynamics were found to be the most sensitive to variations in the metabolic parameters of liver and periphery. In the patient model, glucose metabolism is mathematically described by threshold functions with the following structure:

$$\Gamma_e = E_{re}\{A_{re}\text{-}B_r\tanh[C_{re}(x_i + D_{re})]\} \tag{2.33}$$

The subscript i in equation (2.33) is the state vector element involved in the metabolic effect and subscript e denotes specific effects within the model: the effect of glucose on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU) or the effect of insulin on peripheral glucose uptake (EIPGU), which are given by

$$\Gamma_{EGHGP} = 1.0\{1.425 - 1.406\tanh[0.6199(\frac{G_L^C}{101} - 0.4969)]\} \tag{2.36}$$

$$\Gamma_{EGHGU} = 1.0\{5.6648 + 5.6589 \tanh[2.4375(\frac{G_L^C}{101} - 1.48)]\} \quad (2.35)$$

$$\Gamma_{EIPGU} = 1.0\{7.035 + 6.51623 \tanh[0.33827(\frac{I_P^T}{5.304} - 5.82113)]\} \quad (2.34)$$

These correspond to the last bracketed term in equation (2.12), (2.15) and (2.18) respectively.

Inter- or intra-patient uncertainty could be classified physiologically as either receptor (D_{re} parameter) or post-receptor (E_{re} parameter) defect, and these two parameters are estimated by fitting the actual patient data. Differences in insulin clearance (metabolism) between patients also exist and could be modeled as deviations in the fraction of clearance (i.e., insulin utilized) by a given compartment such as the fraction of hepatic clearance (FHIC or F_{LC}) or the fraction of peripheral insulin clearance (FPIC or F_{PC}). This uncertainty formulation essentially focuses on the liver (variability in five parameters) and the peripheral (muscle/fat) tissues (variability in three parameters) as these are considered to be more relevant to the control study (Parker et al., 2000). Nominal values of these 8 parameters are tabulated in Table 2.2.

In the absence of physical data from which to identify ranges for parametric variations, Parker et al. (2000) assumed ±40% variability in each parameter to represent a broad range of potential patients. The exception was FHIC, which was limited to ±20% to guarantee non-negative glucose concentrations. From these eight parameters, sets of three parameters were chosen. Each of these three parameters was tested at three levels (nominal, low and high) yielding a total of ${}^8C_3 \times 3^3 = 1512$ "patients". Patients with identical values for all the eight parameters were removed and this resulted in a set of 577 unique patients, which are considered as perturbed cases in further

discussion. These patients are assumed to capture all the inter- and intra-patient variability among Type I diabetics. These 577 unique patients are considered as the test bed to assess the controller performance.

Table 2.2. Nominal Values for Uncertain Parameters in Diabetic Patient Model

EIPGU-E_Γ = 1.0	EGHGU-E_Γ = 1.0	EGHGP-E_Γ = 1.0
EIPGU-D_Γ = -5.82113	EGHGU-D_Γ = -1.48	EGHGP-D_Γ = -0.4969
FHIC (F_{LC}) = 0.4	FPIC (F_{PC}) = 0.15	

2.3 Realization of Meal Model

Lehmann and Deutsch (1992) proposed a model to describe absorption rate of glucose into gut from meal taken by the diabetics. This model describes gastric emptying of carbohydrates as a saturating function, with a maximum rate ($Vmax_{ge}$) of 360 mg/min carbohydrates to describe carbohydrate release from the stomach during intestinal adsorption. The shape of the curve is dependent on the carbohydrates ingested by the diabetic patient. If carbohydrates ingested by a diabetic is less than a critical value Ch_{crit} calculated by equation (2.37), then shape of the gastric emptying function is triangular as in Fig. 2.3 (a), $Tasc_{ge}$ and $Tdes_{ge}$ are the rising and falling times of the curve as described in equation (2.38). For carbohydrates ingestion greater than or equal to Ch_{crit}, the shape of the gastric empting rate is trapezoidal as shown in Fig. 2.3 (b), and $Tasc_{ge}$ and $Tdes_{ge}$ have default values of 30 min. In this case, the time of plateau $Tmax_{ge}$ is described by equation (2.39). The $Tasc_{ge}$ and $Tdes_{ge}$ values are at default values when carbohydrates ingestion is critical, hence Ch_{crit} = 10.8 g.

$$Ch_{crit} = [(Tasc_{ge} + Tdes_{ge})\ Vmax_{ge}]/2 \quad (2.37)$$

$$Tasc_{ge} = Tdes_{ge} = Ch / Vmax_{ge} \quad (2.38)$$

$$Tmax_{ge} = [Ch – ½ Vmax_{ge} * (Tasc_{ge} + Tdes_{ge})] /Vmax_{ge} \quad (2.39)$$

Using linear interpolation the rate of gastric emptying rate for meals containing carbohydrates greater than $Ch_{crit,}$ can therefore be defined, according to the time elapsed from the start of the meal, t, as follows:

$$\begin{aligned} G_{empt} &= (Vmax_{ge}/Tasc_{ge})\, t && \text{for} \quad t < Tasc_{ge}, \\ &= Vmax_{ge}; && \text{for} \quad Tasc_{ge} < t \le Tasc_{ge}+Tmax_{ge}, \\ &= Vmax_{ge}-(Vmax_{ge}/Tdes_{ge})(t-Tasc_{ge}-Tmax_{ge}) \\ & && \text{for } Tasc_{ge} + Tmax_{ge} \le t < Tmax_{ge} + Tasc_{ge} + Tdes_{ge} \text{ and} \\ &= 0 && \text{for other t} \end{aligned} \quad (2.40)$$

Either triangular or trapezoidal gastric emptying rate function (G_{empt}) from equation (2.40) is followed by the first-order filter to result in Γ_{meal} representing the absorption rate of glucose into the diabetic patient model gut compartment:

$$\Gamma_{meal} = \frac{1}{60s+1} wf \quad (2.41)$$

The absorption rate of glucose into gut compartment of the diabetic model for 10 and 50 g carbohydrate intake, shown in Fig. 2.4 is obtained by passing the trapezoidal gastric emptying rate function (Fig. 2.3) through the first order filter (equation 2.40).

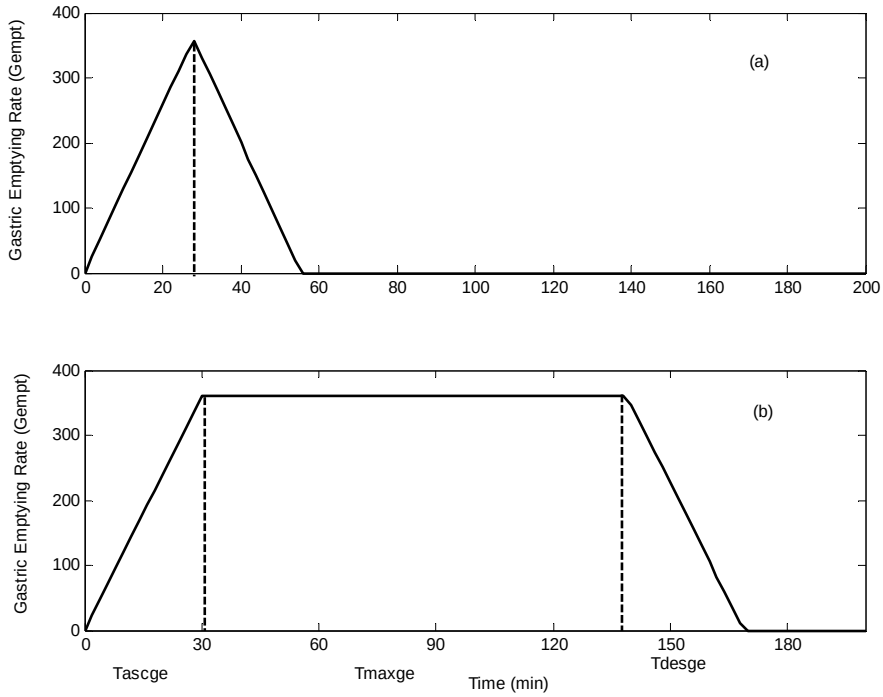

Fig 2.3. The gastric emptying rate for carbohydrate ingestions of (a) 10 g and (b) 50 g.

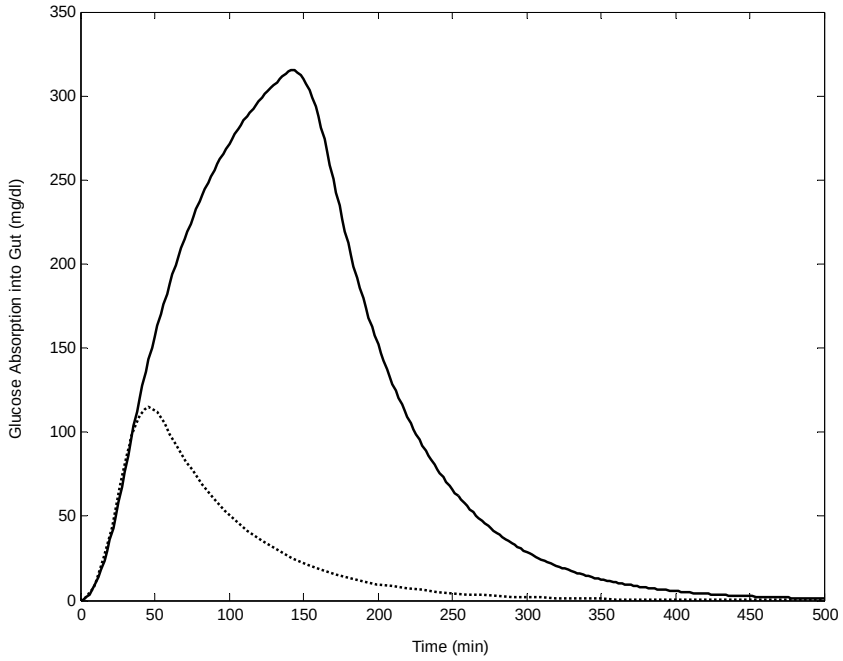

Fig. 2.4. The glucose absorption into gut compartment for 10 g (dotted curve) and 50 g (solid curve) carbohydrate meal ingestion.

2.4 Implementation of Diabetic Model

Diabetic patient model discussed in Sections 2.2 and 2.3 was implemented in Simulink 5.1 along with Matlab 6.5. The DEE block in Simulink is used to solve the nonlinear coupled differential equations presented in Section 2.2. The DEE block requires the user to provide information such as name, number of inputs, first order differential equations in the form of f(x,u), initial guesses (x0), output equations in the form of f(x,u). The inputs to and outputs from DEE should be given as vectors u and x respectively. The input signals to DEE are numbered as u(1), u(2), u(3) etc in top to down order, and outputs are according to the output equations in top to down order. The equations in Section 2.2 with all the parameters are coded in the required notation for DEE with initial guesses and output equations, to simulate a diabetic. The external inputs such as glucose absorption from meal and insulin injection are also present as inputs to DEE, so that it becomes easier for the user to study the open loop dynamics as well as closed loop dynamics with different control strategies.

The absorption of glucose to gut compartment from carbohydrate ingestion through meal was discussed in Section 2.3, and was implemented in Simulink by employing Matlab Fcn block, which can be used to run a function in mfile. The Matlab Fcn in Simulink gets the input from the Simulink environment and runs the function in mfile and the output from the mfile is popped back to Simulink. Thus the diabetic patient model is implemented in Simulink as a combination of both DEE block and Matlab Fcn block for the meal model. The Simulink implementation of diabetic model with DEE, Matlab Fcn and input-output scaling is depicted in Fig. 2.5.

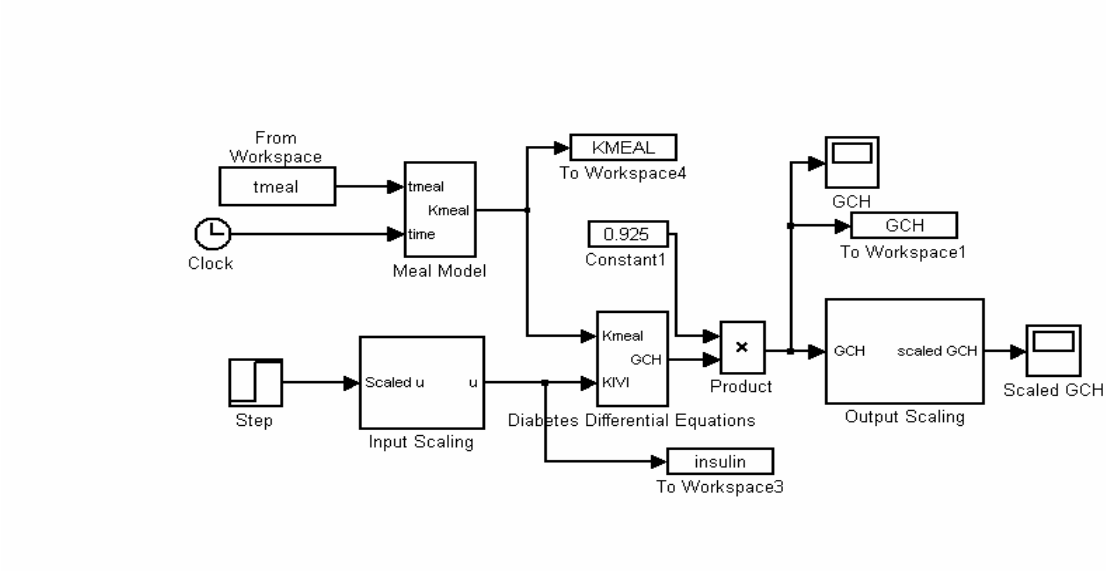

Fig. 2.5(a) Simulink implementation of diabetic model with DEE, meal model and input-output scaling

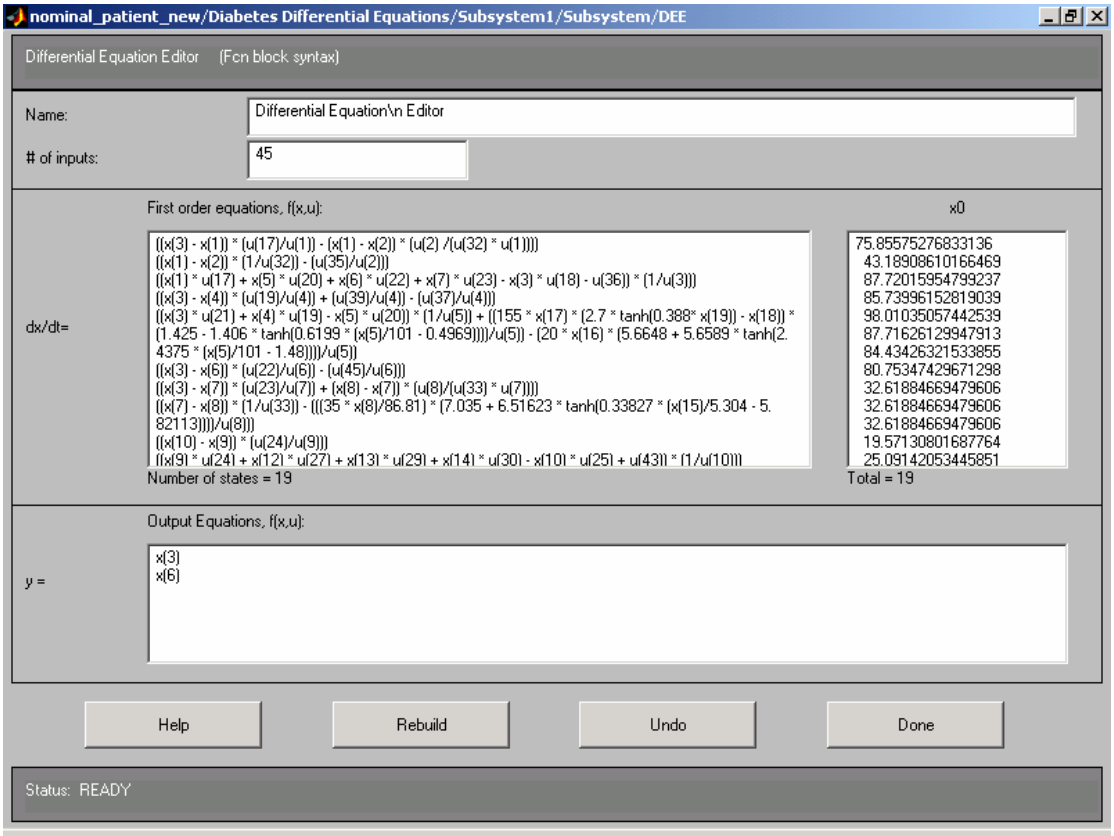

Fig 2.5(b) The differential equations editor with diabetic differential equations, initial guesses and output equations

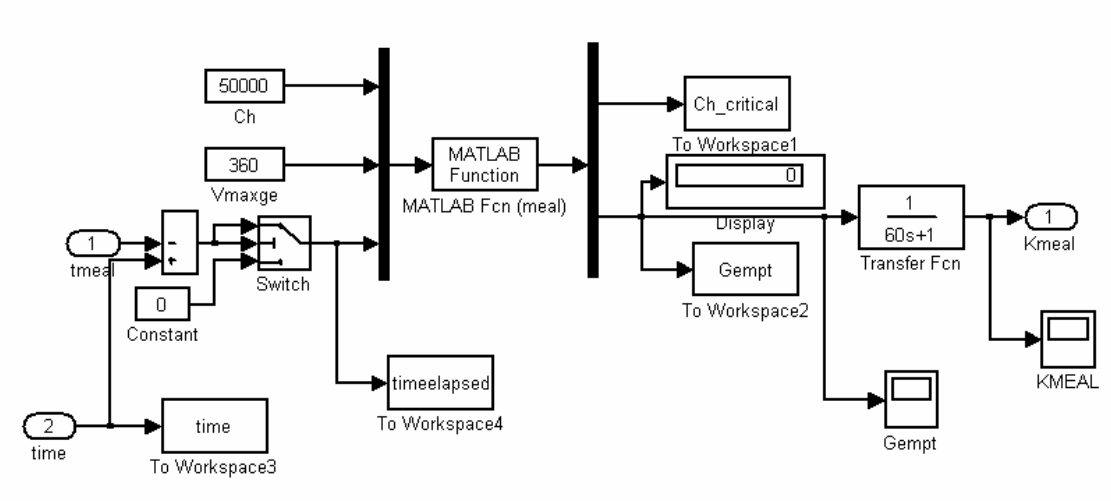

Fig. 2.5(c). Implementation of the meal model in Simulink using Matlab function (Matlab Fcn) block

