REGULATION OF BLOOD GLUCOSE
IN TYPE 1 DIABETIC PATIENTS

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NATIONAL UNIVERSITY OF SINGAPORE

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Dedicated to **My Beloved Parents,**

Brother and Sister

Declaration

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

MAY SU TUN
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Summary

In Type 1 diabetic (T1D) patients, it is crucial to keep the blood glucose (BG) concentration in normoglycemic region (70~126mg/dL) in fasting condition and under 180mg/dL in postprandial condition using exogenous insulin infusion. Such regulation is important in order to avoid *hyperglycemia* (blood glucose values that are above normoglycemic region) and its long term impact on the diabetics (complications such as nephropathy and retinopathy) and dangerous *hypoglycemia* (blood glucose values that are below normoglycemic region) that leads to diabetic coma and possibly death on a short-term basis.

A number of mathematical models that represent T1D patients and control algorithms for blood glucose regulation in diabetic patients have been developed in the literature. These control algorithms were also shown to cope well with inter- and intra-patient variability. The aim of this research is to find efficient and practically implementable control algorithms by employing some state of the art diabetic models (that accurately simulate the diabetes patient) for effective regulation of blood glucose. This thesis also seeks to extend the utility of simple dynamic protocols that are currently practiced for treating hyperglycemia in patients admitted to critical/intensive care units to treat T1D patients. For this purpose, the Yale insulin Infusion Protocol (YIIP) is implemented and studied on different T1D "patients". Studies indicate that the YIIP can be tailored and used for effective BG regulation in T1D "patients". The thesis also examines if the "patients" can be classified into different groups and subject to class-specific tailored algorithms. To achieve this objective, a simple diabetes diagnostic test (Intravenous Glucose Tolerance Test, IVGTT) and a multivariate statistical tool (Principal Component Analysis, PCA) are utilized. Then, YIIP is tailored to work for different patient classes. Applicability of this investigation through validation on different patient models is also attempted. The results show that the developed algorithm can be very useful for BG control in T1D patients.

For the purpose of this thesis, the modeling error compensator (controller) based on a linear reference model (LMEC) is considered and evaluated on three diabetic models. The results demonstrate that the LMEC controller is a good candidate for controlling diabetes. The BG control is more effective with the patient-specific T1D patient model which could be constructed from past data collected from the patient. Multirate system identification (MRID) may be quite handy in this regard. Frequent sampling of BG concentration is also required for effective control but the current glucose sensor technology has its own limitations. In healthy humans, the endogenous insulin response to the BG changes within seconds. The BG control would be more effective if the control algorithm can mimic the healthy human physiological response. To achieve this goal, the availability of frequent BG measurement is a key factor. To solve this problem, a LMEC algorithm with 36 seconds control interval and 3 minute BG concentration sampling interval with estimation of intersample BG measurement using models obtained from MRID is developed. Using simulated data, this idea is shown to be applicable and extendable to situations with larger BG concentration sampling intervals.

The developed schemes are expected to be useful in advancing the goal of achieving better patient outcomes using artificial closed loop pancreatic system.

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List of Abbreviations

BG   Blood Glucose

DSAR   Data Selection And Regression

FOPTD   First Order Plus Time Delay

ICU   Intensive Care Unit

IIP   Insulin Infusion Protocol

IIT   Intensive Insulin Therapy

IVGTT   Intravenous Glucose Tolerance Test

LMEC   Linear Modeling Error Compensator

MAE   Mean Absolute Error

MEC   Modeling Error Compensator

MIMO   Multi Input/ Multi Output

MISO   Multi Input/ Single Output

MIVGTT   Modified Intravenous Glucose Tolerance Test

MODYIIP   Modified Yale Insulin Infusion Protocol

MRID   MultiRate IDentification

NL   NonLinear

NLLS   NonLinear Least Squares

NMPC   Nonlinear Model Predictive Control

NMRID   New MultiRate IDentification

NSOTF   New Second Order Transfer Function

OGTT   Oral Glucose Tolerance Test

PCA   Principal Components Analysis

PI	Plasma Insulin
SID	System IDentification
SISO	Single Input/ Single Output
SOTF	Second Order Transfer Function
SS	State Space
SSID	State Space System Identification
SVO	Single Variable Optimization
T1D	Type 1 Diabetic
YIIP	Yale Insulin Infusion Protocol

Chapter 1

Introduction

1.1 Homeostasis and Blood Glucose Regulation

Homeostasis is the term describing the self-regulation of the process or activities in a biological or mechanical system to maintain stability of the internal environment by adjusting to changing conditions (Wikipedia, 2009b). It is vital to keep human body in homeostasis such as body temperature regulation, blood glucose (BG) regulation and hormonal regulation. The regulation of blood glucose to maintain glycemia (the concentration of glucose in the blood) in normal range is an important aspect of metabolic homeostasis. The mean normal glycemic value for healthy human is 90mg/dL or 5mmol/L. Glucose is the main source of energy for the body and brain and it is enriched mainly from consumed sugar and carbohydrate. BG level rises up mainly due to food intake and is also influenced internally by stress hormones, steroids, cortisone, growth hormones etc. BG is lowered by prolonged and intensive physical exercise and reduction/lack of nutrition.

BG is continuously regulated by insulin and glucagon. Glucagon is released from alpha cells of pancreas when BG level is low. Glucagon stimulates breakdown of glycogen stored in liver (glycogenolysis). The glycogenolysis produces glucose from stored glycogen which gets introduced into the blood stream to raise BG level. Conversely, insulin is produced from the beta cells of pancreas when BG rises up to higher level either due to meal consumption or through glycogenolysis. Insulin activates conversion of glucose into glycogen to be stored in liver (and in muscle) by glycogenesis and helps muscle and adipose tissues to take glucose from blood for their metabolism. Thus BG level is lowered. With these mechanisms, glycemic homeostasis is maintained by the presence of these two hormones (glucagon and insulin) in healthy individuals. When these mechanisms are impaired over long periods of times, the healthy individual becomes afflicted by diabetes mellitus.

There are two main types of diabetes: Type 1 and Type 2 diabetes. Type 1 Diabetes Mellitus (T1D) is caused by inadequate insulin production due to beta cell dysfunction of the pancreas. The body's inability to respond properly to endogenous insulin because of insulin resistance or decreased insulin sensitivity with or without insufficient endogenous insulin is classified as Type 2 Diabetes Mellitus (T2DM). The type of diabetes that can occur in women during pregnancy period is known as gestational diabetes, and another type of glucose impairment can happen to critically ill patients or patients in ICU (intensive care unit) temporarily because of hyperglycemia.

1.2 Diabetes and Glycemic Regulation

The complete lack or insufficient amount of endogenous insulin for an extended period of time causes diabetes. Diabetes is a metabolic disorder that affects the body's ability to regulate glucose concentration in blood resulting in high or low BG concentration. In T1D, improper metabolic response to glucose (with or without inadequate insulin production by the pancreas) can cause the supranormal plasma glucose concentration. T1D patients' response to insulin is normal without loss of insulin sensitivity. This is also known as insulin dependent diabetes mellitus (IDDM). In T2DM, also known as non-insulin dependent diabetes mellitus (NIDDM), in which the very high BG values are a result of insulin resistance. In the gestational diabetes, pancreas can produce normal insulin but it cannot produce extra insulin to counteract the interfering effect of other hormones produced by placenta (placenta is to provide nutrition from mother to the embryo) and the pancreas does not have persistent malfunction. These hormones hinder the body ability to respond insulin properly and it causes insulin resistance and thus hyperglycemia. The critically ill patients or patients in ICU experience stress induced hyperglycemia even if they do not have any past history of diabetes. Other factors such as presence of hypertension, cortisone, steroids and pancreatic disease also results in hyperglycemia.

High BG value results in excessively sweet urine (glycosuria) as the renal clearance (kidney excretes plasma glucose into urine) starts when BG is

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above 190~200mg/dL (also known as renal threshold). It leads to polyuria (frequent urination) and polydipsia (increased thirst) and these are well-known common symptoms of diabetes. It can lead to the cell dehydration, and the increased fluid intake only cannot cure the disease because the whole mechanism is regulated with the hormones and other mechanisms and thus medication is needed. For Type 1 diabetes, external insulin is required to regulate the BG regulation mechanism because of inadequate endogenous insulin. For Type 2 diabetes, a variety of medication, dietary changes and exercise are suggested to improve insulin sensitivity. However, if the medication only cannot lower the very high BG value, external insulin may be required for such patients. The same treatment as in T2D is required for the treatment of gestational diabetes and sometimes external insulin is required to lower the BG level. The intensive insulin infusion is suggested for the control of hyperglycemia in ICU patients.

This thesis focuses on the control of BG concentration in Type 1 diabetes. Type 1 diabetes and glycemic control are discussed further in the next section.

1.3 Type 1 Diabetes and Glycemic Control

T1D is an autoimmune disease defect in pancreas and can happen in both children and in adults. In the pancreas (specifically in the insulin producing beta cells) of those patients, T-cells mediated autoimmune attack by the virus destroyed the pancreatic beta cells and thus pancreas is unable to produce any or sufficient insulin (Wikipedia, 2009a). Exogenous insulin is needed by continuous infusion and/or by bolus for controlling plasma glucose concentration to the levels seen in healthy individuals (70~126mg/dL (=3.9~7mmol/L) in fasting condition and slightly upward levels, 140mg/dL (7.6mmol/L) is expected 2 hours after meals). If insulin is supplied in excess, BG concentration would go below normal (<70mg/dL), and results in a condition known as *hypoglycemia*. The healthy individuals start suffering the symptoms of hypoglycemia when BG goes below 55mg/dL (3mmol/L). On the other hand, if not enough insulin is supplied, the blood glucose

concentration would elevate and persistently stay beyond 180mg/dL (10mmol/L) resulting in a condition known as *hyperglycemia*. Both hypo- and hyper-glycemia can be harmful to an individual's health. The effects of hypoglycemia are critical on short-term basis, and can lead to diabetic coma and possibly death. If insulin amount is very low or insufficient, the breakdown of fatty acids and amino acids occurs and it can lead to ketoacidosis. Sustained hyperglycemia can result in the long-term complications including microvascular diseases such as nephropathy, retinopathy, other tissues damage, and macrovascular diseases such as coronary heart disease, cerebrovascular disease, peripheral vascular disease and neuropathy.