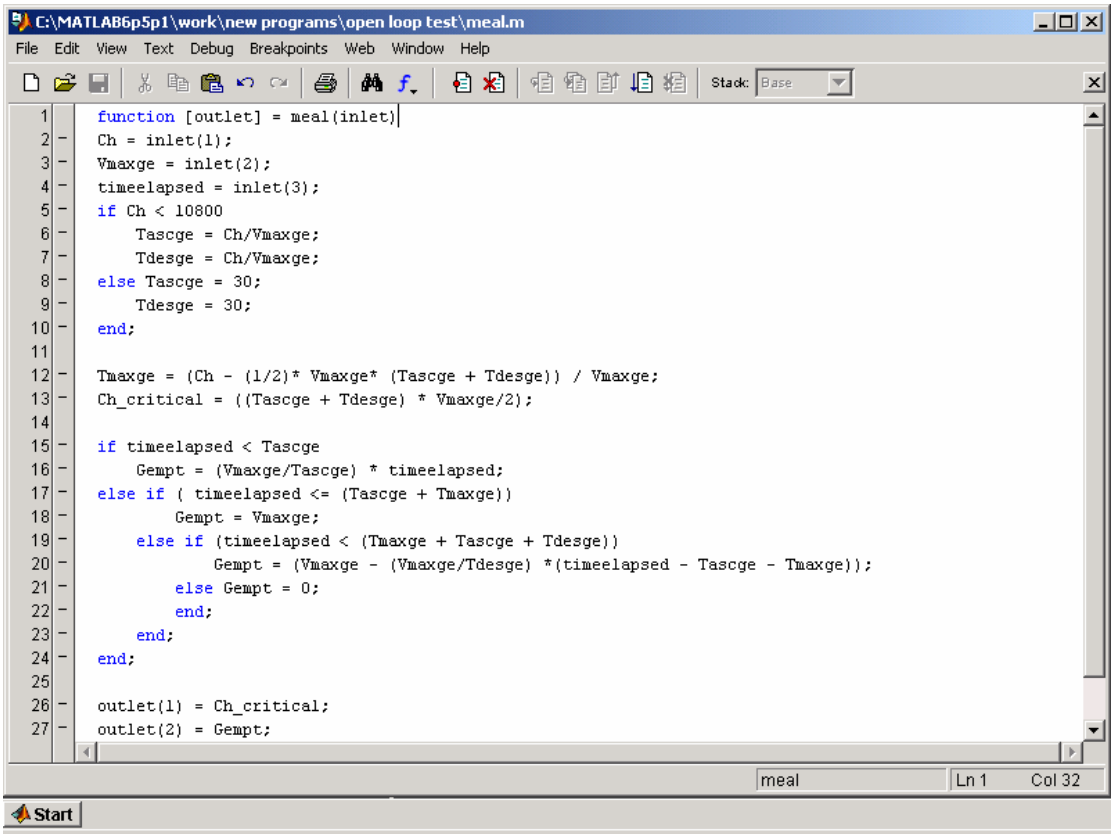

Fig 2.5(d). The Matlab Fcn block for gastric emptying rate of meal (equation 2.40)

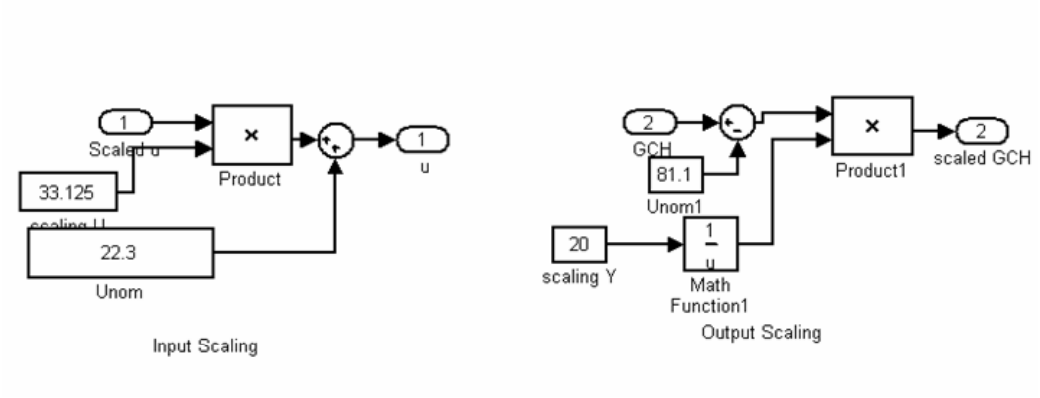

Fig. 2.5(e). Input output scaling of insulin and blood plasma glucose concentration

To incorporate the parametric variations, the diabetic model is developed with provision to specify the values of parameters. Using this model, 577 patients with different parameters can be simulated, and the robustness and disturbance attenuation of the designed controllers can be assessed.

Bounds on open-loop responses of some patient models to a step change in insulin (from the value required to maintain the output at 81.1 mg/dl) to 0 mU/min, are shown in Fig 2.6. These responses are very similar to those reported in Parker (1999), confirming the validity of patient models employed in this study. They also show the broad range of patient dynamics. Note that glucose profiles shown in Fig. 2.6 are for ±50% variation in parameters where as only ±40% variation in parameters is considered to test controller robustness.

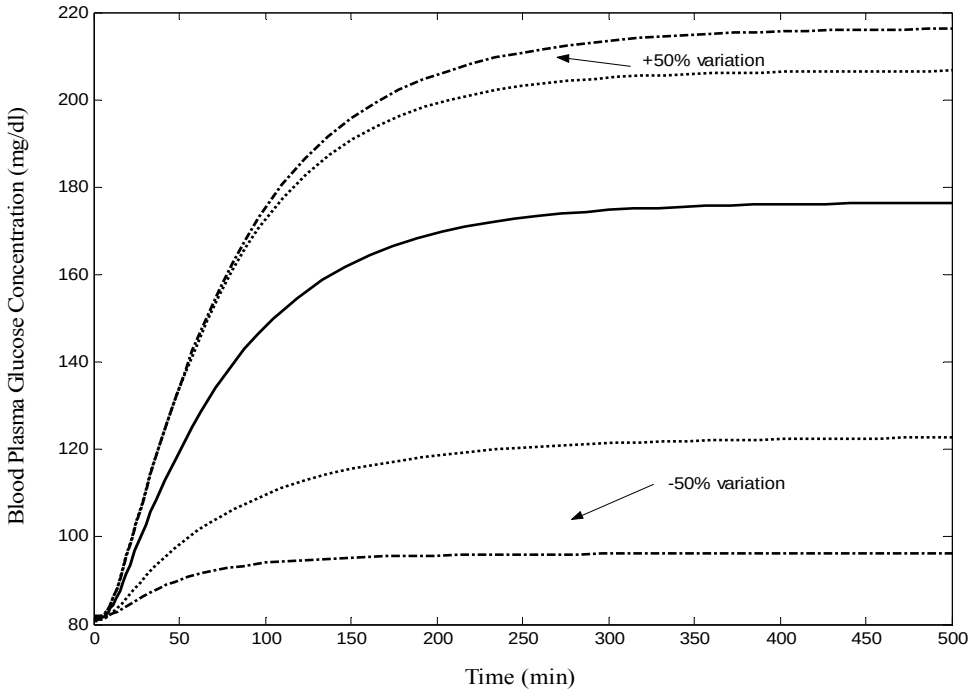

Fig. 2.6. Response of some patient models to the step change in insulin to 0 mU/min: solid - nominal patient model; dot - response bounds for ± 50% variations in EGHGP-E_Γ; dash-dot - response bounds for the simultaneous ± 50% variations in EGHGP-E_Γ and EIPGU-D_Γ.

2.5 Dynamics of Diabetic with Meal

The effect of 10g and 50g carbohydrate ingestion on the glucose absorption into the gut is shown in Fig. 2.4. Its subsequent effect on the measured variable, blood plasma glucose concentration in the nominal patient model is depicted in Fig. 2.7. The important regions based on glucose concentration range for a diabetic are hyperglycaemia (> 120 mg/dl), normoglycaemia (70-100 mg/dl) and hypoglycaemia (< 60 mg/dl). These and the long term complications associated with the sustained prevalence of glucose concentration in these different regions are shown in Fig. 2.7.

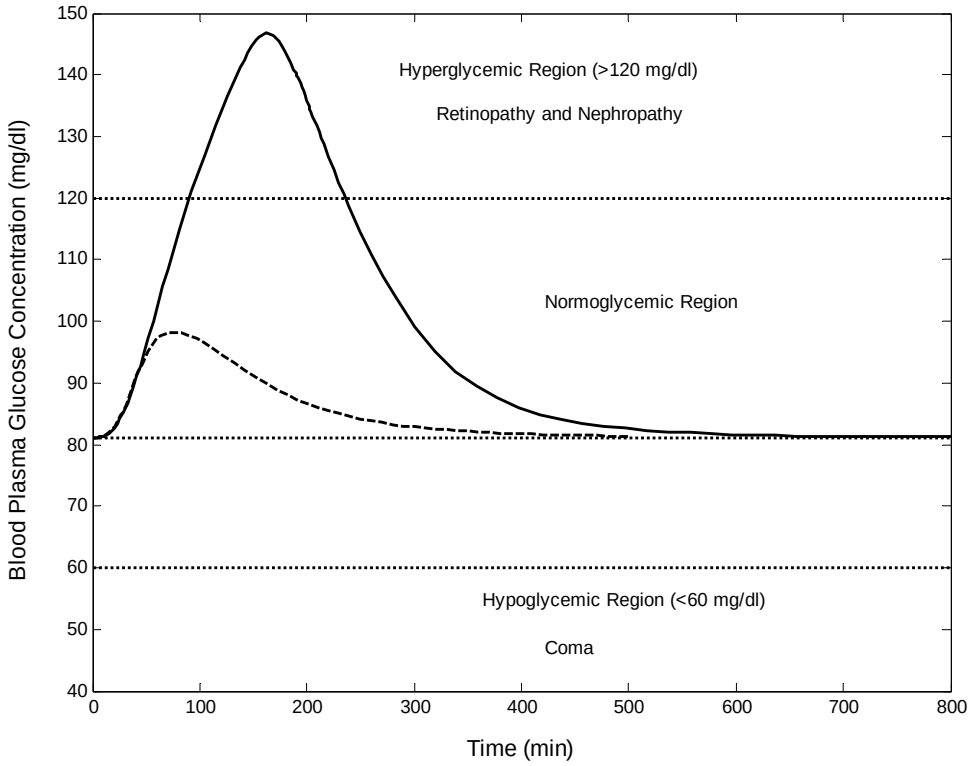

Fig. 2.7. Transient response of blood plasma glucose concentration due to 50 g (solid curve) and 10 g carbohydrate (dashed curve) meal ingestion.

2.6 Summary

Developing the plant/process models from either white-box (fundamental) or black-box models ignorant of process physics is challenging. Both of these have their own advantages and disadvantages. A diabetic model using physiological compartmental division of body with 19 nonlinear coupled differential equations is described. To incorporate the inter and intra-patient variability, deviations in patient models are limited to 8 parameters only. A test bed of 577 perturbed patients with ±40% variations in parameters from the nominal parameter values is generated for assessing the controller performance. As the glucose concentration rises upon intake of carbohydrate meal, a meal model is also presented. Simulink implementation of

diabetic and meal model is discussed. The effect of meal on glucose concentration in both gut compartment and measured blood plasma glucose concentration is studied and some transient responses are provided.

CHAPTER 3

Model Based Control Strategies for Glucose Regulation in Type I diabetics

3.1 Introduction

Diabetes mellitus is a global, public health problem and a leading cause of morbidity and mortality in many parts of the world. In Type I diabetic or insulin dependent diabetes mellitus (IDDM) patient the glucose concentration is elevated beyond the normoglycemic range (70-100 mg/dl) due to the insufficient insulin secretion from the β-cells of islets of Langerhans present in the pancreas. Sustained hyperglycemia (arterial glucose concentration > 120 mg/dl) leads to long-term complications such as nephropathy and retinopathy. The current treatment methods (e.g., injections at regular intervals) of insulin therapy are largely "open loop". Intuitively, it can be said that "closed loop" control approaches can result in good glycaemia control over extended periods of time, and also mimic the glucose control in healthy persons. Such closed loop control strategy consists of three major components – *in-vivo* sensor for blood glucose concentration, a control algorithm to set appropriate insulin dosage based on sensor measurement and a suitable insulin delivery device. The present work focuses on the control algorithm for blood glucose regulation.

For evaluating various controllers, an accurate model of a diabetic patient is essential. The primitive modeling studies of the diabetic condition (Bolie 1961, Ackerman et al., 1965) established a precedent for mathematical analysis of

insulin-glucose interactions. Later studies utilized the more complicated nonlinear models such as Bergman's "Minimal Model" (Bergman et al., 1981) and incorporated physiological system knowledge into the model (Cobelli and Mari, 1983, Sorensen, 1985). With the availability of these models, various model-based optimal control algorithms have been developed utilizing them in either an explicit or implicit fashion (Sorensen, 1985; Ollerton, 1989; Fischer, 1991; Parker et al., 1999). Sorensen (1995) also tested an IMC strategy on his model for a particular set of patient parameters. Parker et al. (1999) have done an extensive study on blood glucose control and compared the performance of several model predictive controllers (MPC) as well as a discrete IMC. Camelia and Doyle (2001) used IMC framework to maintain the blood glucose concentration in diabetics simulated by Bergman and Automatic Insulin Dosage Advisor (AIDA) models. In the synthesis and/or evaluation of these controllers, however, the inherent uncertainty in the model has not been properly addressed. Such control strategies could lead to significant performance degradation in the presence of inevitable patient-model mismatch.

Significant inter- and intra-patient variability has been documented in the literature (Simon et al., 1987; Steil et al., 1994; Puckett and Lightfoot, 1995; Bremer and Gough, 1999). The control algorithm employed for blood glucose control must be able to compensate for the uncertainty that exists between the model used in controller design and the actual patient. This clearly brings forth a need for a controller that can handle the patient-model mismatch. Keinitz and Yoneyama (1993) used the H_∞ framework to treat the model uncertainty on a slightly extended version of metabolic equations of glucose and insulin in Fischer and Teo (1989). Parker et al. (2000) too employed the H_∞ framework to explicitly treat the model

uncertainty but they employed a detailed and fairly complex physiological patient model (a 19-state nonlinear dynamic model) because it allows uncertainty characterization on particular tissues or effects that are responsible for the insulin or glucose variability. Parker et al. (2000) assessed the resulting H_∞ controller based on the disturbance rejection capability on 577 patients by considering the parametric uncertainty, and concluded that it has comparable performance to the computationally-intensive MPC.

Simple and effective controllers are very desirable for complex applications including blood glucose control. IMC and IMC-based tuning are gaining popularity in the control community. Further, enhanced IMC (EIMC) of Zhu et al. (1995) has better uncertainty and disturbance attenuation in addition to its simple structure. A similar structure was proposed for nonlinear processes and experimentally evaluated for pH control (Hu et al., 2000). However, neither IMC nor EIMC has been applied for blood glucose control of patients simulated by the detailed, physiological model of Parker et al. (2000). Motivated by these, the present study has the broad objective of designing and evaluating IMC and EIMC for blood glucose control of many diabetics with typical inter- and intra-patient variability and simulated by the detailed model of Parker et al. (2000). Both single meal and multiple meals in a day are considered as disturbances for glucose control of about 580 perturbed patient models. Typical responses and quantitative results are presented and discussed.

3.2 Diabetic Model and Uncertainty Description

A nonlinear pharmacokinetic/pharmacodynamic compartmental model of the diabetic patient has been constructed previously (Guyton et al., 1978; Sorensen, 1985;

Parker, 1999; Parker et al., 2000). The meal disturbance model of Lehmann and Deutsch (1992) was included in the model of Parker et al. (2000), who reported all the model equations and parameters in detail with 19 state equations, and 47 parameters. The specific operating conditions for the diabetic patient model used in testing the robust controller algorithms are described in Parker (1999). The diabetic patient model had two inputs - insulin delivery and meal disturbance, and one measured output, namely, blood glucose concentration. Insulin delivery rate, represented as deviation from its 22.3 mU/min nominal delivery, was the manipulated variable (represented as $\bar{u}$). The meal disturbance had a nominal value of 0 mg/min (absorption into blood stream), and its signal was denoted as $\overline{m}_d$. The measured variable, $\overline{Y}$ represented the deviation in blood glucose concentration from the nominal value of 81.1 mg/dl. All these three variables are scaled as mentioned in Parker et al. (2000).

$$m_d = \frac{1}{360}\overline{m}_d, u = \frac{1}{33.125}\bar{u}, Y = \frac{1}{20}\overline{Y} \tag{3.1}$$

Here, the disturbance scaling was determined by its maximum value, scaling for the manipulated variable, u is based on its expected range, and the output scaling by maximum allowable deviation in glucose concentration. Note that the measured value, Y is (blood) plasma glucose concentration, obtained by multiplying the arterial glucose concentration (3^{rd} state in the model of Parker et al., 2000) by a factor of 0.925.

Uncertainties exist due to the inevitable patient-model mismatch; the uncertainties between the actual patient and the nominal patient model could be translated to variations in the model parameters. The glucose and insulin dynamics were found to

be most sensitive to variations in the metabolic parameters (Parker et al. 1998). In the patient model, glucose metabolism is mathematically described by threshold functions with the following structure

$$\Gamma_e = E_{re}\{A_{re}\text{-}B_r\tanh[C_{re}(x_i+D_{re})] \quad (3.2)$$

The subscript i in equation (3.2) is the state vector element involved in the metabolic effect and the e subscript denotes specific effects within the model: the effect of glucose on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU) or the effect of insulin on peripheral glucose uptake (EIPGU). Inter- or intra-patient uncertainty could be classified physiologically as either receptor (D_{re} parameter) or post-receptor (E_{re} parameter) defect, and these two parameters are estimated to fit the actual patient data. Differences in insulin clearance (metabolism) between patients also exist, and could be modeled as deviations in the fraction of clearance (i.e., insulin utilized) by a given compartment such as the fraction of hepatic clearance (FHIC) or the fraction of peripheral insulin clearance (FPIC). This uncertainty formulation essentially focused on the liver (variability in five parameters) and the peripheral (muscle/fat) tissues (variability in three parameters) as these were considered to be more relevant to the control study (Parker et al., 2000).

In the absence of physical data from which to identify ranges for parametric variations, Parker et al. (2000) assumed ±40% variability in each parameter to represent a broad range of potential patients. The exception was FHIC, which was limited to ±20% to guarantee non-negative glucose concentrations. From these eight parameters, sets of three parameters were chosen. Each of these three parameters was tested at three levels (nominal, low and high) yielding a total of ${}^8C_3 \times 3^3 = 1512$ "patients". Patients with identical values for all the eight parameters were removed and this resulted in a

set of 577 unique patients. These 577 unique patients are considered as perturbed cases in further discussion. These patients are assumed to capture all the inter- and intra-patient variability among Type I diabetics. Each of these patients was subjected to a 50 g meal disturbance at time t = 0 under closed-loop to test the robustness and disturbance attenuating capabilities of the controller designed.

For the present study, diabetic patient models are developed in Simulink and are available from the authors. Bounds on open-loop responses of some patient models to a step change in insulin (from the value required to maintain the output at 81.1 mg/dl) to 0 mU/min, are shown in Fig 3.1. These responses are very similar to those reported

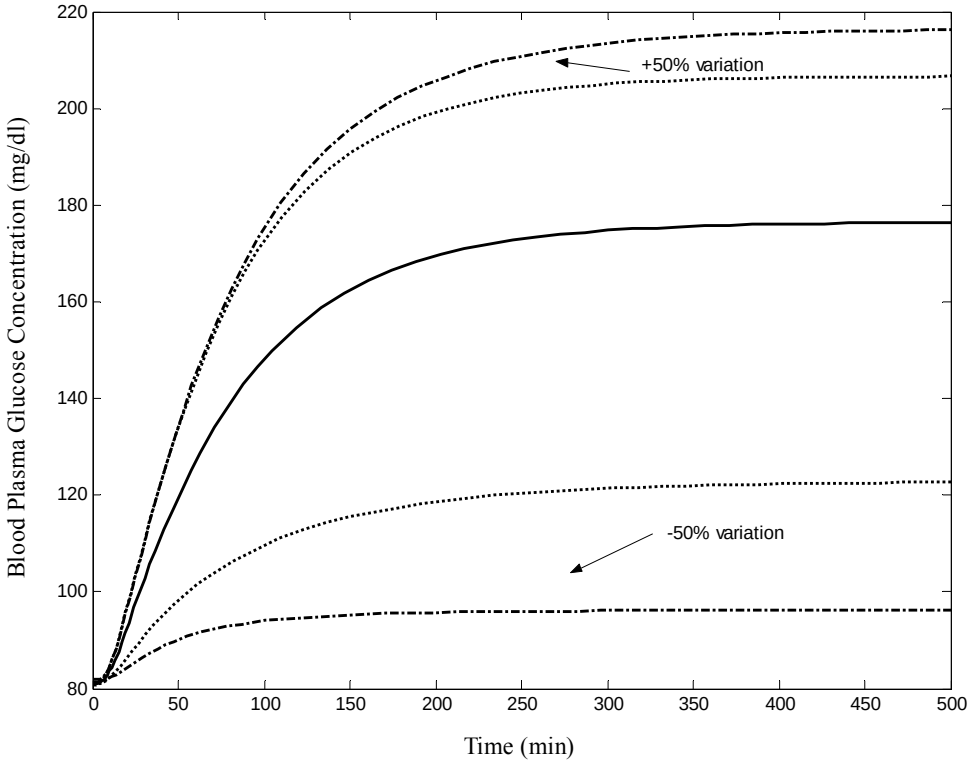

Fig. 3.1. Response of some patient models to the step change in insulin to 0 mU/min: solid - nominal patient model; dot - response bounds for ± 50% variations in EGHGP-E_Γ; dash-dot - response bounds for the simultaneous ± 50% variations in EGHGP-E_Γ and EIPGU-D_Γ

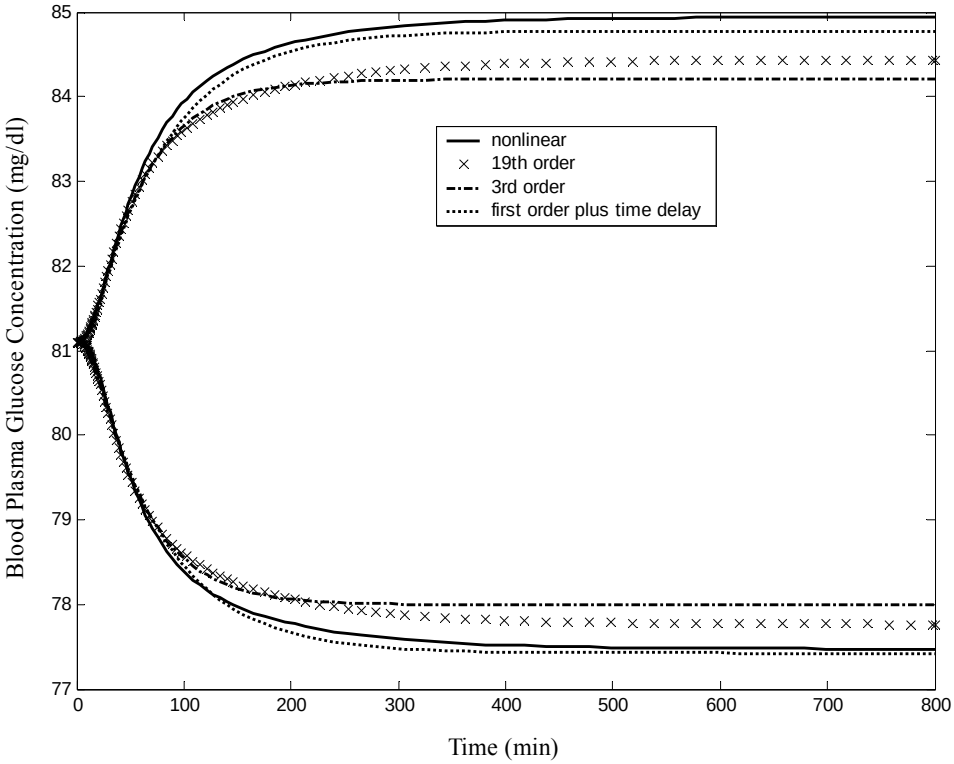

Fig. 3.2. Response of nonlinear (solid), 19th order linear (cross), 3rd order linear (dash-dot), first order plus time delay (dot) models to ±5% step changes in insulin from the nominal 22.3 mU/min.

in Parker (1999), confirming the validity of patient models employed in this study. They also show the broad range of patient dynamics. Note that the glucose profiles shown in Fig. 3.1 are for ±50% variation in parameters whereas only ±40% variation in parameters is considered to test controller robustness.

The synthesis of IMC and EIMC controllers requires a linear model of the system to be controlled. A 19th order linear model was obtained by linearizing the nonlinear model of the nominal diabetic around the nominal plasma glucose concentration of 81.1 mg/dl. Subsequently, the 19th order linear model was reduced to a 3rd order

model using the balanced realization technique. The patient model was also subjected to ±5% step change in the manipulated variable (i.e. insulin) and the resulting step response was used to identify a first order plus time delay (FOPTD) model using the method of Sundaresan and Krishnaswamy (1977). From the step responses of the above-mentioned models (Fig 3.2), it appears that a better fit of the patient dynamics is obtained with the FOPTD model. Hence, this is used for designing IMC and EIMC controllers.

3.3 Synthesis of IMC and EIMC

The conventional IMC structure is shown in Fig 3.3, where G_p is the plant/patient to be controlled, G_m is a model of the plant/patient, C is the IMC controller, R is the reference input to the control system, Y is the system output and D is the equivalent external disturbance. The IMC controller design involves two steps (Marlin, 1995).

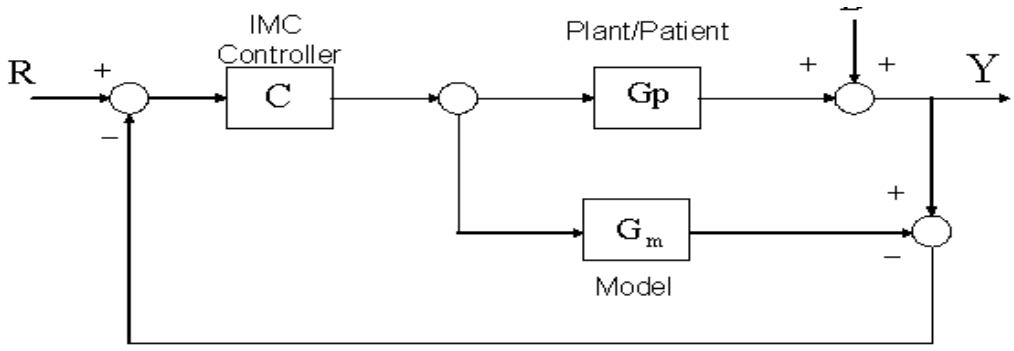

Fig. 3.3. Conventional IMC system

Step1: The model, $G_m(s)$ is factorized as

$$G_m(s) = G_m^+(s)\, G_m^-(s) \tag{3.3}$$

where $G_m^+(s)$ contains any time delays and right-half plane zeros. It is specified so that its steady-state gain is 1. And, $G_m^-(s)$ contains the remaining invertible dynamics of $G_m(s)$.

Step 2: The IMC controller is specified as

$$C(s) = \frac{1}{G_m^-(s)} f(s) \tag{3.4}$$

where f (s) is a low-pass filter with a steady-state gain of 1. This filter typically has the form

$$f(s) = \frac{1}{(\lambda s + 1)^r} \tag{3.5}$$

where λ is the tuning parameter to be selected by the control engineer so as to meet the robustness and performance requirements of the control system. The parameter 'r' is a positive integer that is selected so that either C(s) is a proper transfer function or the order of its numerator exceeds the order of the denominator by 1, if ideal derivative action is allowed.

From Fig 3.3, the closed loop servo transfer function G^R and the closed loop disturbance transfer function G^D of the conventional IMC system can be derived as follows.

$$G^R = [I + (C^{-1} - G_m) G_P^{-1}]^{-1} \tag{3.6}$$

$$G^D = [I + G_P (C^{-1} - G_m)^{-1}]^{-1} \tag{3.7}$$

The EIMC structure (Zhu et al., 1995), shown in Fig 3.4, has an additional path appended to the IMC system within the plant-model parallel structure. Here, in addition to the IMC controller, C_1 (same as C in Fig. 3.3), C_2 is the 'complementary' IMC compensator and K is pure gain. By inserting this additional path into the

original IMC system, a complementary control signal generated from the plant-model error is injected into the output of the original IMC controller. This leads to the EIMC

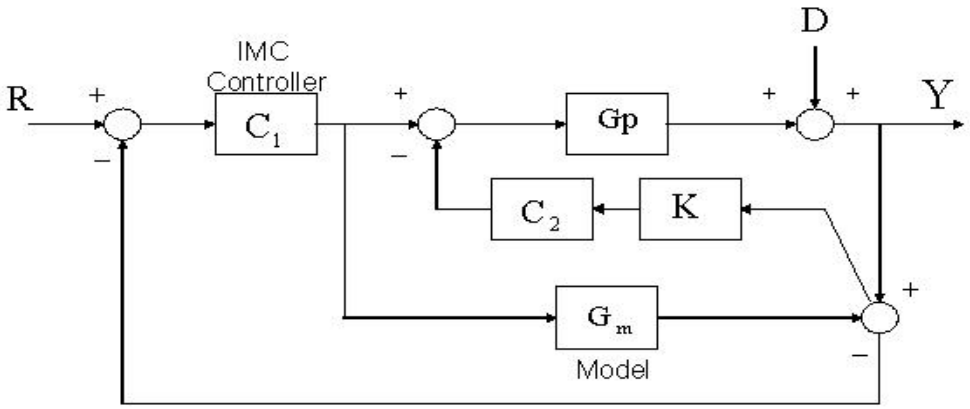

Fig. 3.4. Enhanced IMC structure

structure whose performance was shown to be superior to IMC in the presence of modeling errors (Zhu et al., 1995).

From Fig 3.4, the closed loop servo transfer function (G_1^R) and the closed loop disturbance transfer function (G_1^D) of the EIMC structure can be derived as follows.

$$G_1^R = [I + (C_1^{-1} - G_m)\,M]^{-1} \tag{3.8}$$

$$G_1^D = (I - G_m C_1)\,[I + (G_p - G_m)C_1 + G_p C_2 K]^{-1} \tag{3.9}$$

here $C_1(s) = \dfrac{1}{G_m^-(s)}\, f_1(s);\ C_2(s) = \dfrac{1}{G_m^-(s)}\, f_2(s);\quad f_1(s) = \dfrac{1}{(\lambda_1 s + 1)^{r_1}},\ f_2(s) = \dfrac{1}{(\lambda_2 s + 1)^{r_2}}$

and $M = [G_p (I + C_2 K G_p)^{-1} (I + C_2 K G_m)]^{-1}$. The disturbance attenuating capability of the EIMC is improved with large K and a smaller λ_2 as the denominator in the equation (3.9) becomes high. The values of r_1 and r_2 are identical and equal to 1, and for simplicity both λ_1 and λ_2 are taken as equal to λ in the present study.

3.4 Results and Discussion

Based on the FOPTD approximation of the nominal diabetic model, IMC controller was first developed for the regulation of glucose level in diabetics. The performance of the IMC with various values of filter constant λ was first tested by subjecting the nominal patient to 50 g meal disturbance. Robustness of the IMC was then tested on all 577 patients and the results are summarized in Table 3.1. The number of patients, whose blood glucose concentration was maintained by the IMC within normoglycemic range (70-100 mg/dl), is given in the second column. Glucose concentration below 60 mg/dl is the dangerous hypoglycemic region. Hence, the number of patients whose glucose concentration was maintained by the IMC within 60-100 mg/dl is also presented in Table 3.1. In addition to these, average IAE and standard deviation of IAE based on all 577 patients are also reported in this table. Results in Table 3.1 show that decreasing λ has increased number of patients whose glucose concentration is maintained between 70-100 mg/dl and 60-100 mg/dl while rejecting 50 g meal disturbance, and also the average IAE and standard deviation of IAE decreased. These and transient responses (not shown here) indicate that decreasing λ has improved the performance of IMC. Even with $\lambda = 2$, IMC is not able to maintain the glucose concentration within normoglycemic range in 46% of the patients. Decreasing λ further to 0.5 and 0.2 (not tabulated here) has resulted in sustained oscillations or unstable responses in some perturbed cases. Note that $\lambda = 2$ did not produce sustained oscillations or unstable responses in any of 577 cases. This led us to investigate if the EIMC strategy can deliver better disturbance rejection even in the presence of model uncertainty as compared to the conventional IMC.

Table 3.1: Performance of IMC with various values of filter constant, for all 577 patients subjected to 50 g meal disturbance at time t = 0.

λ	No. of Patients with Glucose Concentration (mg/dl)		Average IAE for all 577 Patients	Standard Deviation of IAE
	70-100	60-100		
25	113	198	318.9	185.9
15	163	294	262.5	170.4
5	251	412	193.5	145.5
2	310	451	169.4	134.7

Note: In this and subsequent tables, IAE values are for simulation time of 800 min for each patient, and the IAE is calculated based on the scaled variable in equation (3.1).

Table 3.1 shows that the number of patients whose glucose concentration is maintained in 60-100 mg/dl range, average IAE and standard deviation of IAE do not improve significantly when λ is changed from 5 to 2. So, a filter constant of either 2 or 5 can be used in the EIMC structure. First, $\lambda (= \lambda_1 = \lambda_2) = 2$ is employed in the EIMC structure and the robustness of EIMC with various K values in EIMC structure in rejecting the 50 g meal disturbance in 577 patients is studied. For some patients, the injected insulin is negative which is unrealistic and so a saturation block is placed for the insulin with a minimum value of 0 mU/min. The EIMC with $\lambda = 2$ and a small K of 0.5 has decreased the average IAE (125.8) and standard deviation of IAE (111.25) than that of IMC with filter constant of 2, but EIMC resulted in sustained oscillations or unstable responses in nearly 2% of perturbed patient cases of the study. A higher

Table 3.2. Effect of K on rejecting the 50 g meal disturbance by the EIMC (with λ_1 = λ_2 = 5) for all 577 patients with lower limit of 0 mU/min on insulin.

K	No. of Patients with Glucose Concentration (mg/dl)		Average IAE for all 577 Patients	Standard Deviation of IAE
	70-100	60-100		
0	251	412	193.5	145.5
1	423	499	116.8	105.8
2	478	513	84.5	82.8
3	481	537	66.3	67.8
4	488	551	54.6	57.3
5	490	567	46.8	49.3

value of K along with λ = 2 has further increased the number of patients with sustained oscillations and unstable responses. Hence, λ = 5 is selected for studying the robustness of EIMC with various K values and the results are tabulated in Table 3.2.