According to the Diabetes Control and Complications Trial (DCCT) (DCCT, 1993), BG should be controlled as close as possible to the normal range. DCCT set the intensive goal of maintaining BG concentration within 70~120mg/dL pre-meal condition and less than 180mg/dL in post-meal condition. It was found that setting intensive goal can lower the rate of microvascular complications in diabetes patients. The American Diabetes Association (American Diabetes Association, 2006) recommends maintaining BG level between 90~130mg/dL (5~7.2mmol/L) in preprandial condition and less a 180mg/dL (10mmol/L) in postprandial condition.

For T1D patients, self-management is required to adjust the insulin according to their BG level so as to regulate BG as closely as possible to mimic the profile seen in healthy individuals. To do this round the clock and in an effective manner, automatic closed loop control has been acknowledged as the best choice. For this purpose, various mathematical models have been developed to represent the glucose dynamics in type I diabetics. Several control algorithms have also been proposed to control the BG level within the acceptable range. While some of these works have been evaluated in clinical trials, many are not. Accurate quantification and understanding of BG dynamics (in relation to infused insulin, meals, exercise and other disturbances) in the form of a mathematical model is crucial in achieving tighter glucose regulation through automatic control schemes.

To cope with different patient characteristics as well as time-varying characteristics in any particular patient, advanced strategies would be required. On the hardware front, glycemic control is still limited by the infrequent nature of glucose sensing but rapid improvements have happened in this front recently (Oliver et al., 2009). The vaccine and stem cell replacement are in investigations and are not fully resolved the problems till date. The effective control of the diabetes patient should lead to a titration where the glucose regulation mimics the healthy person's response. This can be achieved by developing a control algorithm that can cope well with the inter- and intra-patient variability, various situations of a patient such as exercise, anxiety, sickness and the constraints on insulin infusion rate and frequency of BG concentration measurement.

Before going into the motivation and scope of the present work, let us take a quick look at insulin action and insulin analogs in Section 1.4.

1.4 Insulin Action and Insulin Analogues

Insulin plays an important role in our body metabolism. Endogenous insulin (pancreatic insulin) is continuously regulated in the circulation and it changes according to the BG concentration within seconds. It is secreted into circulation through portal vein and about 40% to 80% is utilized by the liver. Then it is diluted into the systemic insulin pool (Young and Koda-Kimble, 2000; Pørksen, 2002), and is diffused as unbound (free insulin) in plasma. In glucose regulation, insulin binds the receptor on the cell wall and translocates the vesicles containing GLUT-4 (glucose transporter 4) to the plasma membrane where the diffusion of the glucose (and amino acid) to the cell takes place. Then it activates the glycogenesis (glycogen synthesis) in peripheral and adipose tissue, glycolysis, fatty acid synthesis and esterification. It promotes DNA replication and protein synthesis in the body. It decreases the undesired proteolysis (hydrolytic breakdown of proteins), lipolysis (hydrolysis of lipids), gluconeogenesis (the formation of glucose from non-carbohydrate sources) and autophagy (self-digestion by a cell within the same cell by enzymes). In addition, it facilitates the arterial blood flow by relaxing the arterial wall

muscle. If insulin is lacking, the blood flow will be reduced because of muscle contraction. After binding the receptor and effected its actions, insulin is degraded by the insulin degrading enzyme and by liver cells or is released back to the extracellular compartment. The endogenous insulin degrades within approximately one hour after entering into circulation.

For the benefit of people who lack adequate endogenous insulin, there are many insulin analogs produced by synthetic routes. These analogs can function in place of endogenous insulin and provide glycemic control. They are injected or infused exogenously by means of intraperitoneal (i.p) or subcutaneous (s.c) or intravenous (i.v) or intramuscular (i.m) routes which are all invasive. They can be administered non-invasively through oral, nasal, pulmonary or transdermal membrane. The short-acting insulin or rapid-acting insulin such as insulin lispro contains monomers and dimers and are soluble more rapidly after injection. Some exogenous insulin analogs are made with hexamer molecules and must undergo dissociation into absorbable dimers and monomers at the injection sites such as regular insulin. The long-acting insulin such as NPH starts its action more slowly than soluble insulin but its effect lasts for longer.

The exogenous insulin delivery is affected by external factors such as mode of insulin infusion (routes) and type of insulin. The exogenous insulin is degraded at liver, muscle and mostly at the kidney (30~80%). Insulin infusion is also the only one therapy that is currently used to control diabetes in ICU patients. According to the literature, tight glucose control effected via exogenous insulin infusion can reduce ICU patient mortality by as much as 43% (Van den Berghe, 2003).

1.5 Motivation for and Scope of the Present Work

This work is motivated by the fact that lowering BG for hyperglycemia prone patients reduces the risk of eye disease, kidney failure and nerve disease by 76%, 50% and 60% respectively (DCCT, 1993). It has been noted by Boutayeb and Chetouani (2006) that a study involving over 5000 non-insulin dependent patients from 23 centers from all parts of England, Scotland and

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Northern Ireland showed that complications of diabetes can be prevented by better control of BG and blood pressure.

The variability in glucose metabolism, insulin sensitivity, effects of other medical conditions are quite large among different patients and within the same patient (over time) leading to inter- and intra-patient variability. No single control algorithm may be able to handle such large uncertainties and it may be useful to classify patients into appropriate classes and apply tailored control algorithms to each of the classes. The classification should possibly be done with a simple diagnostic test. It would be worthwhile to develop a control scheme that is tailored to different patients groups where the patient "group" can be described using a simple diagnostic test.

The insulin infusion rate can be measured more frequently than the measurement of BG leading to a multirate system. Glucose sensor technology is still in development and we are unable to monitor the BG as frequently as we are able to measure insulin infusion rate. It would be interesting to obtain a fast-rate model from multirate patient data. The fast-rate model will ensure better control of the BG level by frequent manipulation of insulin infusion.

The main objectives of this work are to develop effective control algorithms for blood glucose level regulation in type 1 diabetic patients. These algorithms must cope well with the inter- and intra-patient variability. The control algorithms studied here include simple protocol based control, tailored protocol based control with patient classification into sub-groups, linear robust controller and linear robust multirate control. With these objectives, the organization of the thesis is presented next.

1.6 Organization of the Thesis

A review of mathematical models developed for T1D patients and the controller algorithms that are currently employed for controlling BG concentration and other related topics are discussed in Chapter 2. The unique properties of the three chosen diabetes models and the generation of several simulated patients from these three models are described in Chapter 2 also.

Introduction and application of a current hospital protocol (Yale Insulin Infusion Protocol, YIIP) to a cohort of diabetes patients forms the substance of Chapter 3. The classification of patients using the method of principal component analysis (PCA) to data collected from a diagnostic test and tailoring of YIIP for the different patient classes are described in Chapter 4. Validation of the above methodology with other patient models is also demonstrated in Chapter 4. Evaluation of a robust linear controller (LMEC) that can handle the parametric uncertainty explicitly in the three different models and on several simulated "perturbed" patients is demonstrated in Chapter 5. Use of multirate system identification in conjunction with LMEC controller to diabetic patient models (i.e., developing a new algorithm that uses multirate data and multirate system identification and the resulted identified model is used in a linear controller to regulate glucose levels in diabetic patients with more frequent sampling interval in seconds which is closely compatible to human physiological system) is described in Chapter 6. Finally, the conclusions of this research study and proposed future works are outlined in Chapter 7.

Chapter 2

Modeling and Glycemic Control in Type 1 Diabetes Patients

To achieve effective BG control in T1D patients, the artificial pancreas has been proposed (Hovorka et al., 2006). The artificial pancreas involves a continuous glucose sensor to measure the patient's blood glucose (BG), a control algorithm that uses this BG measurement and the target blood glucose value (set point) to determine the appropriate rate of insulin dosage, and an insulin infusion pump to deliver the exact amount of exogenous insulin via the subcutaneous or intravenous route. A review of electrochemical glucose sensors and their application in diabetes management is available in the recent literature (Heller and Feldman, 2008). Current progress in glucose sensor technology is reviewed by Oliver et al. (2009). Insulin pump systems that can store and precisely infuse the required amount of insulin automatically are now available in the market. Currently available insulin pumps, continuous glucose monitoring and the requirement to integrate these systems into closed-loop control are reviewed by Aye et al. (2010). The focus of this chapter is not on the hardware components of the artificial pancreas system but on the soft components such as the mathematical models and the control algorithms employed for BG control in TID patients.

2.1 Mathematical Models

For advanced control applications, a mathematical model that represents the behavior of the physical system as closely as possible is very vital. Mathematical models of biomedical systems are applicable for other purposes such as *in silico* diagnostics test and development and testing of treatment regime (Zheng et al., 2007). Many mathematical models describing the effects of insulin and glucose intake on blood glucose concentration in type 1 diabetes patients have been developed and reported in the literature. These T1D models mainly involve the glucose subsystem, insulin subsystem and/ or meal subsystem. These models do not involve any term(s) related to

endogenous insulin secretion; instead, the pharmacodynamics/ pharmacokinetics of exogenous insulin are involved. In addition to phenomenological models, data-driven models are also available. The latter models are usually obtained based on the best parameter fit to patient data with well-known model structures such as the first order plus time delay structure or one of the standard time series models (autoregressive with exogeneous inputs (ARX), autoregressive moving average with exogeneous inputs (ARMAX), output error (OE), Box-Jenkins (BJ) etc.). Hybrid models that combine the above two model classes are also in vogue. Section 2.1.1 describes some T1D models that are popular in the literature and section 2.1.2 familiarizes the reader with some of the commonly employed meal disturbance models.