From Table 3.2, increasing the K value has resulted in significant improvement in the glucose control with increase in the number of patients whose glucose concentration is maintained within 70-100 mg/dl and 60-100 mg/dl ranges, and decrease in average IAE and standard deviation of IAE. The improvement in the number of patients controlled within the allowable ranges by increasing the K value from 3 is not significant and also the higher value of K resulted in sustained oscillations or unstable responses for some perturbed cases. One of such responses for a perturbed case with parameters EGHGP-E_Γ = 1.4; EIPGU-D_Γ = -3.4927; EGHGU-D_Γ = -0.88; and rest of

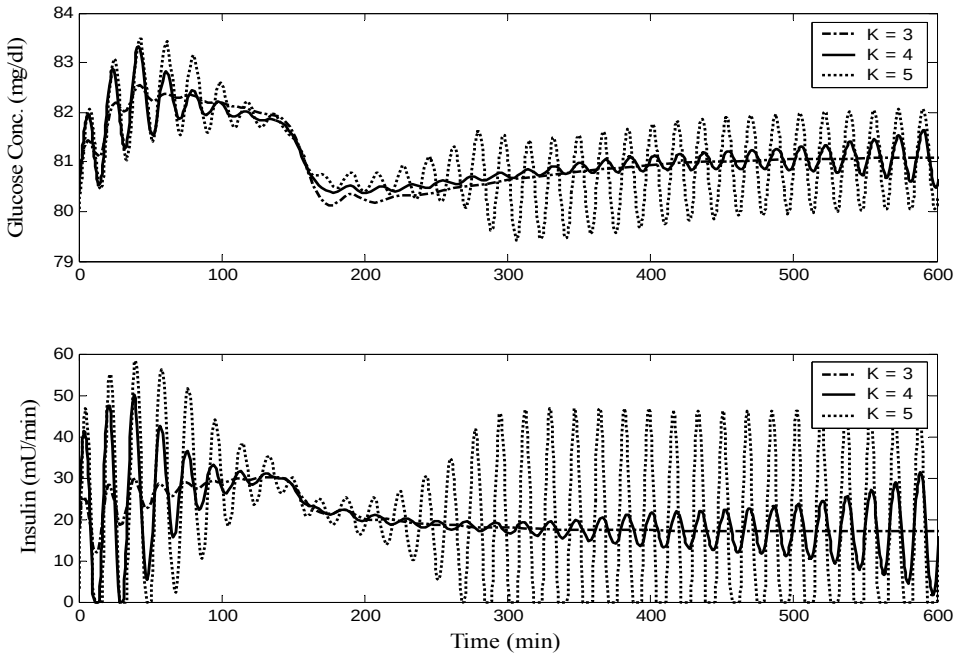

Fig. 3.5. The effect of increasing K in EIMC for a perturbed case with EGHGP-E_Γ =1.4, EIPGU-D_Γ = -3.4927 and EGHGU-D_Γ = -0.88 with remaining parameters at their nominal values.

the parameters at their nominal values, is shown in Fig. 3.5. For K = 4, blood glucose and insulin have steadily growing oscillations while K = 5 has resulted in sustained oscillations due to the lower limit of 0 mU/min on insulin. The response of EIMC with K = 3 is acceptable. Hence, from Fig. 3.5 and Table 3.3, K = 3 seems to be 'optimal' and the parameter values: $\lambda_1 = 5$, $\lambda_2 = 5$ and K = 3 are employed in the EIMC in the subsequent discussion. For these parameter values, only 40 patients (7%) have entered the dangerous hypoglycemic region (i.e. glucose concentration < 60 mg/dl). This is better than 72 patients mentioned by Parker et al. (2000) when H_∞ controller was employed. It is interesting to note that one parameter, namely, FPIC is at 0.21 (a +40% variation from nominal) in the 40 perturbed patients which could not be controlled safely by the EIMC.

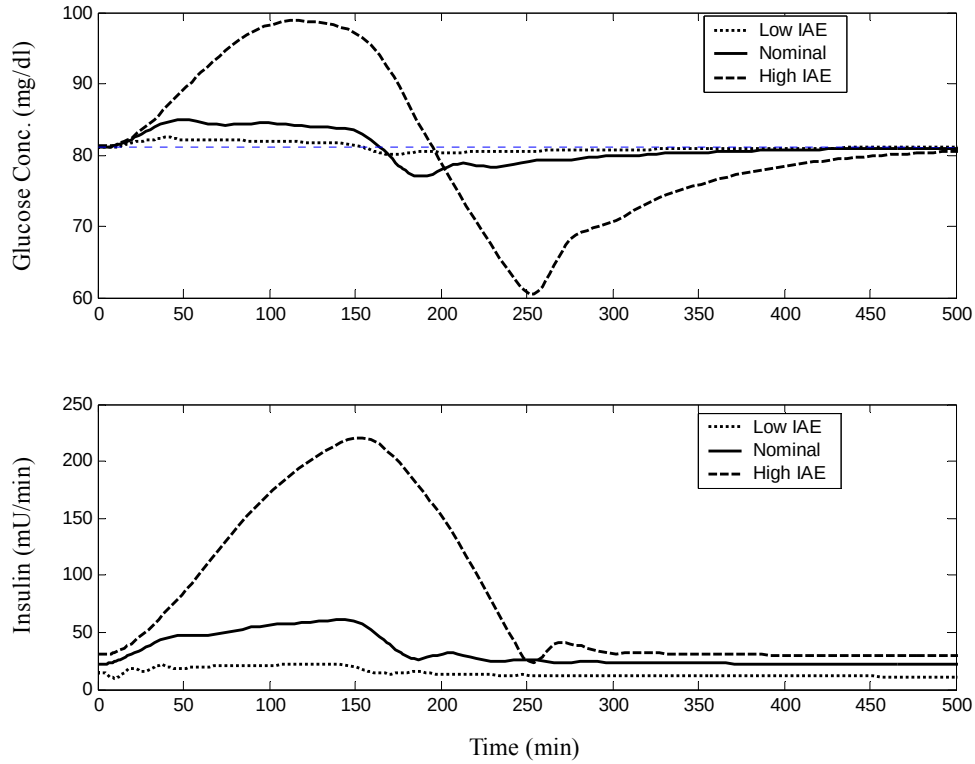

Fig. 3.6. Transient responses of the EIMC for two perturbed patients (giving the lowest and highest IAE) and the nominal case, in attenuating 50 g meal disturbance at time t = 0 min.

Performance of the EIMC on two perturbed patients and nominal patient is depicted in Fig 3.6. The two perturbed patients considered are those having the lowest and highest IAE value among the 537 patients whose glucose concentration was controlled within 60-100 mg/dl. The parameters of the patient with the lowest IAE are EGHGU-D_Γ = -0.88; FHIC = 0.32; FPIC = 0.09, while those of the patient with the highest IAE are EGHGP-D_Γ = -0.29814; FHIC = 0.48; FPIC = 0.21. The rest of the parameters are at their nominal values for both cases. Transient profiles of blood glucose and insulin in Fig. 3.6 are very good with very few oscillations.

Next, the EIMC controller is tested on two patient cases whose disturbance rejection responses by H_∞ controller are given in Parker et al. (2000). Parameters for the first patient case are different from the 577 patients considered above. The parameters of this case are EIPGU-D_Γ = -8.15; EGHGU-D_Γ = -2.072; FHIC = 0.36; rest of the parameters are at their nominal values. This case is specified as the worst-case performance of the continuous-time H_∞ controller, including uncertainty weighting and parametric uncertainty (Parker et al., 2000). Disturbance rejection by the H_∞ controller for this case shown in Figure 9 of Parker et al. (2000) is reproduced along with the response by the EIMC in Fig 3.7. Parameters for the second patient case are

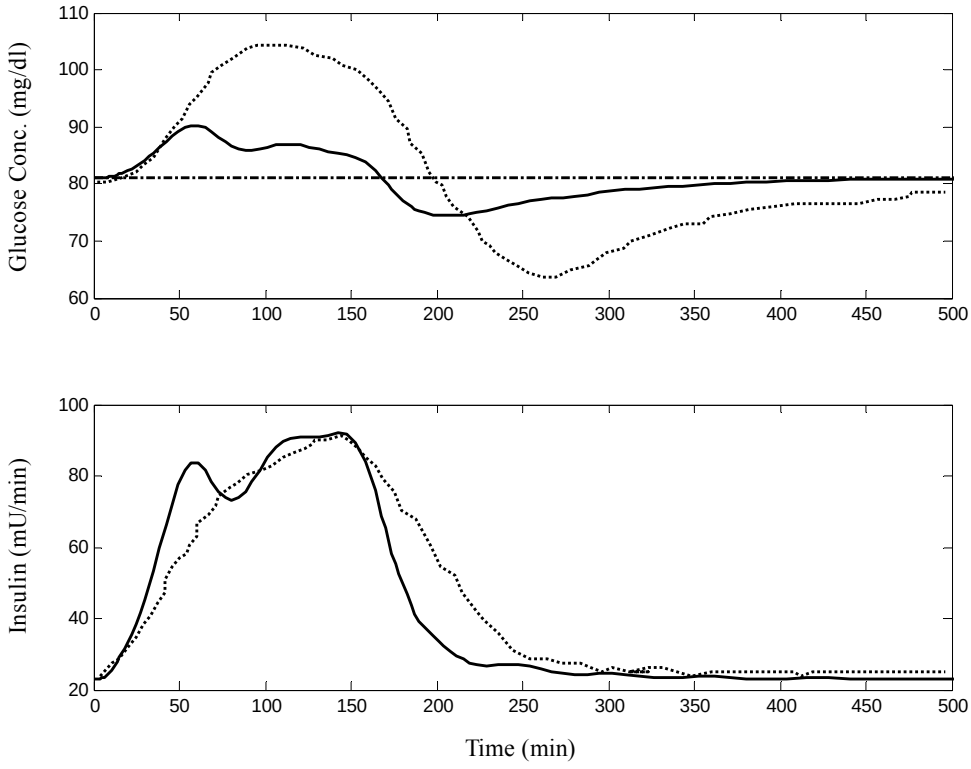

Fig. 3.7. Performance of EIMC (solid) and H_∞ controller (dashed) of Parker et al. (2000) including uncertainty weighting and parametric uncertainty, on a perturbed patient model with EIPGU-D_Γ = -8.15, EGHGU-D_Γ = -2.072, FHIC = 0.36 and the remaining five parameters are at their nominal values.

EIPGU-E_Γ = 0.6; EGHGU-E_Γ = 0.6; EGHGP-E_Γ = 1.4; remaining parameters are retained at their nominal values. The responses by the EIMC and H_∞ controller of Parker et al. (2000) for this patient model are depicted in Fig 3.8. These and those in Fig. 3.7 show that the performance of EIMC compares very favorably and performs even better than the results provided by the H_∞ strategy of Parker et al. (2000).

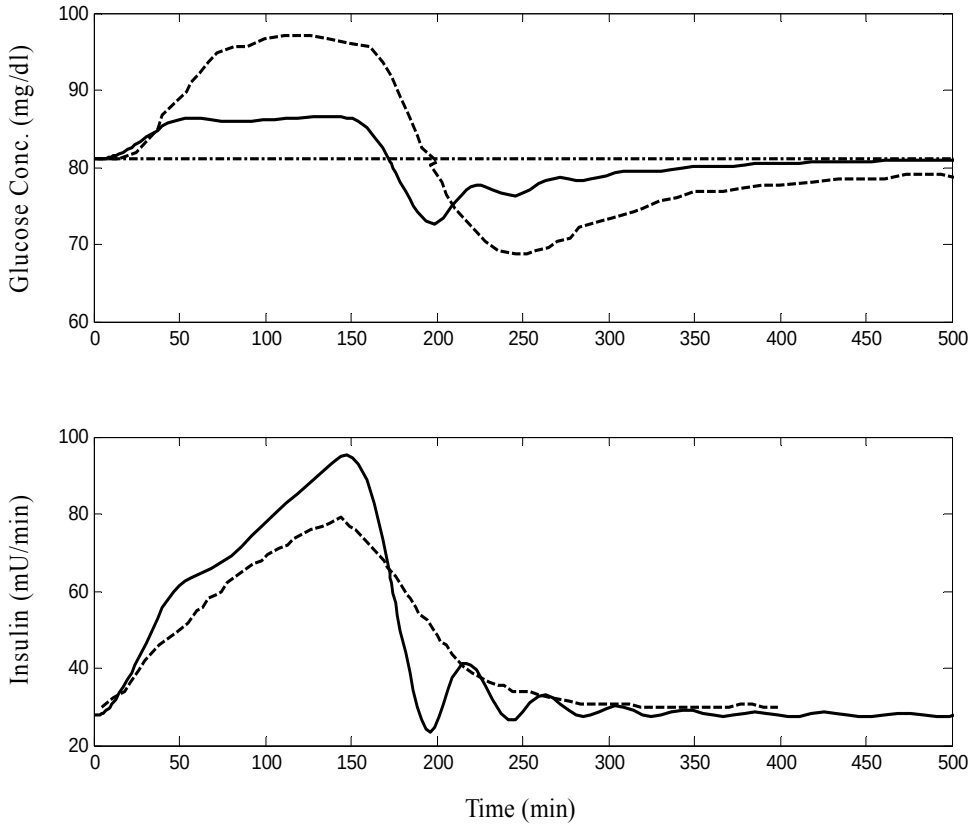

Fig. 3.8. Performance of EIMC (solid) and H_∞ controller (dashed) of Parker et al. (2000) including uncertainty weighting and parametric uncertainty, on a perturbed patient model with EIPGU-E_Γ = 0.6, EGHGU-E_Γ = 0.6, EGHGP-E_Γ = 1.4 and the remaining five parameters are at their nominal values.

The performance of EIMC with parameters $\lambda_1 = \lambda_2 = 5$ and K = 3, in rejecting the typical meal pattern for a day from 7.30 a.m. for 24 hours for all 577 patients, is then studied. The typical meal pattern is assumed to have 50 g, 30 g, 50 g and 10 g of

carbohydrates respectively in the breakfast, lunch, dinner and supper at the following times: breakfast at 7:30 a.m, lunch at 12:30 p.m., dinner at 6:00 p.m. and supper at 9:00 p.m. The EIMC controller is able to maintain the glucose concentration within 60-100 mg/dl range for all the four meal disturbances in 93 % of the 577 patients tested, which are the same as those of the single meal case (Table 3.2). The average IAE and the standard deviation of IAE for this situation of four meals are increased by a factor compared to that of the single meal case. The responses of the patients to four meals for the highest IAE patient case, nominal patient case and the lowest IAE case within the 537 patient cases are shown in Fig. 3.9. These results confirm the effectiveness of the EIMC for blood glucose control of diabetics.

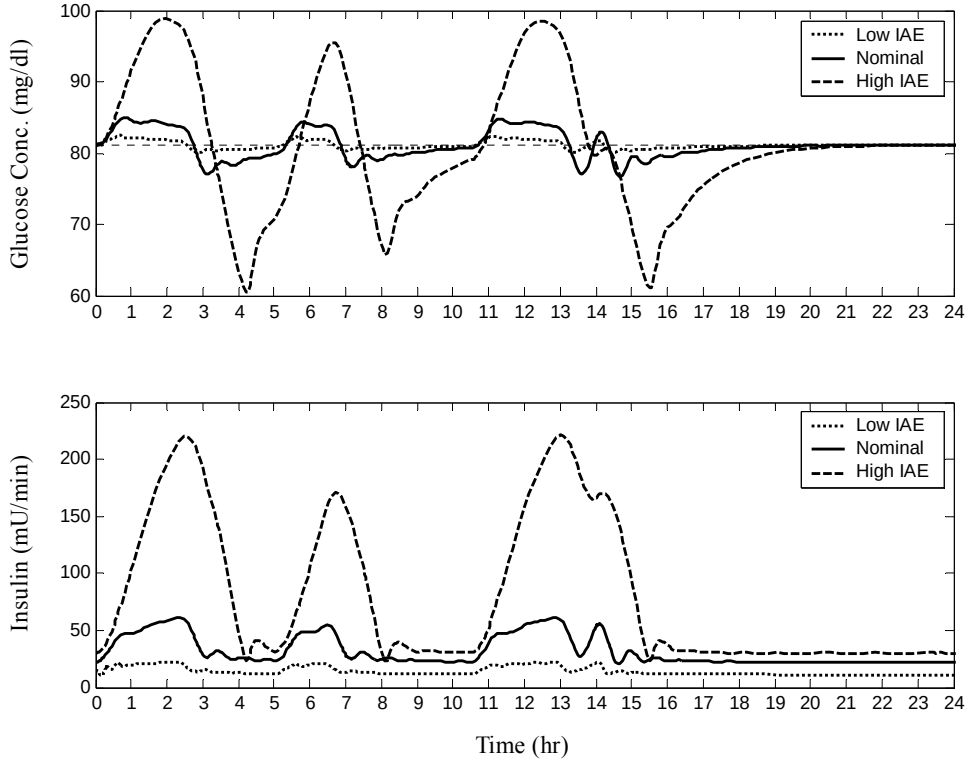

Fig. 3.9. Transient responses of the EIMC for two perturbed patients (giving the lowest and highest IAE) and the nominal case, in attenuating four meals in a typical day.

3.5 Conclusions

The IMC and EIMC are designed using a simple FOPTD model of the nominal patient and their robustness is evaluated for regulation of blood glucose concentration in 577 diabetics obtained by considering ±40% parametric variations from the nominal patient parameter values. The EIMC is able to maintain the glucose concentration above the dangerous hypoglycemic range (< 60 mg/dl) in 93% of 577 patient models tested. For these patients, average IAE and standard deviation of IAE are reduced by a factor of 2 to 3 by the EIMC scheme compared to the conventional IMC. Further, the performance of the former is found to be better than that of a H_∞ controller proposed by Parker et al. (2000). The EIMC is tested on all 577 patients taking four meals per day and the controller is able to maintain the glucose concentration above the dangerous hypoglycemic range in 93% of the cases (same number of cases as for the single meal). Thus, the EIMC strategy is very attractive for blood glucose control owing to its simple structure and design as well as good robustness.