2.1.1 Models for T1D Patients

The first diabetes model was proposed by Bolie in 1961 (Bolie, 1961) and another one was proposed shortly thereafter by Ackerman et al. (1965). The models developed since then can be classified into metabolic species (e.g., glucose, insulin)-based compartmental model and organ-based compartmental models. In the former type of model, the whole body is represented by compartments (e.g., glucose compartment, insulin compartment) and the metabolic species in each compartment is assumed to be homogeneous. In organ-based compartmental models, each major organ is represented as a compartment and metabolic-species balances are written for each compartment. The organ-based compartmental models are in general more detailed than the metabolic species-based compartmental models and consequently involve more parameters.

Compartmental modeling started with the work of Bergman et al. (1981) whose model has come to be known as the 'minimal' model. Bergman's model includes glucose and insulin interaction terms so that it acknowledges that glucose changes are effected by insulin. The nonlinearity of the glucose dynamics in the minimal model is found to closely reflect the true human glucose metabolism. Insulin effects on liver and periphery glucose utilization are modeled as constant terms, and they affect both insulin

appearance and disappearance in the remote insulin compartment. The delay of insulin action and other complex phenomena are lumped in a remote compartment. Glucose effectiveness and insulin sensitivity index (ISI) can be estimated from the parameters of this model. It is to be noted that the ISI indicates how the BG glucose responds to insulin - a very low ISI means a very high resistance to insulin. Generally, high ISI is desirable for controlling the BG level.

Cobelli et al. (1982) incorporated the nonlinear nature of glucose, glucagon and insulin compartments (model for insulin compartment is built based on the pancreatic function) using suitable nonlinear ordinary differential equations. The distinct feature of this model is that it takes into consideration the glucagon effect. This work marked the start of inclusion of glucagon effect into diabetic patient models and led to more comprehensive models (beyond the minimal model). The model by Cobelli et al. is also based on mass balance of each metabolic species and physiological knowledge of human body with threshold functions for biological pools. This model was mainly developed for intravenous glucose infusion and intravenous glucose tolerance test (IVGTT) (Dalla Man et al., 2007).

The model developed by Hovorka et al. (2002) is an extension of the minimal model but insulin action on glucose distribution/transport, disposal and production are differentiated. In a later work by Hovorka et al. (2004), the model was improved to enable direct access of plasma insulin concentration. In their earlier model, only the remote insulin compartment was accessible. These two models are based on mass balances based on the physiological knowledge prevalent at the time. Hovorka et al. (2002) took nonaccessible compartment of both insulin and glucose as well as meal digestion into consideration. Wilinska et al. (2005) further modified the subcutaneous insulin infusion mode of this model by including fast and slow insulin absorption channels and local insulin degradation – this enables the study of glycemic control via subcutaneous insulin infusion. However, the incorporated intrapatient variability in this model may need to be improved further (Wilinska and Hovorka, 2009).

Fabietti et al. (2006) developed a model for type 1 diabetes in which exogenous insulin infusion can be administered through intravenous or subcutaneous route. This model can also be regarded as an extension of the minimal model. Because an interstitial compartment is included, the interstitial glucose concentration is available for this model. The model includes a term for renal clearance and another term for intravenous glucose infusion. This makes the model convenient for simulating intravenous glucose tolerance test (IVGTT). This model is also compatible with subcutaneous glucose sensor and subcutaneous insulin infusion device. In addition, the well-known circadian insulin sensitivity variation is accounted for and the model can therefore represent the dawn phenomena (elevation of blood glucose concentration in the morning hours) commonly experienced by diabetic patients. In addition, the more reasonable mixed meal model according to Arleth et al. (2000a, 2000b) is implemented.

Another type of organ-based compartmental modeling was described by Parker et al. (2000). They developed a more detailed diabetes model - a 19th order model characterized by nonlinear differential equations based on physiological knowledge and the work of Sorensen (1985). In this model, the human body is divided into six compartments. Glucose, insulin balance and kinetics are modeled by ordinary differential equations describing the nature of the interactions between them. This model also includes the effect of glucagon and employs threshold functions for hepatic glucose production, hepatic glucose uptake, peripheral glucose uptake, and kidney clearance. The model contains 47 physiological parameters making it less amenable for parameter estimation and controller design (for artificial pancreas) but is more comprehensive (while not necessarily more accurate) than many other models available in the open literature.

The most comprehensive model of the biochemical pathophysiological processes associated with type 1 diabetes mellitus would be the Archimedes diabetes model elaborated by Eddy and Schlessinger (2003a). This model consists of a network of interrelated variables including biological (mechanism of diabetes), clinical and administrative details linked by differential equations describing the nature of the interactions among the variables. The biological

variables used and the relation between them are selected by the investigators based on the current knowledge of biological systems. It includes severity of symptoms and the presence of vascular complications. The full Archimedes model includes the important factors of real health care system including health care personnel, facilities, equipment, supplies, policies and procedures, regulations, utilities and cost. According to Eddy and Schlessinger (2003b), simulation of a clinical trial takes about 10 min using 250 PCs with this model. It can be concluded that this model is computationally burdensome. The clinical validation of this model gives statistically insignificant results compared with clinical outcomes (Boutayeb and Chetouani, 2006). The limitations of this model are that the functional forms of the equations are given but values of the variables and parts of the model for micro and macro-vascular complication are not provided in the open literature.

2.1.2 Meal Disturbance Models in Diabetes Patient Models

Inclusion of a suitable meal ingestion model to the model describing the glucose and insulin dynamics is essential for any meaningful studies to be conducted on the *in silico* diabetes patient model. In this section, the intention is to provide a description on the most commonly utilized meal models. The mathematical description of these meal models are presented with their associated T1D model in section 2.3.

The meal model of Fisher (1991) is modeled for glucose only and used an exponential function to represent the glucose appearance in glucose compartment from gut absorption for normal subjects. Such modeling is more suitable for glucose clamps such as oral glucose tolerance test (OGTT) and is mostly associated with Bergman's minimal model. The meal model of Lehmann and Deutsch (1992) is built with trapezoidal functions and reflects the saturation of gut absorption rate. It is also modeled for pure carbohydrate (CHO), and has been mostly used in their later studies and by Parker et al. (1999). Hovorka et al. (2002) employed their own meal model, which includes exponential decay function (to represent the decay after the time-of-maximum glucose appearance rate in the accessible glucose compartment) and two identical transfer rates representing two-compartment chain. The innovation of

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this model is the inclusion of bioavailability of ingested carbohydrate. The meal models of both Lehmann and Deutsch (1992) and Hovorka et al. (2002) were validated on the plasma glucose concentration and involved physiological refinement (Dalla Man et al., 2007).

Arleth et al. (2000b) developed a mixed meal (presence of different nutrients) model for glucose absorption from ingested meal (with variable rate). Arleth et al. (2000a, b) modeled the ingested meal with three subcategories of carbohydrates viz. sugar, fast absorption starch and slow absorption starch with different absorption rates. This model is more realistic, and is used by Fabietti et al. (2006) in their diabetic patient model.

Different meal models can account for inter-patient variation. Thus, the T1D model developed by Fabietti et al. (2006) (with Arleth et al, 2000a & 2000b meal model) will be used primarily, and other Type 1 diabetic models with their associated meal models will be employed where necessary.

2.2 Uncertainty Issues in Diabetes Patient Models

The diabetes patients themselves are associated with many uncertainties such as the well-known intraday circadian insulin sensitivity, illness, stress experienced by them, presence of growth hormones and cortisone, extent of exercise etc.; all of these are considered as intra-patient variability. The differences between diabetes patients such as those based on race, age, region, eating habits, life style, insulin sensitivity, rate of insulin transportation, utilization & disposal, severity of the disease, and presence and complications arising out of other diseases all contribute to inter-patient variability. In addition, most of the developed diabetic patient models represent the nominal (average) patient and consequently are associated with the patient-model mismatch (i.e., the difference between the actual patient and the model).

These variations can be described using uncertainty bounds in respective parameters for a cohort of patients. The bounds for the parameters that vary can be obtained from the literature or can be assumed to be within a

certain percentage of their nominal values. For example, Parker et al. (2000) considered parameters in their model to vary anywhere in the range of ±40% (for some parameters) or ±20% (for other parameters) from their nominal values. This range also ensured non-negative metabolic response of the model equations to standard meal inputs. The set of highly sensitive parameters is chosen using parametric sensitivity analysis. The cohort of virtual patients for control performance studies are then obtained by employing different combinations of the highly sensitive parameters within their range (Parker et al., 2000; Ramprasad et al., 2004).

2.3 Chosen Diabetes Patient Models and Associated Meal Models

From the various diabetes patient models available in the literature, the 3rd order nonlinear ODE model of Bergman et al. (1981), the 19th order nonlinear ODE model of Parker et al. (2000), and the 5th order nonlinear ODE model of Fabietti et al. (2006) are chosen for this study. The models and the reasons for choosing them are described below.

2.3.1 Bergman model

Bergman's minimal model is chosen for its simplicity (few states) and because it has a very small number of parameters. The original model parameters were obtained from the data collected on healthy subjects. To mimic the response characteristics of diabetes patients, Lam et al. (2002) used different parameter values ($p_1 = 0$, $p_2 = 0.025$, $p_3 = 0.000013$). The parameter representing the endogenous insulin secretion (p_1) is set equal to 0 because there is no endogenous insulin secretion in T1D patients. The other approach by Lynch and Bequette (2002) estimates the parameters of the diabetic minimal model by fitting the responses of the Parker et al.'s diabetes patient model (1999a). The parameter values obtained by this approach are used in this study.