CHAPTER 4

Regulation of Glucose in Diabetics using PID controller

4.1 Introduction

Type I diabetes or insulin dependant diabetes mellitus (IDDM) is an endocrine carbohydrate metabolic disorder in which blood sugar is increased from the normal 70-100 mg/dl due to the insufficient secretion of insulin by the β-cells of islets of langerhans present in the pancreas. Significant mortality, diabetes-related morbidities such as diabetic retinopathy, neuropathy and cardiovascular disease have also placed a heavy financial burden on society. The economic cost of diabetes in total U.S. health expenditure of US$865 billions was estimated at US$132 billions (in year 2002) by the American Diabetes Association, with US$92 billions spent on direct medical and treatment costs and US$40 billions incurred as indirect costs such as lost work time, disability and premature mortality (American Diabetes Association, 2003). As current clinical treatment methods are “open loop” in nature, it is thought that “closed loop” control approaches can result in good glycaemia control over extended periods of time, and also mimic the glucose control in healthy persons.

This “closed loop” control requires a closed loop device comprising three components, a mechanical pump, in-vivo glucose sensor and a control algorithm to specify the insulin dosage based on sensor measurement. Significant improvements in glucose sensing and insulin pumps have led to the practical feasibility of closed loop regulatory systems (often referred to as "artificial" β-cells) for blood glucose regulation in diabetics. The developments in glucose sensor technology have resulted

in fast (i.e. within 4 min) and reliable glucose concentration measurements (Renard, 2002). This sensor has been approved by the Food and Drug Administration (FDA), USA. The implantable insulin pumps able to deliver insulin accurately and safely are developed and are also approved by the FDA. To complement these improvements in the sensing and insulin delivery devices, the development of an effective control algorithm is vital. Due to the cost and complexity involved in clinically testing control algorithms, studies are done using a suitable model of diabetic patients.

A good review of diabetic modeling studies can be found in Parker (1999). In the present study, the detailed physiological model of the human glucose-insulin system described in Parker et al. (2000) is used. This model is based on models developed earlier by Guyton et al. (1978) and Sorensen (1985). Parker et al. (2001) reviewed the open loop, semi-closed loop and closed loop control efforts concerning the blood glucose regulation in diabetics. Proportional Derivative (PD) and Proportional Integral (PI) type controllers (belonging to the Proportional-Integral-Derivative (PID) controller family) are employed for blood glucose control by Fischer et al. (1990) and Chee et al. (2003) respectively. Even though a significant number of model-based control strategies have been proposed and assessed, the fundamental PID controller is not developed for the detailed physiological model of Parker et al. (2000) and studied for its robustness to parametric uncertainties.

Despite the significant improvements made in control theory and in the control of complex processes, the PID controller continues to be the workhorse for regulatory control in the chemical and process industries. Its simple structure, accumulated

experience in its design and its effectiveness on a wide range of industrial processes make it extremely attractive for biomedical applications as well. Therefore, in the present study, the PID controller is designed for the model described in Parker et al. (2000), using both the classical and the recent tuning methods. The PID controller is tuned with IAE minimization (for disturbance rejection) as the objective, Cohen-Coon tuning and two recently developed tuning methods, namely, Shen (2002) method and DMC-based method of Haeri (2002). The resulting PID controllers are assessed for their ability to track normoglycemic set point in a diabetic while subjected to a 50 g meal disturbance. Their robustness is tested on a population of 577 patient models which are obtained by considering ±40% uncertainty in the model parameters. Both single meal and multiple meals (in a day) scenarios are considered as disturbances for blood glucose control. Quantitative results and typical responses are presented and discussed.

4.2 Diabetic Model and Uncertainty Description

The following diabetic model and uncertainty description is also available in section 3.2. To provide better readability to each chapter independently we included this section. A nonlinear pharmacokinetic/pharmacodynamic compartmental model of the diabetic patient has been constructed previously (Guyton et al., 1978; Sorensen, 1985; Parker, 1999). The meal disturbance model of Lehmann and Deutsch (1992) was included in the model of Parker et al. (2000) who reported all the model equations and parameters in detail. This model has 19 state equations (nonlinear, coupled ordinary differential equations) and uses 47 physiological parameters. The diabetic patient model has been constructed to represent the sedentary 70 kg male patient (Parker, 1999), and has two inputs - insulin delivery and meal disturbance, and

one measured output - blood glucose concentration. Insulin delivery rate, represented as a deviation from its 22.3 mU/min nominal delivery is the manipulated variable (represented as $\bar{u}$). The meal disturbance has a nominal value of 0 mg/min (absorption into blood stream), and its signal is denoted as $\overline{m}_d$. The measured variable, $\overline{Y}$ represents the deviation in blood glucose concentration from the nominal value of 81.1 mg/dl. All these three variables are scaled as mentioned in Parker et al. (2000).

$$m_d = \frac{1}{360}\overline{m}_d, u = \frac{1}{33.125}\bar{u}, Y = \frac{1}{20}\overline{Y} \tag{4.1}$$

Here, the disturbance scaling is determined by its maximum value, scaling for the manipulated variable, u is based on its expected range, and the output scaling by the maximum allowable deviation in glucose concentration. Note that the measured value, Y is the scaled plasma glucose deviation variable, obtained by multiplying the arterial glucose concentration (third state in the model of Parker et al., 2000) by a factor of 0.925.

Uncertainties exist due to the inevitable patient-model mismatch; the uncertainties between the actual patient and the nominal patient model could be translated to variations in the model parameters. The glucose and insulin dynamics were found to be the most sensitive to variations in the metabolic parameters of liver and periphery. In the patient model, glucose metabolism is mathematically described by threshold functions with the following structure:

$$\Gamma_e = E_{re}\{A_{re}\text{-}B_r\tanh[C_{re}(x_i+D_{re})]\} \tag{4.2}$$

The subscript i in equation (4.2) is the state vector element involved in the metabolic effect and subscript e denotes specific effects within the model: the effect of glucose

on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU) or the effect of insulin on peripheral glucose uptake (EIPGU). Inter- or intra-patient uncertainty could be classified physiologically as either receptor (D_{re} parameter) or post-receptor (E_{re} parameter) defect, and these two parameters are estimated to fit the actual patient data. Differences in insulin clearance (metabolism) between patients also exist and could be modeled as deviations in the fraction of clearance (i.e., insulin utilized) by a given compartment such as the fraction of hepatic clearance (FHIC) or the fraction of peripheral insulin clearance (FPIC). This uncertainty formulation essentially focuses on the liver (variability in five parameters) and the peripheral (muscle/fat) tissues (variability in three parameters) as these are considered to be more relevant to the control study (Parker et al., 2000).

In the absence of physical data from which to identify ranges for parametric variations, Parker et al. (2000) assumed ±40% variability in each parameter to represent a broad range of potential patients. The exception was FHIC, which was limited to ±20% to guarantee non-negative glucose concentrations. From these eight parameters, sets of three parameters were chosen. Each of these three parameters was tested at three levels (nominal, low and high) yielding a total of ${}^{8}C_{3} \times 3^{3} = 1512$ "patients". Patients with identical values for all the eight parameters were removed and this resulted in a set of 577 unique patients, which are considered as perturbed cases in further discussion. These patients are assumed to capture all the inter- and intra-patient variability among Type I diabetics. Each of these patients will be subjected to a 50 g meal disturbance at time t = 0 under closed-loop to test the robustness and disturbance attenuating capabilities of the designed controller.

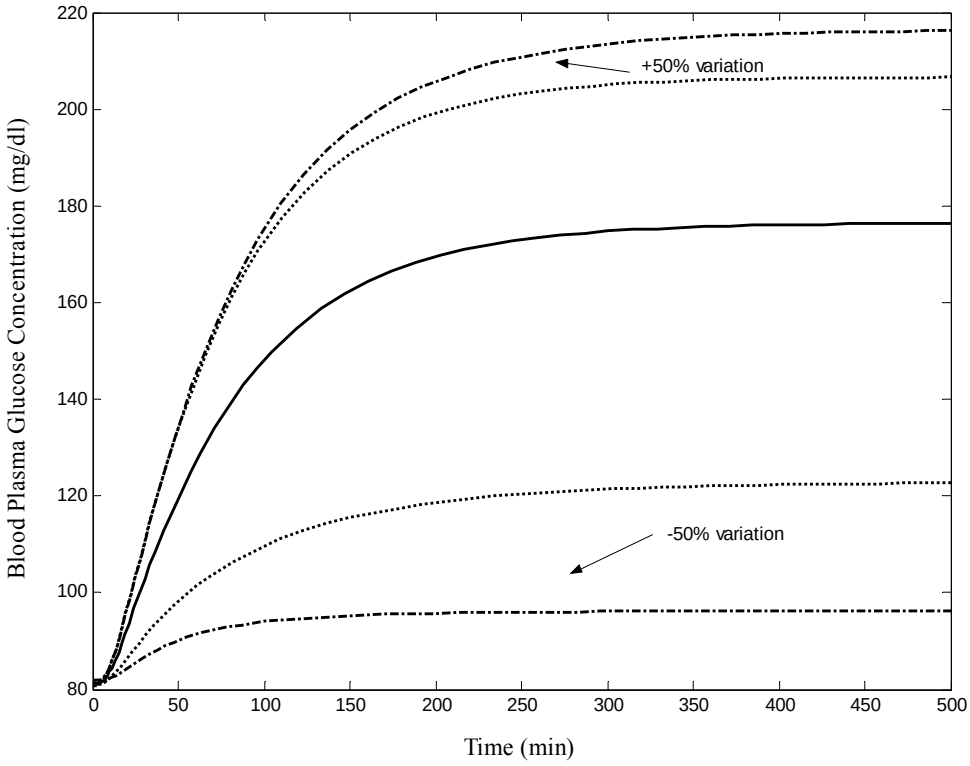

Fig. 4.1. Response of some patient models to the step change in insulin to 0 mU/min: solid - nominal patient model; dot - response bounds for ± 50% variations in EGHGP-E_Γ; dash-dot - response bounds for the simultaneous ± 50% variations in EGHGP-E_Γ and EIPGU-D_Γ.

For the present study, diabetic patient model is developed in Simulink and is available from the authors. Bounds on open-loop responses of some patient models to a step change in insulin (from the value required to maintain the output at 81.1 mg/dl) to 0 mU/min, are shown in Fig. 4.1. These responses are very similar to those reported in Parker (1999) confirming the validity of patient models employed in this study. They also show the broad range of patient dynamics and their nonlinearity. Note that the glucose profiles shown in Fig. 4.1 are for ±50% variation in parameters for comparison with the profiles in Parker (1999), whereas only ±40% variation in parameters is considered to test controller robustness as in Parker et al. (2000).

Available tuning methods for PID controller are often based on a first order plus dead time (FOPDT) model of the system to be controlled. The nominal patient model was subjected to ±5% step change in the manipulated variable (i.e. insulin) and the resulting step response for positive step change was used to identify a FOPDT model using the method of Sundaresan and Krishnaswamy (1977). The step responses of the nominal patient model and FOPDT model are depicted in Fig. 4.2. This FOPDT model (with gain = -3.29 (mg/dl)/(mU/min) or -5.46 in units consistent for u and Y in equation (1), time constant = 68.3 min and dead time = 12.8 min), is then employed to find the PID controller parameters: K_P, K_I and K_D using different tuning methods.

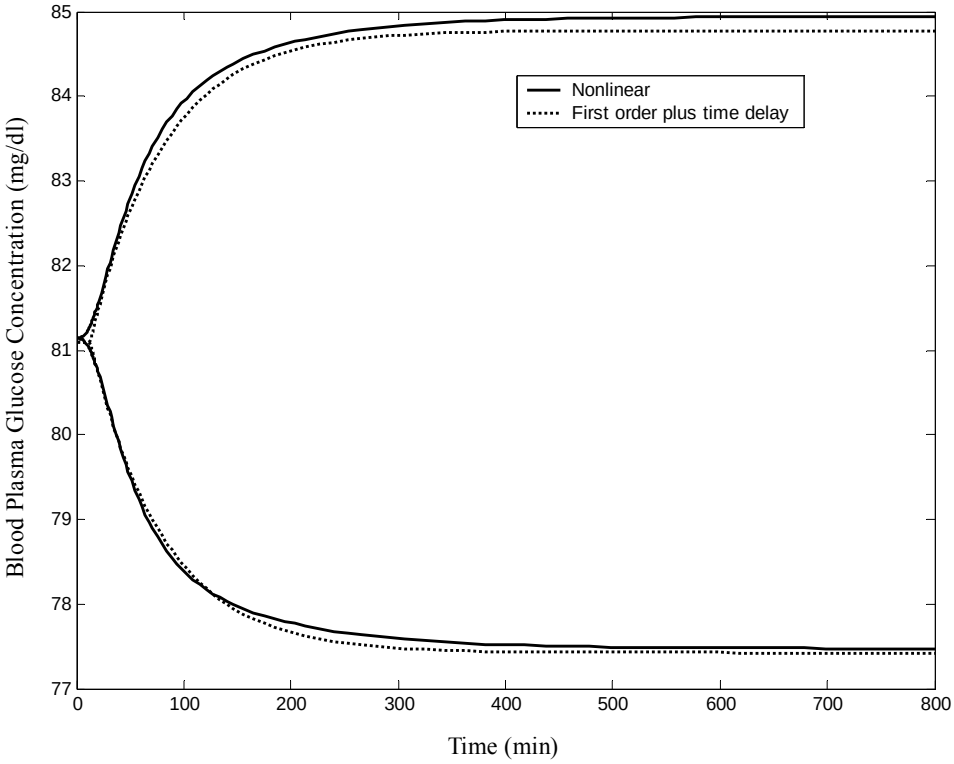

Fig. 4.2. Response of nonlinear (solid) and first order plus time delay (dot) models to ± 5% step changes in insulin from the nominal 22.3 mU/min.

4.3 PID Controller Tuning

The ideal PID controller has the form:

$$u(t) = K_P e(t) + K_I \int e(t)dt + K_D \frac{de(t)}{dt} \quad (4.3)$$

where u(t) = controller output, e(t) = error = $Y_{sp}(t) - Y(t)$, $Y_{sp}(t)$ = set point = 0 and Y(t) is the scaled plasma glucose concentration (expressed as deviation from the nominal value). The parameters K_P, K_I and K_D are relative weights of proportional, integral and derivative components of the control action respectively.

Ziegler and Nichols (1942) proposed the first set of PID tuning rules. A significant number of tuning rules based on Ziegler and Nichols tuning procedure have since been developed. These tuning methods can be classified as direct and indirect methods. Direct tuning methods do not require a process model - tuning is performed in a closed-loop manner. This is a relatively time consuming procedure requiring an initially tuned controller and a predefined "desired" closed-loop response (Chen and Seborg, 2002). On the other hand, indirect methods are based on the process models obtained from a step or frequency response experiment. The quality of the controller parameters obtained is dependent on the quality of the identified process model. Several tuning rules available in the literature are based on optimizing integral performance criteria like IAE, ISE or ITAE and consider either set point tracking, disturbance rejection or both (with equal or variable weighting factors). For example, Ciancone PID controller tuning correlations (Marlin, 1995) are developed based on minimization of the cumulative sum of IAE by considering ±25% variation in the process parameters with limits on manipulated variable movement for disturbance rejection or set point tracking. Simple PI, PD and PID controller settings for

integrating plus time delay processes, unstable processes are developed based on matching the coefficients of corresponding powers of 's' in the numerator and denominator of closed-loop transfer function to a servo problem (Chidambaram and Padma Sree, 2003). Shen (2002) has recently developed PID controller tuning relations by minimizing the sum of equally weighted IAE due to set point change and disturbance, using a genetic algorithm. In view of the increasing popularity of the Dynamic Matrix Control (DMC) in the chemical industry, Haeri (2002) has developed a tuning method for PID in which the controller parameters are adjusted to have performance similar to that of DMC. In this study, PID with IAE minimization (for disturbance rejection) tuning, Cohen-Coon tuning and the recently developed Shen (2002) tuning and DMC-based method (Haeri, 2002) are used for blood glucose control in diabetics. The different PID controllers are assessed based on their ability to attenuate a 50 g meal disturbance as well as their robustness to parametric uncertainties due to the inevitable patient-model mismatch.

4.4 Results and Discussion

The FOPDT model is obtained by approximating the step response of the nominal diabetic patient. The parameters K_P, K_I and K_D of the PID controller using the aforementioned four tuning methods are obtained for this FOPDT model and are given in Table 4.1; the relations employed in the four methods are summarized in Appendix. The performance of PID by the four tuning methods in rejecting the 50 g meal taken by the nominal patient is depicted in Fig. 4.3. The overshoot, undershoot and IAE observed in each case are tabulated in Table 4.1. From Fig. 4.3 and Table 4.1, it is evident that the performance of PID with Shen method of tuning is better than the other three methods, in terms of the highest and lowest glucose concentration

Table 4.1. The performance of PID controllers tuned by four methods, on the nominal patient case in attenuating the 50 g meal disturbance.

Tuning	K_P	K_I	K_D	Overshoot (mg/dl)	Undershoot (mg/dl)	IAE	Total insulin injected (mU)
IAE minimization	-1.23	-0.055	-6.034	6.98	10.32	46.9	23180
Cohen-Coon	-1.35	-0.046	-6.076	6.95	9.94	49.4	23125
DMC-based	-0.84	-0.007	-6.724	12.67	8.54	158.5	22574
Shen	-3.87	-0.08	-36.5	2.46	2.97	25.8	22987

Note: In this and subsequent tables, IAE values are for a simulation time of 800 min for each patient, and the IAE is calculated based on the scaled variable in equation (4.1).

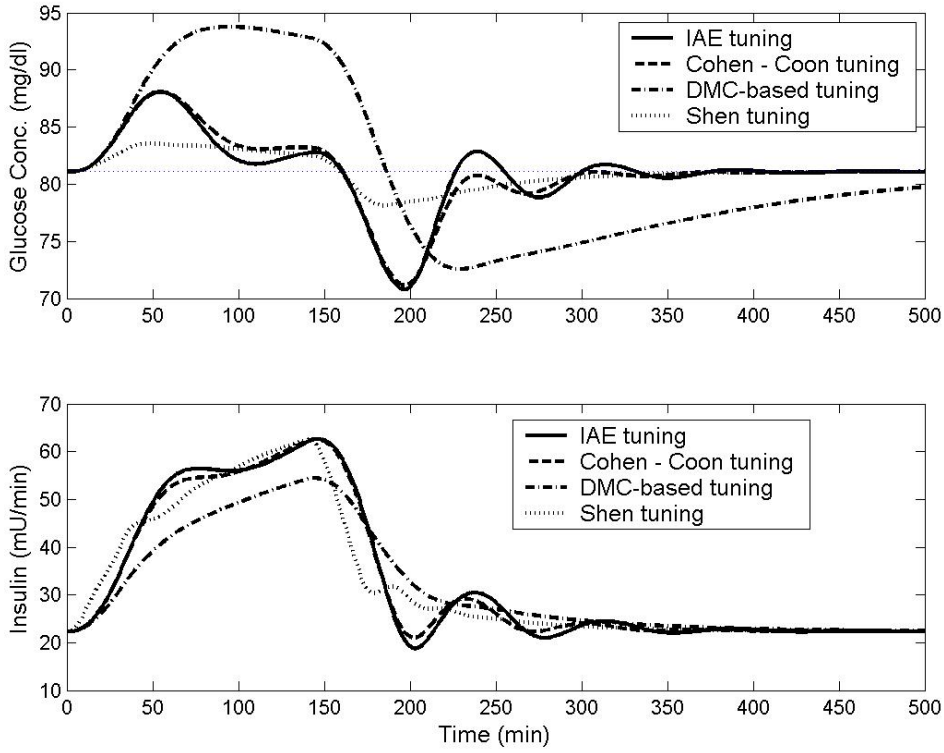

Fig. 4.3. Performance of PID controllers tuned by four methods on the nominal patient model in rejecting the 50 g meal disturbance at time, t = 0 min.

observed in the rejection of the meal disturbance. The IAE by Shen method is almost half of the next best method. Even though the PID controller designed with the Shen method outperformed other tunings, it is interesting to note that total amount of insulin injected in rejecting the 50 g meal is almost the same (Table 4.1). A steep insulin delivery profile is seen early on for the PID controller tuned by Shen method (Fig. 4.3); this helps in minimizing the deviations observed in the glucose level as compared to other controllers. The superiority of the Shen tuning over the other tunings including IAE minimization, may be due to the ability of optimization algorithm (i.e. Genetic Algorithm) to find the global optimum, use of equally weighted IAE due to set point change and disturbance, and/or a more appropriate structure of correlations used in developing the tuning relations.

The robustness of the various PID controllers in rejecting the 50 g meal disturbance on 577 patients is studied and the results are summarized in Table 4.2. From Table 4.2, one can conclude that Shen method of PID tuning outperformed the other three tuning methods in terms of the number of patients whose blood glucose concentration remains within 70-100 mg/dl and 60-100 mg/dl ranges. The average IAE and standard deviation of IAE by the Shen method are two to three times lower than those obtained with the other three tuning methods considered here. Therefore, only tuning method of Shen (2002) is considered for further discussion. For this PID tuning, only 26 patients (5% of the patient population) have entered the dangerous hypoglycemic region (blood glucose concentration less than 60 mg/dl). This result is better than the 72 patients who entered the hypoglycemic region in the H_∞ controller based blood glucose regulation work (Parker et al., 2000) and the 40 patients in the enhanced

Table 4.2. The performance of PID controllers tuned by the four methods on the 577 patients in attenuating the 50 g meal disturbance.

Tuning	No. of Patients with Glucose Conc. (mg/dl)		Average IAE for all 577 patients	Standard Deviation of IAE
	70-100	60-100		
IAE minimization	296	479	76.3	76.8
Cohen-Coon	327	481	79.5	81.9
DMC-based	359	426	200.8	148.4
Shen	488	551	42.7	46.4

internal model control (EIMC) strategy considered by Ramprasad et al. (2004). It is interesting to note that one parameter, namely, FPIC is at 0.21 (a +40% variation from its nominal value) in the 26 "patients" who could not be controlled safely by using the Shen method of PID tuning. Patients with such values of FPIC are perhaps more difficult to control using linear feedback control strategies.

The performance of PID with Shen tuning on two perturbed patients and the nominal patient is depicted in Fig. 4.4. The two perturbed patients considered had the lowest and highest IAE among the 551 patients whose glucose concentration was controlled within 60-100 mg/dl. The parameters of the patient with the lowest IAE are EGHGU-D_Γ = -0.88; FHIC = 0.32 and FPIC = 0.09 while those of the patient with the highest IAE are EGHGP-E_Γ = 1.4; EGHGU-D_Γ = -2.072 and FPIC = 0.21. The rest of the parameters are at their nominal values for both cases. Transient profiles of blood glucose and insulin in Fig. 4.4 are very good with little or no oscillations.

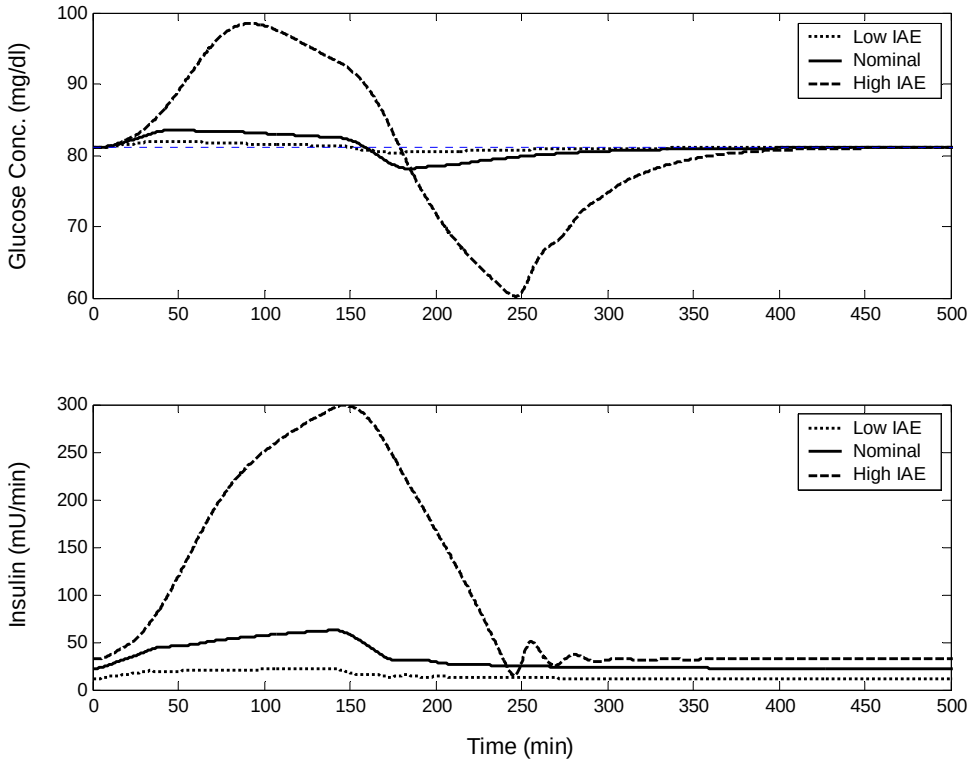

Fig. 4.4. Transient responses of PID controller with Shen tuning for two perturbed patients (giving the lowest and highest IAE) and the nominal case, in attenuating 50 g meal disturbance at time, t = 0 min.

PID controller with Shen tuning is now tested on two patient cases whose disturbance rejection responses are given in Parker et al. (2000). The parameters for the first patient are different from the 577 patients considered above; they are EIPGU-D_Γ = -8.15; EGHGU-D_Γ = -2.072; FHIC = 0.36 and rest of the parameters are at their nominal values. This case is specified as the worst-case performance of the continuous-time H_∞ controller, including uncertainty weighting and parametric uncertainty (Parker et al., 2000). Disturbance rejection by the H_∞ controller for this case shown in Figure 9 of Parker et al. (2000) is reproduced along with the response by the PID controller in Fig 4.5. Parameters for the second patient case are EIPGU-E_Γ = 0.6; EGHGU-E_Γ = 0.6; EGHGP-E_Γ = 1.4 and the remaining parameters

are retained at their nominal values. The responses by the PID controller and H_∞ controller (Parker et al. 2000) for this patient model are depicted in Fig 4.6. Figures 4.5 and 4.6 show that the performance of PID controller is very good and better than the H_∞ strategy of Parker et al. (2000).

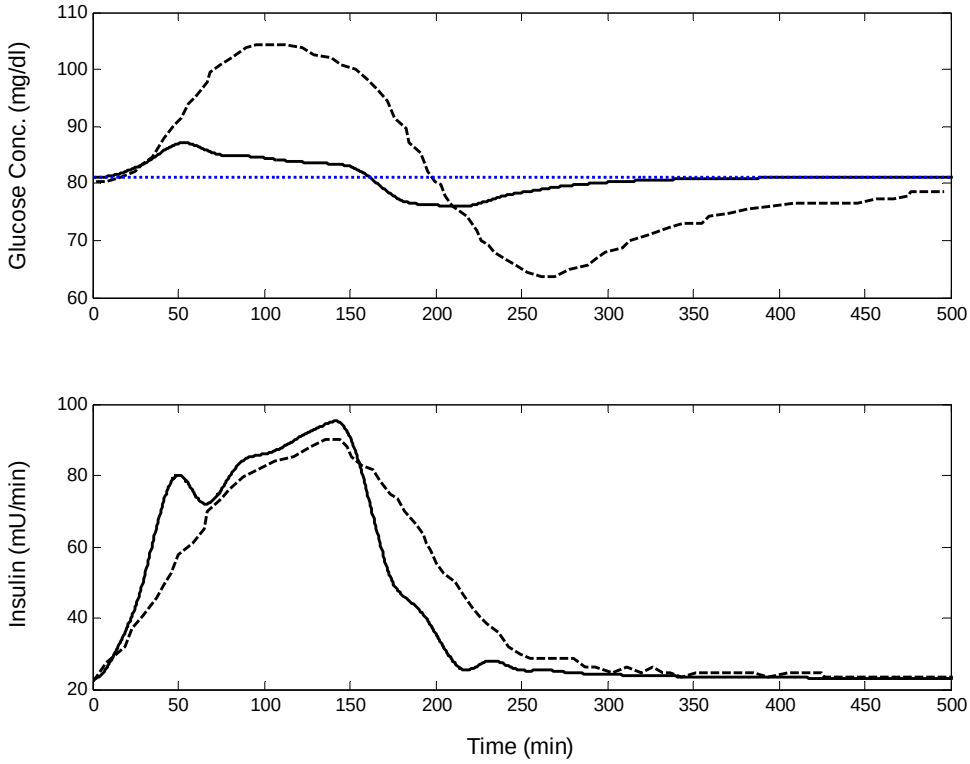

Fig. 4.5. Performance of PID controller with Shen tuning (solid) and H_∞ controller (dashed) including uncertainty weighting and parametric uncertainty (Parker et al., 2000), on a perturbed patient model with EIPGU-D_Γ = -8.15; EGHGU-D_Γ = -2.072, FHIC = 0.36 and the remaining five parameters are at their nominal values.

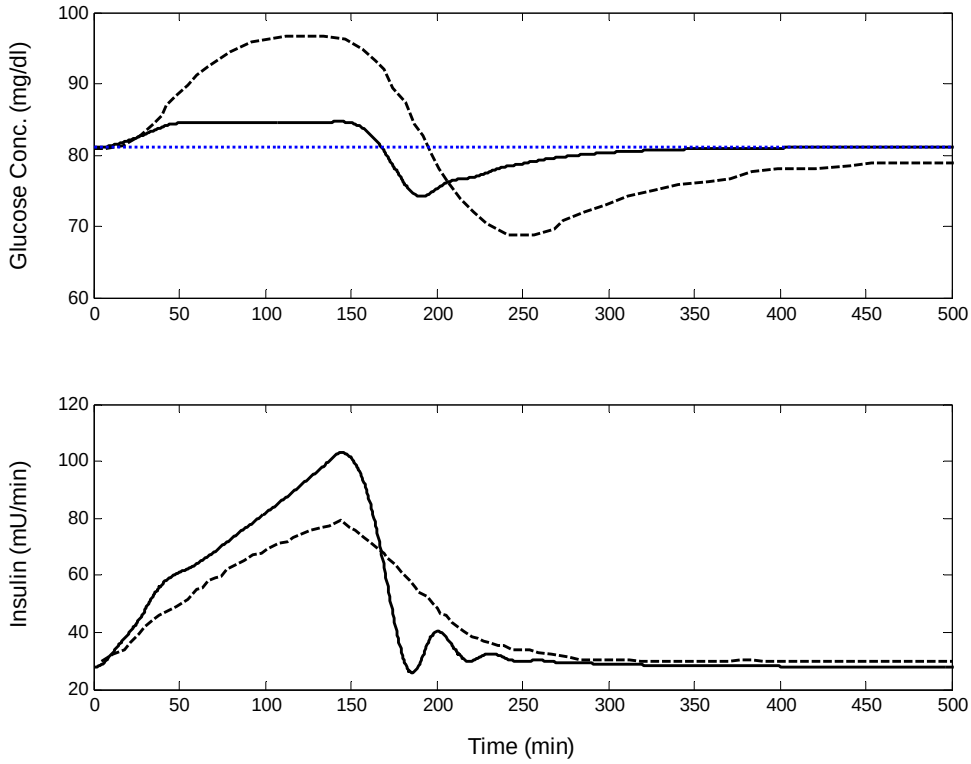

Fig. 4.6. Performance of PID controller with Shen tuning (solid) and H_∞ controller (dashed) including uncertainty weighting and parametric uncertainty (Parker et al., 2000), on a perturbed patient with EIPGU-E_Γ = 0.6; EGHGU-E_Γ = 0.6, EGHGP-E_Γ = 1.4 and the remaining five parameters are at their nominal values.

The performance of the PID controller with Shen tuning in rejecting the typical meal pattern for a 24 hour period (one day) is then studied for all the 577 patients. The typical meal pattern is assumed to have 50 g, 30 g, 50 g and 10 g of carbohydrates respectively in the breakfast, lunch, dinner and supper at the following times: breakfast at 7:30 a.m., lunch at 12:30 p.m., dinner at 6 p.m. and supper at 9 p.m. The PID controller tuned by the Shen method is able to maintain the blood glucose concentration within 60-100 mg/dl range for all the four meal disturbances in 95% of

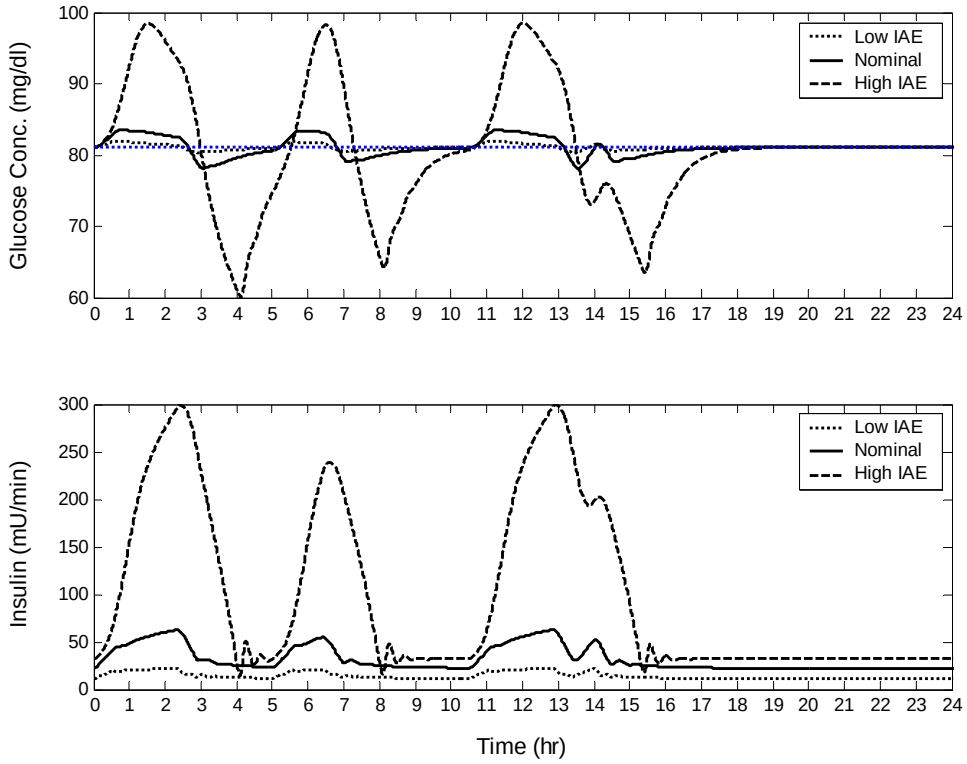

Fig. 4.7. Transient responses of the PID controller with Shen tuning for two perturbed patients (giving the lowest and highest IAE) and the nominal case, in attenuating four meals in a typical day.

the 577 patients tested. This is essentially the same as those of the single meal case (Table 4.2). The average IAE and the standard deviation of IAE for this situation of four meals are increased by a constant factor compared to that of the single meal case. The responses of the patients to four meals for three patient cases: having the highest IAE, nominal patient and having the lowest IAE patient case (from the well controlled 551 patient cases) are shown in Fig. 4.7. These results confirm the effectiveness of the PID controller with the Shen method of tuning for blood glucose control of diabetics.

Table 4.3. The performance of PID controllers tuned by Shen method but with various values of K_P on the 577 patients in attenuating the 50 g meal disturbance.