Glucose compartment: $\dot{G} = -p_1 G - X(G + G_B) + P(t)$ (2.3.1.1)

Insulin compartment: $\dot{I} = -n(I + I_B) + u(t)/V_I$ (2.3.1.2)

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Insulin remote compartment that lumps delays and other complexities is modeled as:

$$\dot{X} = -p_2 X + p_3 I \tag{2.3.1.3}$$

where,

G = concentration of the plasma glucose above the basal level (mmol/L)

G_B = basal level for plasma glucose concentration (mmol/L), (= 4.5 mmol/L typically)

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

I = concentration of the plasma insulin above basal level (mU/L)

I_B = basal level for plasma insulin concentration (mU/L), (= 15 mU/L typically)

$P(t)$ = exogenous glucose infusion rate (mmol/L/min)

$u(t)$ = exogenous insulin infusion rate (mU/L/min)

n, p_1, p_2 = subject dependent model parameters (min^{-1}) (5/54 min^{-1}, 0.028735 min^{-1}, 0.028344 min^{-1} respectively)

p_3 = subject dependent model parameter (L/mU/min^2), (5.035×10^{5}L/mU/min^2)

V_I = insulin distribution volume (L), (12 L)

Fisher Meal Model

The Fisher meal model is closely associated with the Bergman model. The exogenous glucose infusion rate $P(t)$ is replaced by a term representing the Fisher meal model. The original idea of constructing this model is to represent the oral glucose test of a normal subject in which BG rises up to the maximum glucose peak after 30 min of food intake and then falls to the basal level within 2 to 3 hours. For this reason, the exponential function is used with the model parameter values that can represent the above mentioned behavior of glucose appearance rate from gut absorption (Fisher, 1991).

$$P(t) = \beta e^{(-kt)}, \, t \geq 0 \tag{2.3.1.4}$$

where,

$\beta = 0.5$ and $k = 0.05$.

2.3.2 Parker Model

This model is based on the work of Sorensen (1985) and comprises of 19 ordinary differential equations. The equations and nominal values of parameters are listed in Table 1. The key parameters and their uncertainty range have been provided in Parker et al. (2000). The meal disturbance model of Lehmann and Deutsch (1992) is incorporated into their model. The model (Parker et al., 2000) has been shown to accurately model the glucose dynamics of a healthy subject; their model can be simulated with null pancreatic secreted insulin to mimic a diabetic patient but has its shortcomings as pointed out by Farmer et al. (2009). The Parker model shows only small excursions in blood glucose values even for a significant glucose meal challenge. This makes it easy to control the "Parker" patient with proportional only control (Farmer et al., 2009) or by Proportional Derivative controllers (Ramprasad et al. 2004). Despite this shortcoming, we chose to study the performance of our developed algorithms on this model because it can represent certain patient population.

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

$$\dot{G}_B^C = (G_H^C - G_B^C)\frac{q_B}{v_B^c} - (G_B^C - G_B^T)\frac{v_B^T}{T_B v_B^c} \tag{2.3.2.1}$$

$$\dot{G}_B^T = (G_B^C - G_B^T)\frac{1}{T_B} - \frac{\Gamma_{BU}}{v_B^T} \tag{2.3.2.2}$$

(subscript B denotes brain)

$$\dot{G}_H^C = (G_B^C q_B + G_L^C q_L + G_K^C q_K + G_P^C q_P + G_H^C q_H - \Gamma_{RBCU})\frac{1}{v_H^c} \tag{2.3.2.3}$$

(subscript H denotes hearts and lungs)

$$\dot{G}_S^C = (G_H^C - G_S^C)\frac{q_s}{v_S^C} + \frac{\Gamma_{meal}}{v_S^C} - \frac{\Gamma_{SU}}{v_S^C} \tag{2.3.2.4}$$

(subscript S denotes gut (stomach/intestine))

$$\dot{G}_L^C = (G_H^C q_A + G_S^C q_s - G_L^C q_L)\frac{1}{v_L^C} + \frac{\Gamma_{HGP}}{v_L^C} - \frac{\Gamma_{HGU}}{v_L^C} \tag{2.3.2.5}$$

(subscript L denotes liver)

$$\dot{G}_K^C = (G_H^C - G_K^C)\frac{q_K}{v_K^C} - \frac{\Gamma_{KE}}{v_K^C} \tag{2.3.2.6}$$

(subscript K denotes kidney)

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$$\dot{G}_P^C = (G_H^C - G_P^C)\frac{q_P}{v_P^C} - (G_P^T - G_P^C)\frac{v_P^T}{T_P^G v_P^C} \qquad (2.3.2.7)$$

$$\dot{G}_P^T = (G_P^C - G_P^T)\frac{1}{T_P^G} - \frac{\Gamma_{PGU}}{v_P^T} \qquad (2.3.2.8)$$

(subscript P denotes periphery (muscle/adipose tissue))

(superscript C denotes capillary space)

(superscript T denotes tissue space)

where,

$$k_B^C = G_B^C \frac{v_B^T}{T_B} \quad \text{and} \quad k_B^T = G_B^T \frac{v_B^T}{T_B}.$$

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

$$\Gamma_{BU} = 70 \qquad (2.3.2.9)$$

$$\Gamma_{RBCU} = 10 \qquad (2.3.2.10)$$

$$\Gamma_{SU} = 20 \qquad (2.3.2.11)$$

$$\Gamma_{HGP} = 155\, A_{IHGP}[2.7\tanh(0.388N) - A_{NHGP}]$$
$$[1.425 - 1.406\tanh\{0.6199\,(\frac{G_L^C}{101} - 0.4969\,)\}] \qquad (2.3.2.12)$$

$$\dot{A}_{IHGP} = \frac{1}{25}\left[1.2088 - 1.138\tanh\{1.669(\frac{I_L^C}{21.43} - 0.8885)\} - A_{IHGP}\right] \qquad (2.3.2.13)$$

$$\dot{A}_{NHGP} = \frac{1}{65}[\frac{2.7\tanh(0.388N) - 1}{2} - A_{NHGP}] \qquad (2.3.2.14)$$

$$\Gamma_{HGU} = 20 A_{IHGU}[5.6648 + 5.6589\tanh\{2.4375(\frac{G_L^C}{101} - 1.48)\}] \qquad (2.3.2.15)$$

$$\dot{A}_{IHGU} = \frac{1}{25}[2\tanh(0.549\frac{I_L^C}{21.43}) - A_{IHGU}] \qquad (2.3.2.16)$$

$$\Gamma_{KE} = 71 + 71\tanh[0.011(G_K^C - 460)], \qquad \text{for } G_K^C < 460 \qquad (2.3.2.17)$$
$$= 0.872 G_K^C - 330, \qquad \text{for } G_K^C \geq 460$$

$$\Gamma_{PGU} = \frac{35 G_P^T}{86.81}[7.035 + 6.51623\tanh\{0.33827(\frac{I_P^T}{5.304} - 5.82113)\}] \qquad (2.3.2.18)$$

The insulin sub-model mass balances are given by

$$\dot{I}_B^C = (I_H^C - I_B^C)\frac{Q_B}{V_B^C} \qquad (2.3.2.19)$$

$$\dot{I}_H^C = (I_B^C Q_B + I_L^C Q_L + I_K^C Q_K + I_P^C Q_P - I_H^C Q_H + \Gamma_{IVI})\frac{1}{V_H^C} \qquad (2.3.2.20)$$

$$\dot{I}_S^C = (I_H^C - I_S^C)\frac{Q_S}{V_S^C} \qquad (2.3.2.21)$$

$$\dot{I}_L^C = (I_H^C Q_A + I_S^C Q_S - I_L^C Q_L)\frac{1}{V_L^C} + \frac{\Gamma_{PIR} - \Gamma_{LC}}{V_L^C} \qquad (2.3.2.22)$$

$$\dot{I}_K^C = (I_H^C - I_K^C)\frac{Q_K}{V_K^C} - \frac{\Gamma_{KC}}{V_K^C} \qquad (2.3.2.23)$$

$$\dot{I}_P^C = (I_H^C - I_P^C)\frac{Q_P}{V_P^C} - (I_P^C - I_P^T)\frac{V_P^T}{T_P^I V_P^C} \qquad (2.3.2.24)$$

$$\dot{I}_P^T = (I_P^C - I_P^T)\frac{1}{T_P^I} + \frac{\Gamma_{SIA} - \Gamma_{PC}}{V_P^T} \qquad (2.3.2.25)$$

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

$$\Gamma_{LC} = F_{LC}(I_H^C Q_A + I_S^C Q_S + \Gamma_{PIR}) \qquad (2.3.2.26)$$

$\Gamma_{PIR} = 0$, as there is no pancreatic insulin release $\qquad (2.3.2.27)$

$$\Gamma_{KC} = F_{KC} I_K^C Q_K \qquad (2.3.2.28)$$

$$\Gamma_{PC} = \frac{I_P^T}{\dfrac{1-F_{PC}}{F_{PC}}\dfrac{1}{Q_P} - \dfrac{1}{V_P^T/T_P^I}} \qquad (2.3.2.29)$$

The mass balance of glucagon is modeled as follows:

$$\dot{N} = (\Gamma_{PNR} - N)\frac{F_{PNC}}{V_N} \qquad (2.3.2.30)$$

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

$$\Gamma_{PNR} = [1.3102 - 0.61016\tanh\{1.0571(\frac{I_H^C}{15.15} - 0.46981)\}]\times$$
$$[2.9285 - 2.095\tanh\{4.18(\frac{\Gamma_{KC}}{91.89} - 0.6191)\}] \qquad (2.3.2.31)$$