K_P	No. of Patients with Glucose Conc. (mg/dl)		Average IAE for all 577 patients	Standard Deviation of IAE
	70-100	60-100		
-3.87	488	551	42.7	46.4
-5	496	573	39.0	42.4
-6	515	577	36.2	39.4
-7	541	577	33.9	36.8

A careful observation of the PID controller parameters (K_P, K_I, K_D) obtained by the four tuning methods investigated here (see Table 4.1) indicates that the proportional gain, K_P in the Shen method is higher than that obtained by the other three tuning methods by a factor of at least 3. From our observations, K_P seems to play an important role in effectively rejecting the meal disturbance. Hence, the PID controller performance with higher values of K_P, while keeping the integral action K_I (-0.08) and derivative action K_D (-36.5) as constant, is studied and the results are tabulated in Table 3. Interestingly for a K_P value of -6, the PID controller is able to maintain the glucose concentration above the dangerous hypoglycemic region (< 60 mg/dl) for all the 577 patients under study. Further increase of K_P to -7 has decreased the average IAE and standard deviation of IAE, but resulted in sustained oscillations for some patient cases. One such perturbed patient response with three different K_P values is depicted in Fig. 4.8. The parameters for this perturbed patient are EGHGP-E_Γ = 1.4; FHIC = 0.32 and FPIC = 0.09 with the rest of parameters retained at their nominal

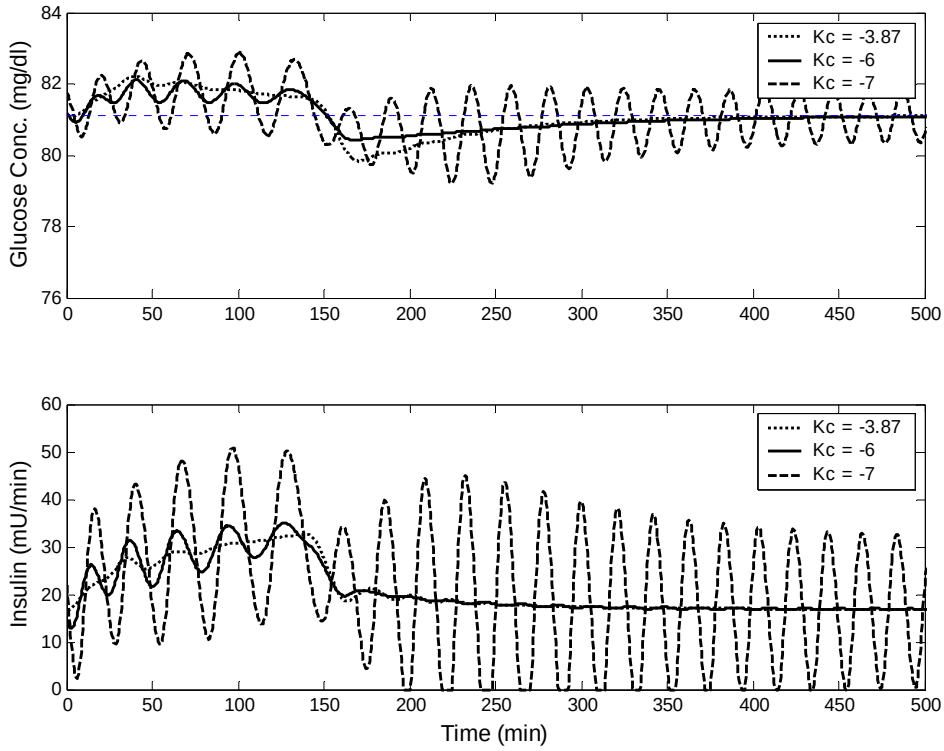

Fig. 4.8. Transient response of PID controllers with three different values of K_P for a perturbed patient with parameters EGHGP-E_Γ = 1.4, FHIC = 0.32, FPIC = 0.09 and rest of the parameters are at their nominal values.

values. The average IAE and standard deviation of IAE have decreased by using a higher K_P of -6 in lieu of -3.87 (Table 4.3), but oscillations and settling time have increased slightly (Fig. 4.8). Assuming these are acceptable, K_P = -6 is recommended in order to achieve better robustness for blood glucose regulation of all patients.

4.5 Conclusions

The performance and robustness of different PID controllers obtained using four tuning methods are investigated for maintaining blood glucose concentration of a population of 577 diabetics. Controller parameters have been determined using a FOPDT approximation of a detailed first principles physiological model representing

a nominal diabetic patient. The Shen tuning method outperformed the other three tunings (i.e. IAE minimization for disturbance rejection, Cohen-Coon, DMC-based) both in disturbance rejection and robustness characteristics. The PID controller tuned by it is able to maintain the glucose concentration above the dangerous hypoglycemic range (< 60 mg/dl) in 95% of 577 patient models of the study. The average IAE and standard deviation of IAE are reduced by a factor of two by the Shen method than IAE minimization tuning for disturbance rejection and Cohen-Coon tuning, whereas the reduction is by a factor of about five compared to DMC-based PID tuning. The PID controller with Shen method, when tested on all 577 patients considering a typical meal pattern of four meals per day, is also able to maintain the glucose concentration above the hypoglycemic range in 95% of the cases (same number of cases as for the single meal). Further fine tuning of this PID controller is able to maintain the glucose concentration above the hypoglycemic range in all the 577 patients considered. Thus, results of this study show that the PID controller with proper tuning is very attractive for blood glucose control owing to its simple structure and good robustness.

CHAPTER 5

Input Output Linearization for Glucose Regulation in Type I Diabetics

5.1 Introduction

Nonlinearity in many common processes such as distillation columns, chemical reactions and acid base neutralization process is observed. Model based control strategies for nonlinear processes have been based on local linearization and a linear controller based on the linearized model. For highly nonlinear processes detuning of linear feedback controllers is required to ensure their stability, which in turn degrades the performance. The development of geometric methods to arrive at exact linearization of nonlinear models independent of the operating points (Isidori, 1989) allowed designing the linear controllers for the equivalent linear system to meet the performance requirements. One such controller synthesis and experimental evaluation using Nonlinear Internal Model Controller (NIMC) and Augmented Internal Model Controller (AuIMC) for a highly nonlinear neutralization process was discussed by Hu et al. (2000). In the present study, the synthesis and evaluation of a nonlinear controller with NIMC structure for a diabetic is discussed.

5.2 Synthesis of IOL Controller

Consider a single input single output process, P of the form:

$$\begin{aligned} \dot{x} &= f(x) + g(x)u \\ y &= h(x) \end{aligned} \tag{5.1}$$

where $x \in R^n$ is the vector of states, u is the manipulated input, y is the output, f(x) and g(x) are smooth vector fields on R^n, and h(x) is a smooth function on R^n.

The Lie Derivative of function $\lambda(x)$ is expressed as follows

$$L_f \lambda(x_1,...,x_n) = (\frac{\partial \lambda}{\partial x_1},...,\frac{\partial \lambda}{\partial x_n}) \begin{pmatrix} f_1(x_1,...,x_n) \\ \vdots \\ f_n(x_1,...,x_n) \end{pmatrix} \quad (5.2)$$

The following notation is used for repeated Lie Derivatives: $L_f(L_f \lambda(x)) = L_f^2 \lambda(x)$.

Similarly for any system described in the form of equation (5.1), the Lie Derivatives $L_f h(x), L_f^2 h(x), L_f^3 h(x), \cdots, L_g L_f h(x), L_g L_f^2 h(x), ..., \text{etc}$ are calculated. The relative degree of the nonlinear system in equation (5.1) is the smallest integer r for which $L_g L_f^{r-1} h(x) \neq 0$ and $L_g L_f^{r-2} h(x) = L_g L_f^{r-3} h(x) = ... = L_g h(x) = 0 \forall x$ in some neighborhood of the defined operating point x_0. The relative degree of the diabetic system is found to be 4.

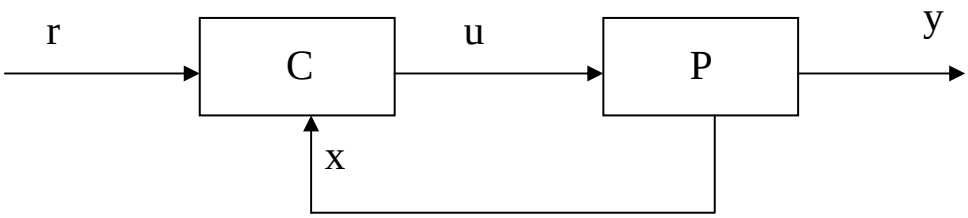

Fig. 5.1(a) Nonlinear controller with input output linearization

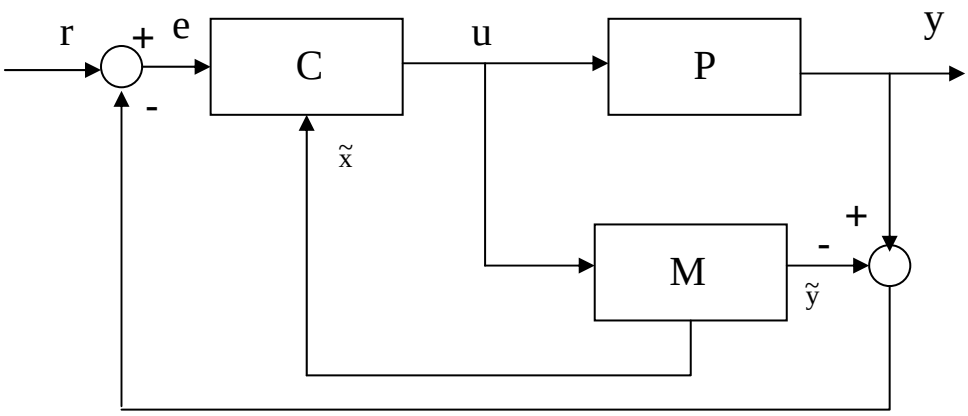

Fig. 5.1(b) Nonlinear Internal Model Control (NIMC) Structure

An input-output linearizing controller (Isidori, 1995) is

$$u = \frac{v - L_f^{\gamma} h(x)}{L_g L_f^{\gamma-1} h(x)} \tag{5.3}$$

with the transformed input to the controller,

$$v = -\alpha_{\gamma} L_f^{\gamma-1} h(x) - \alpha_{\gamma-1} L_f^{\gamma-2} h(x) - \cdots - \alpha_1 h(x) + \alpha_1 r \tag{5.4}$$

where r is the set-point, and $\alpha's$ are the tuning parameters chosen such that the closed-loop system is input-output stable. (Fig 5.1 a)

The input-output linearizing controller (i.e. equation 5.3 and 5.4) requires the measurement of all the states of the nonlinear system, which is not possible in all the cases. So a new controller structure NIMC (Fig. 5.1b) in IMC form is developed. Advantages of NIMC are offset-free response and model M acts as open-loop observer (Hu and Rangaiah, 1999).

For the process in equation (5.1), assume that the model, M available for the controller design has the form:

$$\begin{aligned} \dot{\tilde{x}} &= \tilde{f}(\tilde{x}) + \tilde{g}(\tilde{x})u \\ \tilde{y} &= \tilde{h}(\tilde{x}) \end{aligned} \tag{5.2}$$

where $\tilde{x}$ is the vector of model states, $\tilde{y}$ is the model output, $\tilde{f}(\tilde{x})$, $\tilde{g}(\tilde{x})$ and $\tilde{h}(\tilde{x})$ are defined similar to the corresponding functions for the process equation (5.1). Thus, tilde on a variable indicates that the quantity refers to the model, which is also used in the NIMC controller.

The standard IOL controller system shown in Fig. 5.1(a) (Isidori, 1995), can be put into the NIMC structure shown in Fig. 5.1(b) with the controller,

$$u = \frac{\tilde{v} - L_{\tilde{f}}^{\gamma}\tilde{h}(\tilde{x})}{L_{\tilde{g}}L_{\tilde{f}}^{\gamma-1}\tilde{h}(\tilde{x})} \tag{5.5}$$

where

$$\tilde{v} = -\alpha_{\gamma}L_{\tilde{f}}^{\gamma-1}\tilde{h}(\tilde{x}) - \alpha_{\gamma-1}L_{\tilde{f}}^{\gamma-2}\tilde{h}(\tilde{x}) - \cdots - \alpha_1\tilde{h}(\tilde{x}) + \alpha_1 e \tag{5.6}$$

where $e = r - y + \tilde{y}$.

Thus the control law does not require derivatives of the output. Since the relative order for the diabetic system is 4, the resulting transfer function between output and error for the diabetic patient system is:

$$\frac{y(s)}{e(s)} = \frac{\alpha_1}{s^4 + \alpha_4 s^3 + \alpha_3 s^2 + \alpha_2 s + \alpha_1} \tag{5.7}$$

The controller in equation (5.6) involves r tuning parameters. As suggested by Kravaris and Wright (1989), the transfer function (5.7) can be modified to the form in (5.8) with a single parameter ε.

$$\frac{y(s)}{e(s)} = \frac{1}{(\varepsilon s + 1)^4} \tag{5.8}$$

If there are no modeling errors, M and P are identical, and the NIMC structure simplifies to the standard implementation in Fig. 5.1(a). The closed-loop system under the controller equation (5.5) will be internally stable, if the process is minimum-phase and asymptotically stable (Hu and Rangaiah, 1999). Advantages of the NIMC structure in Fig. 5.1(b) are: sensor measurement of all the states is not required as model M estimates the state variables and offset-free response.

5.3 Implementation of NIMC for diabetic

A nonlinear controller using input output linearization technique is developed for a diabetic in Simulink. The governing differential equations of the diabetic model are written in the form of equation (5.1). The diabetic model with NIMC structure is depicted in Fig. 5.2.

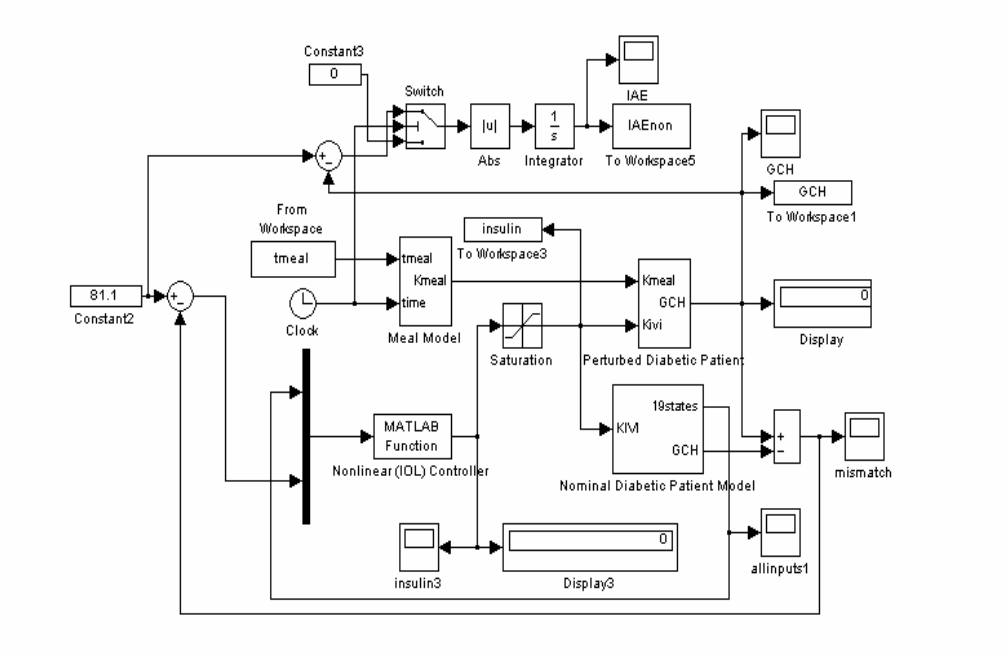

Fig. 5.2. Nonlinear controller in NIMC structure for the diabetic system.

Perturbed diabetic patient, nominal diabetic patient model and nonlinear (IOL) controller in Fig. 5.2 corresponds to the P, M and C in the NIMC structure in Fig. 5.1(b) respectively. The nonlinear controller is synthesized using equations (5.4 – 5.8) and was implemented in Simulink by employing Matlab Fcn block, which can be used to run a function in m-file. The Matlab Fcn in Simulink gets the states of the nominal diabetic model and error as the inputs from the Simulink environment and runs the function in m-file and the manipulated variable (i.e. insulin) as output from the m-file is popped back to Simulink. The coding for the implementation of the nonlinear controller is depicted in Fig. 5.3. The Lie derivatives and the nonlinear controller expression are shown in this figure. The expressions of the Lie derivatives are very long and only some part is visible in lines 10 to 14 of Fig. 5.3.

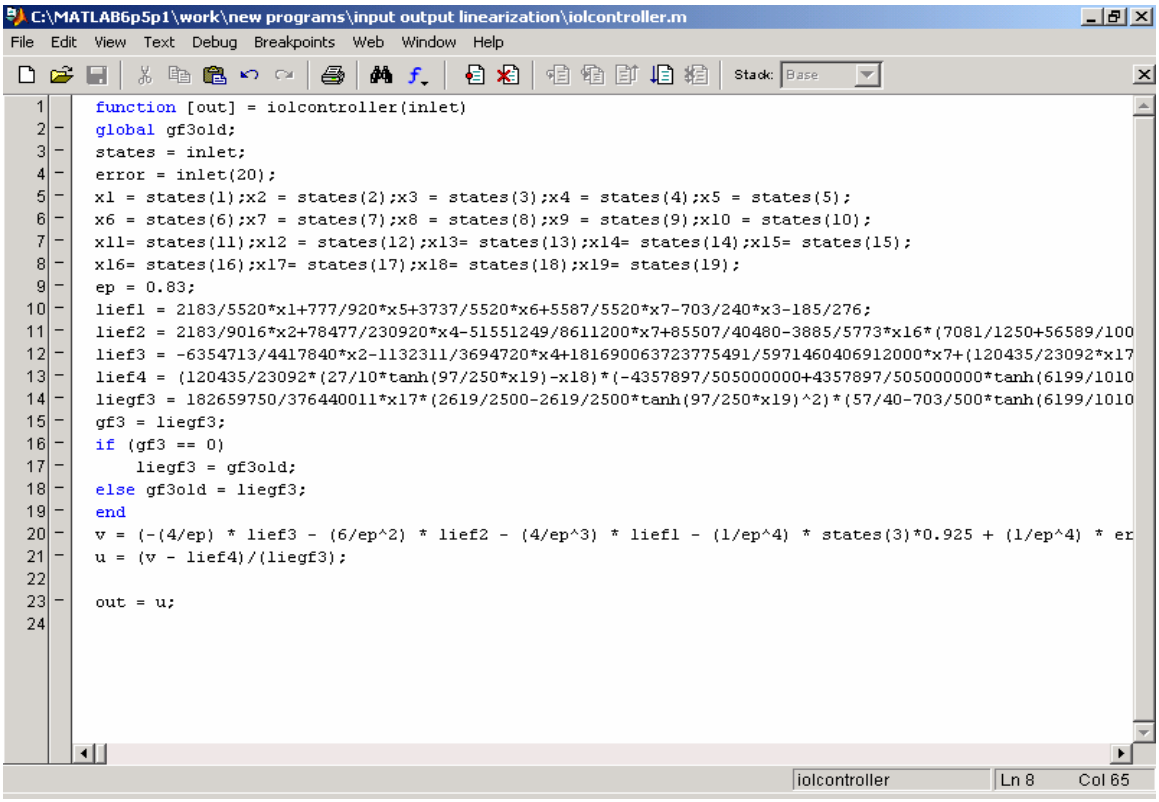

Fig 5.3. The Math Fcn block for the implementation of nonlinear controller with input output linearization technique

5.3 Evaluation

The NIMC is synthesized for a Type I diabetic as discussed in section 5.2. The ε in equation (5.8) is generally chosen to have desired closed loop time constant. In this study ε value of 0.83 is used. The assessment of the designed controller is done based on its ability to reject the meal disturbances, while tracking normoglycemic set point of 81.1 mg/dl. Note that input and output scaling are not considered in the design of the nonlinear controller.

The performance of NIMC and EIMC with parameters ($\lambda_1 = \lambda_2 = 5$ and K = 3) in rejecting the 10g, 30g and 50 g meal ingestion for the nominal patient case is depicted in Fig. 5.4, 5.5 and 5.6. These transient responses show that NIMC is able to control the glucose levels better than that by EIMC. From the transient response in Fig. 5.6,

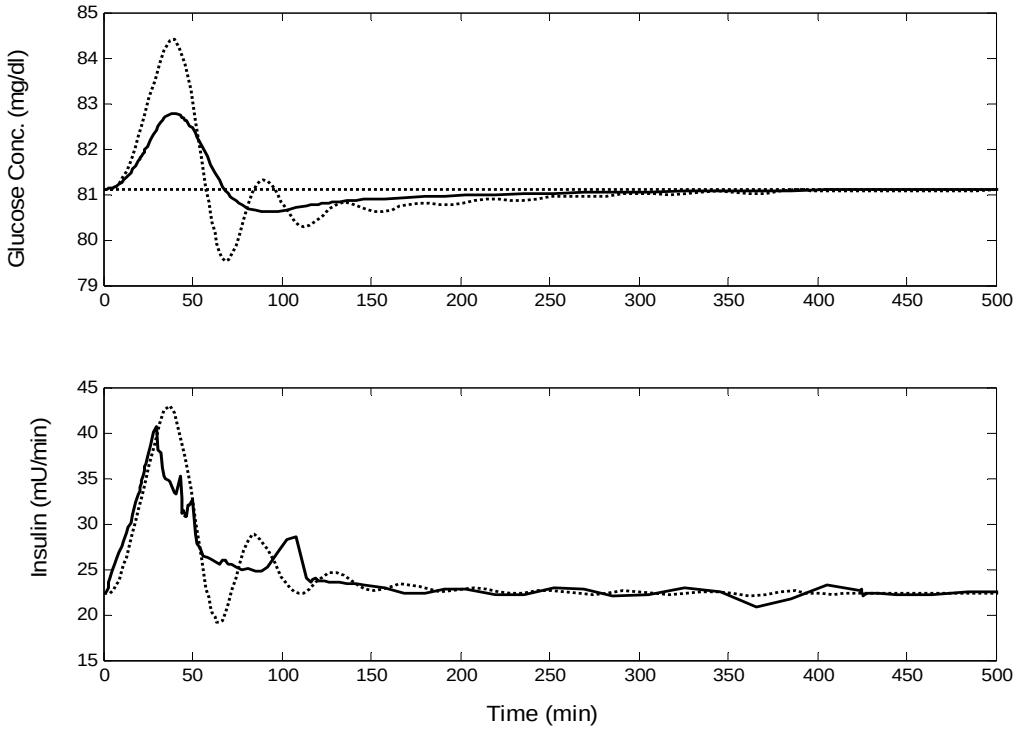

Fig 5.4. Transient response of the nominal diabetic patient in rejecting 10 g meal disturbance by NIMC (solid) and EIMC (dotted).

the nonlinear controller is able to maintain the glucose concentration within ±2.3 mg/dl of the set point in rejecting 50 g meal disturbance. The IAE measure observed in rejecting the 10 g, 30 g and 50 g meal disturbances by NIMC is reduced by 30% compared to that of EIMC. But the number of spikes in the insulin computed by using NIMC increases with the size of the meal disturbance.

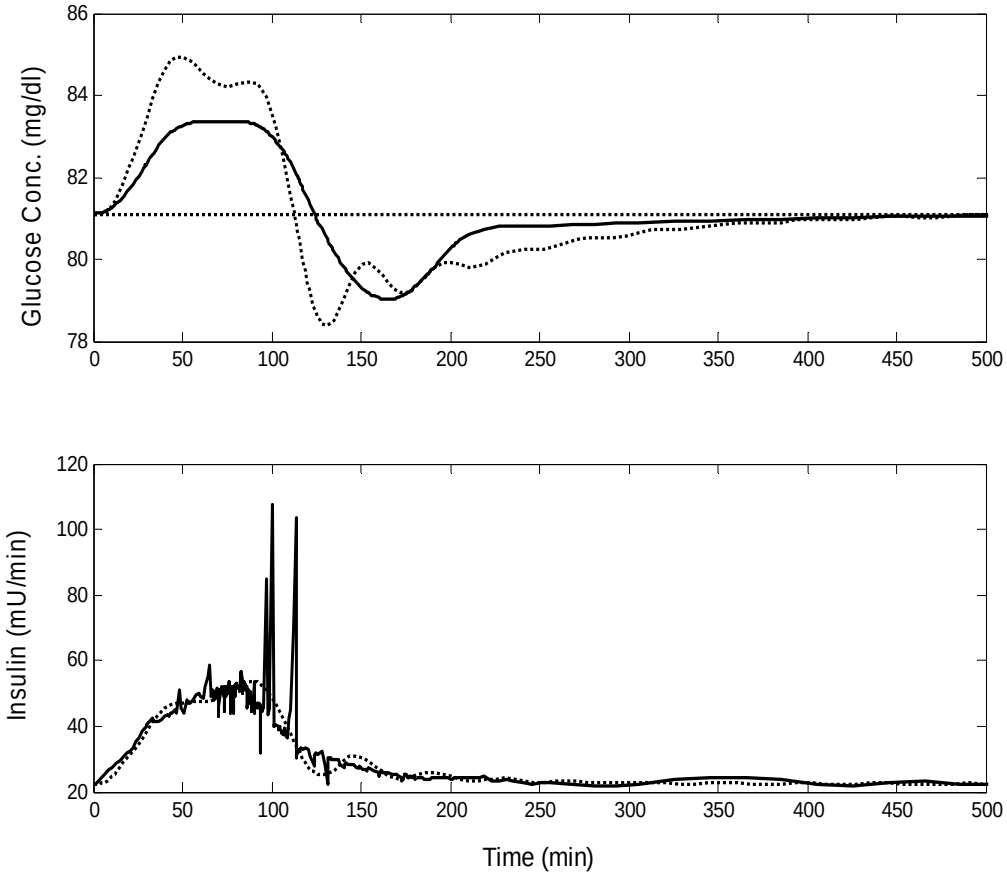

Fig. 5.5. Transient response of the nominal diabetic patient in rejecting 30 g meal disturbance by NIMC (solid) and EIMC (dotted).

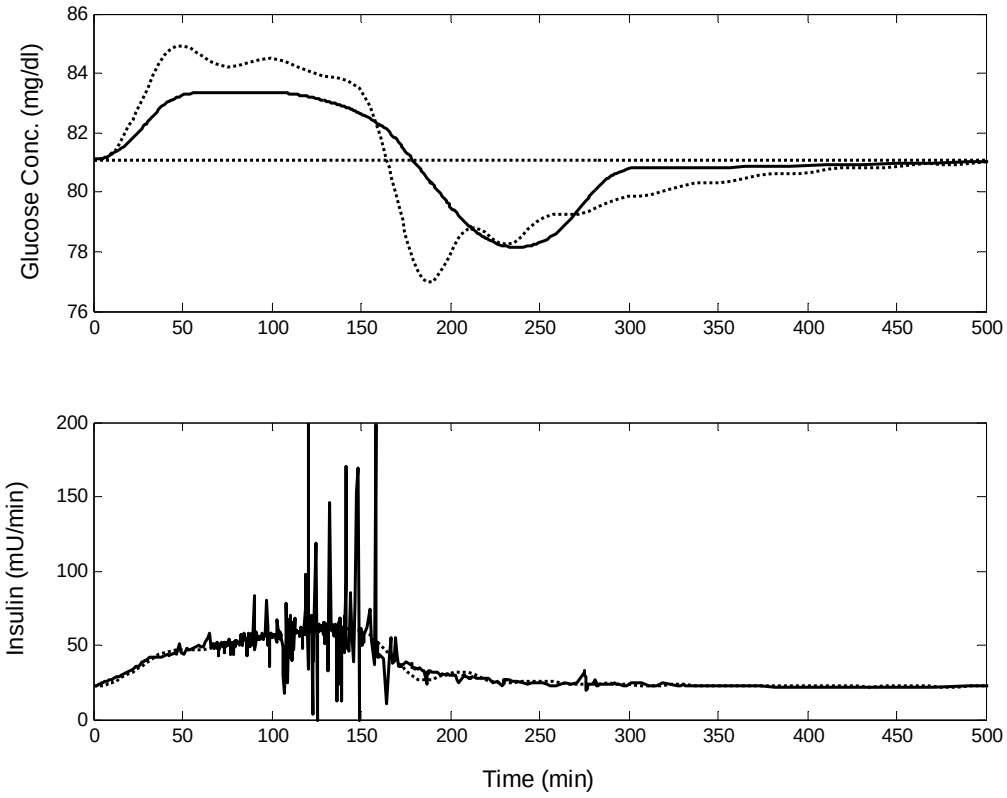

Fig. 5.6. Transient response of the nominal diabetic patient in rejecting 50 g meal disturbance by NIMC (solid) and EIMC (dotted).

The spikes observed in the insulin profile in rejecting meal disturbances could be attributed to the numerical problems in the ode15s solver. Implementation of NIMC is done in two different ways. One is completely implemented in Simulink, other by using Matlab Fcn in Simulink to run a m-file to calculate manipulated variable. But spikes do appear in both of these implementations. The computational time required for the application of nonlinear controller to perturbed cases is high. The stiffness of the perturbed cases causes the selection of smaller step size in ode15s solver, which results in higher computational time and more spikes and abnormal termination in some cases while rejecting the meal disturbances. Thus the performance of the nonlinear controller for perturbed cases in rejecting the meal disturbances could not be studied.

5.4 Summary

Nonlinear internal model controller synthesis using input output linearization technique is summarized and developed. The designed controller is assessed based on its ability to track the normoglycemic set point in the presence of 10 g, 30 g and 50 g meal disturbances. Better performance in glucose regulation by nonlinear controller over enhanced internal model control (with K = 3) is observed for the case of nominal patient model. But the nonlinear controller could not be studied for all perturbed patient models due to computational problems.

CHAPTER 6

Conclusions and Recommendations

6.1 Conclusions

Several model-based controllers for blood glucose regulation in Type I diabetics are designed and studied using a detailed and recent physiological model. A meal disturbance model is also included. First, IMC and EIMC are designed using the FOPTD approximation of the nominal patient model and their robustness is evaluated for regulation of blood glucose in 577 patient models obtained by considering ±40% variation in the parameter values of the nominal patient model. The EIMC is able to maintain the glucose concentration above the dangerous hypoglycemic range in 93% of 577 patient models tested while rejecting meal disturbance. For these patient models, average IAE and standard deviation of IAE are reduced by a factor of 2 to 3 by the EIMC compared to the conventional IMC. Further, the performance of the former is found to be better than that of an H_∞ controller proposed by Parker et al. (2000). The EIMC is further tested on all 577 perturbed patient models taking four meals per day, and the controller is able to maintain the blood glucose above the dangerous hypoglycemic range in 93% of the cases, which is the same number of cases as for the single meal. Thus, the EIMC strategy is attractive for blood glucose regulation owing to its simple structure and design as well as good robustness.

The performance and robustness of PID controllers obtained using four tuning methods are investigated for maintaining blood glucose in all the 577 perturbed patient models. Controller parameters have been determined using a FOPTD

approximation of the detailed physiological model for the nominal patient. The recent tuning method by Shen (2002) outperformed the other three tuning methods (i.e., IAE minimization for disturbance rejection, Cohen-Coon and DMC-based) both in disturbance rejection and robustness characteristics. The PID controller tuned by it is able to maintain blood glucose above the dangerous hypoglycemic range in 95% of 577 patient models tested for rejecting disturbances due to both single meal and four meals in a day. For the single meal disturbance, the average IAE and standard deviation of IAE are reduced by half when the PID controller is tuned by the Shen's method compared to controllers tuned by IAE minimization for disturbance rejection and Cohen-Coon; the reduction is by a factor of about 5 when compared to DMC-based tuning.

The superiority of the Shen's (2002) method over the other tuning techniques including IAE minimization, may be due to the ability of the optimization algorithm (i.e., genetic algorithm) to find the global optimum, use of equally weighted IAE due to set point change and load disturbance, and/or a more appropriate structure of the tuning correlations. Controller gain is observed to play a vital role for disturbance rejection in diabetics. Superior performance in disturbance rejection and robustness, of the PID controller tuned by Shen's (2002) method over EIMC is observed. Further fine tuning of this PID controller is able to maintain the blood glucose above the hypoglycemic range in all the 577 perturbed patient models considered. Thus, the PID controller is very attractive for blood glucose regulation owing to its simplicity, proven usage and good robustness.

Nonlinear internal model controller (NIMC) using input-output linearization is also developed and implemented for a Type I diabetic. This controller performance in rejecting meals of different size taken by the nominal diabetic patient model is studied and found to be better than that by the EIMC and PID controllers. However, spikes occur in the profile of the insulin injected (manipulated variable), which may be due to numerical problems associated with solving differential equations. Owing to this, NIMC could not be tested on all the perturbed patient models.

6.2 Recommendations for Further Study

The "closed-loop" device to monitor and administer insulin consists of sensor, control algorithm and insulin pump. Glucose sensing is possible through intra-venous sampling or subcutaneous measurement, and glucose measurements are available with a sampling interval of several minutes. Also,the diabetic model should include the effect of exercise on glucose dynamics. Future work on designing and evaluating model-based controllers for blood glucose regulation should address and include these practical aspects.

Recently, Ruiz-Velazquez et al. (2004) have formulated blood glucose regulation for diabetics as a tracking problem to track the glucose profile of healthy patients subjected to meal disturbances. They studied the performance of H_∞ controller for tracking the specified set-point profile. The model-based controllers considered in the present work and model predictive controllers can be studied for tracking the glucose profile in diabetics.

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APPENDIX

Relations in the four methods of PID controller tuning used in this study, are summarized in this appendix assuming the process model is $G(s) = \frac{Ke^{-\theta s}}{\tau s + 1}$. These relations provide values of K_c, τ_I and τ_d which can then be employed to calculate K_P, K_I and K_D in equation (3) from $K_P = K_c$, $K_I = K_c/\tau_i$ and $K_D = K_c\tau_d$.

IAE minimization tuning for disturbance inputs (Smith and Corripio, 1985):

$$K_c = \frac{a_1}{K}\left(\frac{\theta}{\tau}\right)^{b_1}; \qquad \tau_i = \frac{\tau}{a_2}\left(\frac{\theta}{\tau}\right)^{b_2}; \qquad \tau_d = a_3\tau\left(\frac{\theta}{\tau}\right)^{b_3}$$

where $a_1 = 1.435$, $a_2 = 0.878$, $a_3 = 0.482$, $b_1 = -0.921$, $b_2 = 0.749$ and $b_3 = 1.137$.

Cohen-Coon tuning (Coughanowr, 1991):

$$K_c = \left(\frac{\tau}{K\theta}\right)\left(\frac{4}{3} + \frac{\theta}{4\tau}\right); \qquad \tau_i = \theta\left(\frac{32 + 6\theta/\tau}{13 + 8\theta/\tau}\right); \qquad \tau_d = \theta\left(\frac{4}{11 + 2\theta/\tau}\right)$$

DMC based PID tuning (Haeri, 2002):

$$K_c = \tilde{K}_C/K, \tau_i = \tilde{\tau}_i\tau, \tau_d = \tilde{\tau}_d\tau, L = \frac{\theta}{\tau};$$

$$\tilde{K}_c(L) = \frac{6.84}{1 + 2.33L^{0.7} + 7.82L^{3.5}} + 0.64$$

$\tilde{\tau}_i = 0.95+2.58L+3.57L^2$ for $0 < L \le 0.29$

$= 2.15-0.76L+0.33L^2$ for $0.29 < L < 4$

$$\tilde{\tau}_d = 0.29\left(\frac{L}{1+L}\right) + 3.94\left(\frac{L}{1+L}\right)^2 - 4.65\left(\frac{L}{1+L}\right)^{2.8} \qquad \text{for} \qquad 0 < L \le 1.79$$

$$= 0.87L - 0.49L^2 + 0.09L^{2.8} \qquad \text{for} \qquad 1.79 << L < 4$$

Shen tuning formula (Shen, 2002):

These tuning formula for disturbance rejection are given by:

$$\alpha = K\frac{\theta}{\tau} \text{ and } T = \frac{\theta}{\theta + \tau}$$

where αK_c, τ_i/θ and τ_d/θ are given by empirical correlation of the form: $\exp(a_0 + a_1 T + a_2 T^2)$ and the coefficients, a's are given in the following table.

	A_0	a_1	a_2
αK_c	2.94	-11.63	11.15
τ_i/θ	1.88	-3.63	0.86
τ_d/θ	-0.25	-0.06	-1.99