The above model consists of 47 physiological parameters: values of 35 parameters are given 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: Parameter Values in Parker et al.'s (2000) Diabetic Patient 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

Table 2.2: Nominal Values for Uncertain Parameters in Parker et al.'s (2000) 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	

Lehmann and Deutsch Meal Model

Lehmann and Deutsch (1992) modeled the gut glucose absorption from meal taken by the T1D patients. This model considered the saturation of gastric emptying rate of carbohydrates from the stomach during intestinal adsorption. The shape of the curve depends on the consumed carbohydrates. It is triangular if the amount of ingested carbohydrate is less than a critical value Ch_{crit}. The shape of the curve is trapezoidal if the amount of ingested carbohydrate is greater than or equal to Ch_{crit}.

$$Ch_{crit} = [(Tasc_{ge} + Tdes_{ge})\ Vmax_{ge}]/2 \qquad (2.3.2.32)$$

$$Tasc_{ge} = Tdes_{ge} = Ch\ /\ Vmax_{ge} \qquad (2.3.2.33)$$

$$Tmax_{ge} = [Ch - \tfrac{1}{2}\ Vmax_{ge} * (Tasc_{ge} + Tdes_{ge})]\ /Vmax_{ge} \qquad (2.3.2.34)$$

The gastric emptying rate for meals containing carbohydrates greater than $Ch_{crit,}$ is

G_{empt} $= (Vmax_{ge}/Tasc_{ge})\ t$ $\qquad$ for $\qquad t < Tasc_{ge},$

$\qquad = Vmax_{ge};$ $\qquad\qquad$ for $\qquad Tasc_{ge} < t \le Tasc_{ge}+Tmax_{ge},$

$\qquad = Vmax_{ge}-(Vmax_{ge}/Tdes_{ge})\ (t-Tasc_{ge}-Tmax_{ge})$

$\qquad\quad$ for $Tasc_{ge} + Tmax_{ge\ \le}\ t < Tmax_{ge} + Tasc_{ge} + Tdes_{ge}$ and

$\qquad\qquad = 0$ for other t $\qquad\qquad\qquad\qquad (2.3.2.35)$

The absorption rate of glucose into the gut compartment is

$$\Gamma_{meal} = \frac{1}{60s+1}\,wf \qquad (2.3.2.36)$$

where,

$Tasc_{ge}$, $Tdes_{ge}$ = the rising and falling times of the curve (default values = 30 min). $Tasc_{ge}$ and $Tdes_{ge}$ are at their default values when carbohydrates ingestion is critical and cannot exceed the critical values.

Ch_{crit} = the critical value of ingested carbohydrates (10.8 g)

$Tmax_{ge}$ = the time of plateau for maximum carbohydrate ingestion rate

$Vmax_{ge}$ = the maximum gastric emptying rate (360 mg/min)

G_{empt} = the gastric emptying rate

wf = the wave form of the gastric emptying rate

2.3.3 Fabietti Model

Fabietti et al.'s (2006) model uses 3 equations for insulin dynamics: one equation each for intravenous insulin infusion, subcutaneous insulin infusion, and the remote insulin compartment. For glucose, two equations are used: one for interstitial glucose balance and another for intravenous glucose balance. This model embeds intrapatient variability (by including the well-known circadian insulin sensitivity variation), mixed meal characteristics and enables the use of both subcutaneous or intravenous insulin infusion and glucose sensor. This model implements the mixed meal model by Arleth et al.

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(2000a, 2000b). The mixed meal model includes three terms corresponding to classes of carbohydrates in mixed meals (viz. sugar, fast absorption starch, and slow absorption starch), and is presented below along with Fabietti et al.'s model.

The insulin sub-model is described as follows:

For plasma insulin compartment,

$$\dot{I} = \frac{1}{T_{xi}}(-I + K_i(V_{iv} + S)) \tag{2.3.3.1}$$

($I = \mu U / mL$, plasma insulin concentration)

For remote compartment, lumping some complex phenomena yields:

$$\dot{X} = \frac{1}{T_m}(-X + I) \tag{2.3.3.2}$$

($X = \mu U / mL$, equivalent insulin concentration in the remote compartment)

For the subcutaneous compartment:

$$\dot{S} = \frac{1}{T_i}(-S + V_{sc}) \tag{2.3.3.3}$$

($S = \mu U / h$, insulin flow from the subcutaneous to the plasma compartment)

The glucose sub-model is described as follows:

For plasma glucose compartment,

$$\dot{G} = -\frac{G}{T_{yg}} + \frac{Y}{T_{gy}} + \frac{1}{V_g}(-M_i + E_g + E_b + G_{iv}) - E_r \tag{2.3.3.4}$$

($G = mmol / L$, blood glucose concentration)

For the interstitial glucose, the dynamical equation is:

$$\dot{Y} = K_{yg}(\frac{G}{T_{yg}} - \frac{Y}{T_{gy}}) - K_{is}P_{circ}XY \tag{2.3.3.5}$$

($Y = mmol / L$, glucose concentration in the interstitial compartment)

where,
$$P_{circ} = 1 + A_c \sin(\frac{\pi t}{12} + P_c) \tag{2.3.3.6}$$

$$M_c = (t_{ini} + 24(\frac{P_c}{2\pi} - \frac{1}{4}))_{\bmod 24} \tag{2.3.3.7}$$

$$E_m = 0.117(0.87 + \tanh(0.0045(G - 175)) \tag{2.3.3.8}$$

$$E_r = \begin{cases} E_m & if \ E_m \geq 0 \\ 0 & else \end{cases} \tag{2.3.3.9}$$

$$E_g = A_g + A_s + A_m \qquad (2.3.3.10)$$

The ingestion rate R_i is filtered (Arleth et al., 2000b) to get

$$A_g(s) = (1 - F_s) \frac{16.6}{(s + 1.44)(s + 135)} R_i(s), \qquad (2.3.3.11)$$

$$A_s(s) = F_s(1 - F_m) \frac{467}{(s + 1.61)(s + 7.2)(s + 7.18)} R_i(s), \qquad (2.3.3.12)$$

$$A_m(s) = F_s F_m \frac{75.1}{(s + 0.466)(s + 5.54)(s + 5.86)(s + 6.43)} R_i(s). \quad (2.3.3.13)$$

The hepatic glucose uptake E_b is described as follows:

$$E_b = Q_r - Q_c \qquad (2.3.3.14)$$

Glucose release Q_r is expressed as:

$$E_{rel} = 840 / I - 10 \qquad (2.3.3.15)$$

$$Q_r = \begin{cases} 52.6 & if\ E_{rel} > 52.6 \\ E_{rel} & if\ 52.6 \geq E_{rel} \geq 0 \\ 0 & otherwise \end{cases} \qquad (2.3.3.16)$$

Glucose uptake Q_c is modeled as follows:

$$Q_g = \begin{cases} 3.64G - 15 & if\ 3.64G - 15 \geq 14 \\ 14 & otherwise \end{cases} \qquad (2.3.3.17)$$

$$Q_c = 0.25 E_g + Q_g \qquad (2.3.3.18)$$

This model was clinically validated on T1D patients and found to have satisfactory performance (Fabietti et al., 2006). The parameter values are provided in Table 2.3.

Table 2.3: Values of Parameters in Fabietti Model

T_{xi}	1.81 h
K_i	0.0101 mL/h
T_m	2.45 h
T_i	1.52 h (regular insulin) 0.152 h (insulin lispro)
T_{yg}	0.194 h
T_{gy}	0.194 h
K_{is}	0.0481 mL/μU/min
V_g	9.91 L
K_{yg}	0.952

2.4 Generating a Cohort of Patients for Robustness and Performance Studies

The dynamics of blood glucose can vary from one patient to another and indeed in the same patient over time. To reflect these realities, we allow the dominant parameters in the mathematical models to vary over certain range around their nominal values (e.g. ±40% variation around the nominal values). A cohort of patients can be generated by sampling from the space of parameter values – each unique combination of these parameters results in a virtual patient who is then used to test the robustness and performance of the control algorithms. Such an approach was followed in Parker et al. (2000) and Ramprasad et al. (2004).

In Parker et al.'s study (2000), parametric sensitivity analysis was performed and 8 parameters namely EIPGU-E_Γ, EIPGU-D_Γ, EGHGU-E_Γ, EGHGU-D_Γ, EGHGP-E_Γ, EGHGP-D_Γ, F_{LC} (FHIC), and F_{PC} were identified as being most influential in changing the blood glucose and insulin dynamics. These are the metabolic parameters described by the threshold functions (equation 2.4.1) in metabolic state equations 2.3.2.12, 2.3.2.15, 2.3.2.18, 2.3.2.26 and 2.3.2.29.

$$\Gamma_E = E_{\Gamma E} \{A_{\Gamma E} + B_{\Gamma E} \tanh[C_{\Gamma E} (x_i + D_{\Gamma E})]\} \qquad (2.4.1)$$

Subscript 'i' in equation (2.4.1) represents the state vector element involved in metabolic effect and subscript 'E' represents the specific effect within the model such as the effect of glucose on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU), the effect of insulin on peripheral glucose uptake (EIPGU), or the effect of hepatic insulin clearance (F_{LC}). The receptor and post-receptor terms ($D_{\Gamma E}$ and $E_{\Gamma E}$ respectively) reflect the inter- and intra-patient variability. These parameters are perturbed from their nominal values by ± 40% (± 40% is assumed here due to the lack of real physiological data) except for F_{LC} that is limited to ± 20% to guarantee non-negative glucose concentrations (Parker et al., 2000). However, these combinations of parameters do capture the broad range of physiology found in potential patients.

The nominal values of these eight parameters are presented in Table 2.2. In Parker et al. (2000) , sets of any three parameters were chosen from

these 8 parameters resulting in 56 combinations and each parameter set was varied over five levels (max, 0.5*max, no change (nominal value), min, 0.5*min) resulting in 125 possible variations and a total of 7000 variations (including duplicates). However, in Ramprasad et al. (2004), the sets of any three parameters are chosen from these 8 parameters, and the chosen parameter set was varied over three levels (max, no change (nominal value), min) resulting in $^8C_3 * 3^3 = 1512$ combinations. Patients with identical values for all eight parameters were removed and a set of 577 unique patients was generated. These 577 unique virtual patients will be used as test cases in this study.

In the Bergman model, n, p_1, p_2 and p_3 are patient dependent parameters. Here, $p1$, p_2 and p_3 are chosen as the dominant parameters and are perturbed by ±50% from their nominal values. The parameters in the chosen parameter set (p_1, p_2 and p_3) are varied in three permutations (max, no change (nominal value), min) and the combination of these three parameters resulted in $3^3 (= 27)$ virtual patients. These 27 virtual patients are used for testing the different control strategies employed in this study. The parameter n describes the body mass of average weight person, and is assumed not to vary for purposes of this investigation.

In Fabietti model, K_i, T_{xi}, T_m and K_{is} are chosen for the parametric variation study according to Fabietti et al (2006). The range of parameter variation is assumed to be ±40% in preliminary studies and ±50% or ±70% in later studies as a wider range of patient population is desired. A similar procedure as in Bergman model case is used to produce 81 virtual patients which are used for validation of the control algorithms considered in this study.

2.5 Automatic Control of Glycemic Regulation in Diabetes

Conventionally, an open loop approach such as continuous subcutaneous insulin infusion therapy is employed to manage T1D patients. Such methods require that finger pricks be performed anywhere between 3 to 7 times each day to get BG measurements followed by as many times of

insulin injection of insulin. This can place a heavy burden on patients. Automatic control strategies are now being studied for T1D glycemic regulation and are found to be promising. Many control algorithms for regulation of blood glucose concentration using insulin infusion are developed in the literature. These range from simple Proportional- Integral-Derivative (PID) controllers to nonlinear controllers to advanced model based control algorithms that are able to handle practical constraints in a formal manner (e.g. Model Predictive Control (MPC)). Some of the more significant works in this area are reviewed here.

2.5.1 Insulin Administration Routes Used by Control Algorithms

Automatic controllers have been proposed for administering insulin via the intravenous or subcutaneous route. Intravenous insulin delivery comes with inherently significant advantages such as: (1) reduction of the time delay that is experienced with subcutaneous insulin delivery (2) faster response to hyper- and hypo-glycemia, and (3) high potential for improving closed-loop performance (mainly as a result of the first two points mentioned). For these reasons, some studies have preferred to consider intravenous insulin administration. However, this type of administration is associated with catheter in-dwelling, dislodging from vein and occluding. To overcome these disadvantages, subcutaneous insulin administration is utilized in current technology and insulin pumps capable of subcutaneous administration are available in the market. Subcutaneous insulin infusion using these insulin pumps is associated with irritation and infections at the site of administration.

2.5.2 Control Strategies used for Glycemic Regulation in Diabetes

A comprehensive review of control algorithms that used intravenous route is available in Parker et al. (2001). Their work covers research reported until 1999. Here, we summarize the work on T1D control algorithms with particular emphasis on works reported from 1999 to 2009. A control algorithm that utilized intravenous insulin administration was first employed in the glucose controlled insulin infusion system (GCIIS) by Pfeiffer et al. (1974). The Biostator algorithm of Clemens (1979) used the feedback controller with a

dual infusion system (insulin and dextrose) to keep blood glucose concentration at user-specified values. A nonlinear proportional plus derivative controller with a five-point moving average of glucose measurements was used to reduce the effect of noisy glucose measurement. This algorithm may be appropriate for bedside implementation but the dual-reservoir system makes it somewhat difficult to use in mobile patients or for use on a regular basis. Individualization of the algorithm is also required to make it effective on patients.

Albisser et al. (1974) also used dual-channel system (insulin and dextrose infusion) in which insulin infusion is controlled by a projected value of blood glucose concentration that was computed using current measurement value of BG along with an exponential difference factor obtained from four-minute average rate of change of BG. Individualization of patient dependent parameters was also required for this algorithm. This algorithm was modified later by many researchers: Botz (1976) lessened the postprandial hypoglycemia by modification on the rate dependent component to be similar to absolute rate of BG and eliminated the dextrose infusion; Marliss et al. (1977) also lessened the postprandial hypoglycemia by modification on the rate dependent component but retained dextrose infusion for safety reason although it was rarely used. Kraegen et al. (1977) used weighted average rate of BG over previous four minutes to reduce the controller response to the noise. Fischer et al. (1978) developed a linear control algorithm based on the experimental data. Broekhuyse et al. (1981) compared the performance of these algorithms and concluded that significant further development in controller design was needed for BG regulation in diabetes patients. Bellomo et al. (1982) extended the static Biostator control algorithm by updating the patient model parameters using the experimental data by minimizing an integral of squared performance index in the glycaemia excess and insulin infusion rate but the results still showed significant hyperglycemic peaks. Furler et al. (1985) developed a control algorithm using a saturation function in which the insulin delivery rate was calculated as a function of current glucose measurement on the extended version of 'minimal model' but meal disturbance rejection was not considered.

Fischer et al. (1987) developed a control algorithm in which controller performance was markedly improved by customization to the specific patient; however, a one minute sampling interval was used for glucose measurements. Such fast sampling is not yet possible on a routine basis. Sorensen (1985) designed an internal model controller (IMC) based on a First Order Plus Time Delay (FOPTD) approximation of the 19th-order nonlinear model and obtained adequate BG regulation performance. However, significant performance degradation was experienced if patient parameters were uncertain. Parrish and Ridgely (1997) used state-dependent Riccati equations and designed a controller based on partial linearization but the tracking performance showed steady-state offset. Kienitz and Yoneyama (1993) used H_∞ control for BG regulation and the controller performance was found to be satisfactory for patients whose parameters were within the design set. However, over a wider range of parameter values, retuning of the controller parameters was required.

Optimal control theory has also been applied for blood glucose control in Type 1 Diabetic (T1D) patients. Swan (1982) used optimal control theory on the linear diabetic patient model in which the insulin delivery rate was a function of both the current insulin and glucose concentrations. The author focused on a diabetic patient with initial hyperglycemic condition; however, meal disturbance attenuation was not treated. Fischer and Teo (1989) tested various insulin infusion protocols with the objective to minimize the sum of squares of glucose tracking error. They considered a patient with initial hyperglycemia and also the regulation of blood glucose during meal consumption. Impulse control was found to be efficient if a good estimate of the rate of glucose entering into blood from intestinal absorption of ingested meal was available. Lim and Teo (1991) used impulse control for the same situations but included parameter uncertainty and reported their strategy to be robust and numerically stable.

Optimal control theory was applied on the 'minimal model' by Ollerton (1989) using the integral squared error (ISE) objective function to minimize the deviation of measured glucose value from the desired glucose value using 10 min and 180 min sampling intervals. However, their insulin profiles were physiologically unrealistic as they displayed high amplitude

sustained oscillations about the basal state. Fischer (1991) used optimal control theory with an ISE-type objective function on 'minimal model'. A secondary objective of minimizing the amount of insulin infusion for a patient with an initial hyperglycemic state was also considered. However, their controller was not robust to parametric uncertainty. It was also found that if the 180 min sampling interval was adopted, there was a very high chance and penalty of missing the inter-sample disturbance(s).

Parker et al. (1999) and Parker (1999) implemented MPC with and without state estimation for blood glucose control on the modified version of the Sorensen (1985) model. Constraints were set for insulin delivery rate and for the rate of change of insulin. The controller performance was found to be good for an unmeasured 50g meal disturbance. The nonlinear quadratic dynamic matrix control with state estimation (Gattu and Zafiriou, 1992) was also studied but the nonlinear controller did not show any significant improvement over the linear MPC. Parker et al. (2000) used the H_∞ framework on the 19-state nonlinear ODE model with the model uncertainty and evaluated the disturbance rejection criteria on 577 virtual patients (generated with parametric perturbations) and found that the performance of the H_∞ controller was comparable to that of the computationally-intensive MPC.

Camelia and Doyle (2001) used the IMC framework on the minimal model and on the Automated Insulin Dosage Advisor (AIDA) model of Lehmann and Deutsch (1992) but the inherent uncertainties in the model were not addressed. Lam et al. (2002) employed heavy derivative PD controller on Bergman's minimal model and tested the performance of the proposed controller on the simulated model (with multiple meals) with the available sensor sampling time. They tested the effect of three successive sensor failures and sensor lag. Promising results were obtained but oscillations and instability were observed in the presence of measurement noise.

Ruiz-Velazquez et al. (2004) used H_∞ controller for set point tracking of blood glucose in the presence of meal disturbance. Their work used Sorensen (1985) T1D model with Lehmann and Deutsch (1992) meal model. With their strategy, hyperglycemic condition was found to persist for a

significant amount of time leading to questions on the appropriateness of this controller.

Hovorka et al. (2004) employed an adaptive nonlinear model predictive controller (adaptive NMPC) to keep blood glucose in normoglycemic region. This controller used the model developed by Hovorka et al. (2002). Bayesian parameter estimation was used for re-estimating parameters at each control step with the objective of minimizing the weighted sum of squares of residuals (actual BG minus estimated BG) and a penalty due to the deviation from prior distribution of standardized model parameters in the learning window. The controller performance was validated clinically on a cohort of T1D patients who were fasting overnight. Subcutaneous insulin infusion was provided using an insulin pump with the input constraint on insulin infusion rate. Hovorka et al. used an intravenous glucose sampling interval of 15 min. The results were promising for blood glucose control during overnight fast but the performance of the controller on meal disturbance rejection criterion was not considered.

Ramprasad et al. (2004) employed PID controller for blood glucose control in T1D patients with different tuning methods and tested the robustness of these controllers for meal disturbance rejection scenarios (both single- and multiple-meal disturbance(s)). They obtained best results with Shen's (2002) tuning method, and demonstrated that hypoglycemia (<60mg/dL) could be avoided in 95% of a cohort of 577 virtual patients constituted from Parker et al.'s (1999) model. Frequent sampling was assumed for blood glucose measurement according to current glucose sensor technology (available at every 4 min).

Schlotthauer et al. (2005) used NMPC for the control of blood glucose in T1D patients. In their work, Multi-Layer Perceptron networks (MLP) were used for prediction of BG values. They used the Cobelli's (1983, 1998a, 1998b) model to represent the T1D patient, introduced linear first order dynamics for subcutaneous BG measurement and employed subcutaneous insulin injections for blood glucose control. Their results were quite promising in the context of meal disturbance rejection but they did not consider the presence of measurement noise or changing patient dynamics. Therefore,

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robustness and stability issues were left unresolved. A good review on the use of adaptive control for blood glucose control in T1D patients can be found in Hovorka (2005).

Canonico et al. (2006) used a novel PID-type controller named Proportional-Derivative-2nd derivative (PDD2) controller and tested it on virtual patients constituted from the T1D patient model of Fabietti et al. (2006). Better results were obtained compared with the standard insulin therapy of continuous subcutaneous insulin infusion (CSII) protocol. However, the authors did not mention the frequency of measurement of blood glucose concentration.

An overview of mathematical models and software tools employed in the study of glucose-insulin regulatory system can be found in Makroglou et al. (2006).

Ibbini (2006) proposed a PI-fuzzy logic controller (PI-FLC) for blood glucose control in T1D patients. While there is no need for precise mathematical models with this strategy, it appears to require considerable human expertise to make it work well. The simulation results showed smaller overshoot, shorter settling time, smaller area under the curve above the set point and acceptable BG limits in the presence of meal disturbances and in the presence of uncertain parameter values when compared to other controllers such as LQR (Optimal Linear Quadratic Regulators), PI, PID and FLC with frequent BG sampling. However, Ibbini (2006) did not consider the presence of measurement noise.

An advanced model based controller based on parametric programming was investigated by Dua et al. (2004). In their strategy, optimal insulin infusion was calculated off-line as an explicit function of the current blood glucose concentration of the patient. This has the advantage of using simple function evaluations for calculating insulin infusion in on-line applications. The Bergman 'minimal model' was used as a virtual patient with the model discretized with a sampling time of 5 minutes (to be compatible with current glucose sensor technology). The model predictive controller with the objective of minimizing a quadratic function of state variables and insulin infusion rate with constraints on glucose concentration (60~120mg/dL) and on

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insulin infusion rate (0~100mU/min) was solved using the multi-parametric quadratic programming (mp-QP). This work was later extended in Dua and Pistikopoulos (2007) where patient parametric uncertainty was taken into account. Two meal disturbance models (Fischer (1991), and Lehmann and Deutsch (1992)) were used. An asymmetric function that penalizes hypoglycemia more than hyperglycemia was also considered. Hypoglycemia was successfully avoided but high glucose peak values resulted with the meal disturbance. A tutorial and overview on the model-based constrained control of T1D is provided in Doyle et al. (2007).

Marchetti et al. (2008a) applied PID switching control in which bolus injection is applied for meal disturbances (prior to meals) and a switch to PID controller between meals. Time varying setpoint and measurement noise were considered in their work. A derivative filter was used to deal with sensor noise. Marchetti et al. (2008a) used the Hovorka model (2004) along with the update proposed by Wilinska et al. (2005). They also leveraged the switching strategy to tackle the tradeoff between hypoglycemia and the peak value of postprandial BG response. The robustness of their strategy was demonstrated by considering daily insulin sensitivity variation that may arise from physiological changes. Marchetti et al. (2008b) studied a kind of feedforward-feedback control using PID for T1D patients on the same model. They proposed the use of pre-prandial snack or insulin bolus or the reduction of BG setpoint before meal to reduce the BG peak of postprandial responses. The results of feedforward-feedback control strategy (5 min BG sampling) with PID controller were found to be promising even in the face of changes in insulin sensitivity. A model reference approach was also evaluated with the feedback controller – this pointed out the need for a reasonably accurate reference model. The results are promising and deal with many practical considerations that are relevant for diabetic patient care. Other scenarios such as exercise effect and robustness while considering a broad range of patients have not been addressed.

Eren-Oruklu et al. (2009) demonstrated an adaptive control strategy using general predictive controller (GPC) and linear quadratic controller (LQC) for regulation of blood glucose levels in patients with T1D patients.

System identification methods were used to obtain the patient model in Auto Regressive Moving Average (ARMA) form which was then used to predict glucose level 30 min (6 steps) ahead. In closed loop condition, the Auto Regressive Integrated Moving Average with eXogenous input (ARIMAX) model is used. The model parameters are updated continuously using recursive least squares (RLS) method to handle the intra- and inter-patient variability. Both subcutaneous BG measurement and subcutaneous insulin infusion are employed along with a delay compensator and one step ahead BG prediction. The algorithm is quite successful and is applicable to single rate data system.

All the algorithms described above have only dealt with single rate system, and this can be a limitation in BG control for T1D patients.

2.6 Intensive Insulin Infusion Therapy and Diabetes Control

Critically ill patients or patients in ICU experience stress induced hyperglycemia even if they do not have any past history of diabetes. Other factors such as presence of hypertension, cortisone and pancreatic disease also result in hyperglycemia. From the extensive literature, it is clear that intensive insulin therapy (IIT) can reduce morbidity, mortality and duration of patients' stay in ICU. According to Leuven study, an IIT that maintains BG in the 80~110mg/dL range can reduce ICU mortality by 42%, bloodstream infections, the incidence of acute renal failure, the need for prolonged ventilatory support and the duration of ICU stay (Goldberg et al., 2004).

Many IIT protocols have been developed for glycemic control in ICU - some protocols have been developed in medical ICU (MICU) and some protocols have been proposed for use in surgical ICU (SICU). These protocols still need to be optimized so as to be effective on a broad range of patients (i.e. tight and safe blood glucose control). Use of the ad-hoc protocols based primarily on experience is practiced in many ICUs. Avoiding hypoglycemia is the primary intention for patients in ICUs. It would be worthwhile to develop a protocol that can: (i) avoid hypoglycemia, (ii) provide tight glycemic control for the different conditions of patients with minimal physician intervention, and (iii) is easy to use by ICU medical staff involved in patient care. Other

control algorithms used in glycemic control for ICU patients include PID using sliding scale method (Chee et al., 2003) and MPC (Plank et al., 2006).

The patient model used for ICU patients includes the pancreatic function (Chbat et al., 2005), which is different from almost all other T1D patient models. Developing a patient model that takes into account conditions such as hypertension, corticosteroid expression, enteral (i.e., nutrition administered through a tube via the nose or stomach or the small intestine) or parenteral (i.e., nutrition administered via a peripheral or central vein) is still an open problem that, when solved, can be highly useful in ICU settings.

2.7 Diagnostic Tests

The most common diagnostic test for diabetes is based on fasting plasma glucose (FPG) concentration. The FPG of normal subjects is 110mg/dL (6.1mmol/L) and diabetes is suspected (diagnosed) if FPG is more than 126mg/dL (7.0mmol/L). If the FPG value is between 110mg/dL and 126mg/dL, this condition is defined as pre-diabetes and may need further confirmatory tests.

Alternate indications of diabetes is based on the causal plasma glucose (CPG) i.e. BG value at any time of the day. If CPG is more than 200mg/dL, further tests such as FPG and measurement of glycated hemoglobin (HbA1c) levels are recommended. Sometimes, the oral glucose tolerance test (OGTT) is conducted. Herein, if the post-prandial glucose (PPG) measure taken after 2hr. following an oral intake of 75g glucose exceeds 200mg/dL (11.1mmol/L), the patient is diagnosed as having diabetes. In another test known as the intravenous glucose tolerance test (IVGTT), glucose with/without insulin is infused intravenously and BG is measured frequently for up to 3 hours. This test is definitely more invasive and involves the deployment of more human and material resources and therefore seldom used. However, with IVGTT, the dynamics of blood glucose and insulin interaction can be understood distinctly and so is employed for research purposes. A modified version of this test is developed and applied in this study as a classification test; details of the test will be described in chapter 4.

2.8 Finding a Model from Diabetic Patient Data

In the above sections, the patient's model is pre-specified and an appropriate control algorithm that employs nominal patient parameters is applied. Such an approach relies significantly on the benevolent nature of feedback mechanism in its tolerance to model-patient mismatch. An alternate approach that intends to make the medical care personalized to the patient is possible. Here, a suitable mathematical model is identified based on data collected from the patient prior to and during the period of treatment. A suitable controller is designed based on the deduced model with sufficient safeguards to take care for imprecision in parameter estimates. System Identification (SID) tools are quite handy in obtaining an adequate mathematical model from the input and output data collected from the patient even when the biochemical, biophysical characteristic of the disease is unknown; this type of modeling is called black-box modeling. As mentioned earlier, the study by Eren-Oruklu et al. (2009) used such an approach. The data sets used for system identification is generally assumed to have regular and similar sampling intervals for all input and output variables. Such regular and single-rate sampling is sometimes not possible particularly in medical settings. In many practical situations, data are sampled at different sampling rates and results in the so-called multirate system. Making models from such data is more difficult compared to making models from single-rate data, and calls for special multirate system identification methods. The nature of diabetic patient data is described next.

2.8.1 Multirate Nature of Diabetic Patient Data

Different from single rate systems in which inputs and outputs are measured at one identical sampling interval, multirate systems are sampled-data systems with non-identical sampling intervals. Multirate systems are very common in chemical process industries where different variables are sampled at different rates for some practical reasons.

In the chemical industries, measurements from the units such as distillation columns and reactors are available at different sampling rates.

Variables such as temperature, pressure, flowrate etc. can be measured frequently while composition measurements, molecular weight distribution, melt flow index etc. can be obtained once every several minutes or even several hours due to hardware limitations. These features naturally lead to a multirate system.

Data obtained from diabetic patients tend to be multirate in nature: BG measurement is usually obtained infrequently and may be available on an irregular basis; however, the insulin infusion rate is measured more frequently. Such multirate data needs multirate system identification tools to identify the relevant models that may be beneficially used to achieve tight BG control.

2.8.2 Multirate System Identification

Most of the successful system identification methods in both polynomial (transfer function) domain and state space domain are applicable only to single-rate input/output data. Very few algorithms have been developed for multirate identification (MRID) which can process multirate input/output data. Conventionally, engineers interpolate the inter-sample input/output from the slowly sampled measurements and then estimate the model (fast-rate model) based on both the measured and interpolated data set. The model obtained from traditional interpolation techniques cannot capture the actual model dynamics very well when the ratio of sampling intervals (slow measurement interval/fast measurement interval) becomes large. This is because the interpolation does not take the actual dynamics of the process (between the intervals of each successive slowly sampled instance) into account. It is clear that a more reasonable systematic approach which takes into account the multirate nature of the process is required. This is offered by multirate system identification.

Lifting technique plays an important role in multirate system identification; it converts a multirate system into a single rate system to which most of the system identification techniques can be applied successfully. Verhaegen and Yu (1995) presented a technique to estimate the lifted model of a multirate system in state-space (SS) form. They represented the multirate

system as a periodic system, and they estimated the lifted model using the multivariable output-error state space method. Their method cannot handle the crucial causality constraint (i.e., the state space model should be observable and controllable) in the identification of lifted models if the system time delay is greater than p (Li et al., 2001) for Single Input/Single Output (SISO) multirate system with input (U) and output (Y) which are sampled with sampling interval ($m \times p$) and ($n \times p$) respectively ($m \prec n, n : m = \gamma$ and $p =$ base time period, both m and n are coprime). Li (2001) made modification (shifting the data for the system with time delay greater than p) of their earlier work to effectively overcome the causality constraint when both m and n are coprime. With this modification, most of the existing system identification algorithms can be applied for identification of the lifted (slow-rate) system.

Identification of the slow rate model is possibly best accomplished using state space methods which can handle multivariable processes. Li et al. (2001) also proposed some approaches to extract the fast rate model with sampling interval mp (where $m >1$) from the slow rate model. Wang (2004) improved Li et al.'s work in a manner such that the fast rate model could be readily extracted at the fastest sample time (base time period, p) with (1) matrix roots approach based on the condition that slow-rate state matrix A in SS model is diagonalizable and (2) frequency-domain approach in which applying the polyphase decomposition developed by Khargonekar et al. (1985) to the lifted slow rate system. Note that all of these works are valid in the context of linear systems only. The application of multirate system identification onto nonlinear systems can be seen in Ooyama et al. (1999).

Gopaluni et al. (2003) proposed a multirate identification algorithm in which they used an iterative identification algorithm. In this work, they first identified a Finite Impulse Response (FIR) model from multirate data. Based on this model, the missing data points in the slow sampled measurement are estimated using the expectation maximization approach. Then, they estimated a new model iteratively using the estimated missing data points and original data set until the models converge. Their method is also applicable to irregularly sampled data system. May Su Tun et al. (2006) developed data selection and regression (DSAR) method for the identification of multirate

system. The advantage of DSAR is that it is able to handle the large ratio of sampling intervals as well as irregularly sampled data.

2.9 Conclusions

In this chapter, the literature review and basic elements regarding regulation of BG in T1D using artificial pancreas are discussed. The review of Type 1 diabetic patient models and associated meal models is presented in section 2.1. The uncertainty issues regarding patient models, the detailed description of chosen T1D model and associated meal model for this study and the generating cohort of patients to test robustness and performance of control algorithms that will be developed in later chapters are described in section 2.2, 2.3 and 2.4 respectively. The automatic control of BG in T1D patients and review of control algorithms is presented in section 2.5. This pointed out the need for robust control algorithms that can handle a broad range of patient variations and the need for a more realistic approach to obtain the personalized model and control algorithm. To achieve these goals are the scope of the present study. The intensive insulin infusion therapy applied in ICU is described briefly in section 2.6 and it appears that such an approach may be extended for BG control in T1D patients. The descriptions of patient diagnostic tests and a modified test that will be used for patient classification in later chapters to develop a more personalized care are expounded in section 2.7. Finally, estimating patient models from multirate data (that is more realistic) using multirate system identification is introduced in section 2.8 to develop a more personalized approach for BG control.

Chapter 3

Effectiveness of Intensive Insulin Infusion Protocol in Treating T1D Patients

3.1 Background

It is well understood that the maintenance of plasma glucose concentration in normoglycemic range is crucial to the individuals' well-being in all types of diabetics. This is mainly achieved by administering the right dose of insulin around the clock in an effective manner. To achieve this, closed loop feedback control has been considered by many researchers. Chee and Fernando (2007) provide an excellent introduction to the modeling, control and miniaturization aspects of the blood glucose control (artificial pancreas) problem. Control algorithms of varying sophistication from PID (proportional, integral and derivative) control to Model Predictive Control (MPC) have been employed for BG control in T1D patients (Bequette, 2005).

Different from these automatic feedback controllers, rule-based insulin infusion protocols (IIP) have been developed and employed in hospitals for glycemic control in ICU (Intensive Care Unit) patients. Patients in surgical and/or medical ICUs frequently experience stress induced hyperglycemia and impaired glucose metabolism even though they may or may not have a prior history of diabetes. Poor glycemic control in ICU patients has been linked to increased morbidity and mortality rates for patients who have been treated for three or more days in the medical ICU (Van den Berghe et al., 2006). The seminal study by Van den Berghe et al. (2001) showed the benefits of tight glycemic control in patients at a surgical ICU. Later trials by other medical teams in other ICUs indicated that the Van den Berghe's protocol (and other similar ones) resulted in hypoglycemic episodes and needed reconsideration. Since then, several IIPs that have been fine-tuned to prevent hypoglycemia have been proposed and are in practice (e.g., Studer et al., 2010).

3.2 Motivation and Objectives

A thorough study on how a typical IIP (Yale IIP, YIIP is used here as an example; its details are described in Appendix A. 1) fares in treating T1D patients would be instructive. Even though the IIPs are originally intended for treating ICU patients, would it be applicable for routine insulin-infusion based treatment of T1D patients (with normal meal of three meal disturbances:- 10g, 50g & 50g for breakfast, lunch & dinner respectively). This is the main objective of the present study. If the IIP (with some modifications) works as well as a traditional control algorithm, it can be easily used by T1D patients (because an IIP is based on a table lookup and simple calculations) to adjust their periodic insulin intake or be easily programmed for use by feedback control schemes.

Note that the IIPs are very amenable to straightforward implementation into integrated sensing and programmed implantable insulin delivery devices. The main difference between a T1D patient and a typical ICU patient is the absence of pancreatic insulin secretion in the former while the pancreatic function is existent but possibly inadequate in the latter (Chbat et al., 2005). If hypoglycemic episodes are observed in the predefined broad range of patients, the standard YIIP will be modified so as to avoid hypoglycemia.

3.3 Yale Insulin Infusion Protocol

Stress during critical illness induces glucose counter regulatory hormones, increases insulin resistance and relative insulin deficiency resulting in hyperglycemia. Furthermore, several common interventions such as corticosteroids, vasopressors, enteral or parenteral nutrition also result in higher BG levels. Van den Berghe et al. (2003) reported that the use of intensive IIP in patients of a surgical ICU (SICU) resulted in normalization of BG level and reduced mortality rates.

Yale IIP (YIIP) by Goldberg et al. (2004) is the outcome of a similar study on ICU patients but implemented in a Medical ICU (MICU). It was designed to implement effective IIP for strict glycemic control in MICU of Yale New Haven Hospital, USA. The protocol was intended for easy use by

nursing staff without the need for frequent physician input. YIIP was aimed to keep the patients' BG level within a conservative BG target of 100~139mg/dL. This algorithm is based on three main data elements used by experienced clinicians to adjust insulin infusion: (1) the current BG value, (2) the previous BG value, and (3) the current insulin infusion rate. Thus, the IIP is based on the rate of BG changes rather than on absolute BG values. In reported IIP works, the initial insulin infusion (including bolus) is based on the current BG level of the patient. Admittance to IIP starts when the patient's BG level exceeds 200 mg/dL. The same amount of insulin the initial insulin infusion amount is injected as bolus at the initialization of this IIP. Initial insulin infusion lasts for one hour before continuous BG monitoring is started. The rate of insulin infusion is updated whenever BG value is monitored - the frequency of BG monitoring may also change depending on the value of the last noted BG value and the most recent BG trend. The monitoring of patients' BG level is done on hourly basis in general but a different frequency of monitoring (30 minutes or 15 minutes) can be used depending on the severity of patient's hypoglycemic condition: the BG monitoring is required at every 15 min when the patient's BG value is under 75mg/dL, it changes to at every one hour when the patient's BG is within target range (100~139mg/dL), it changes to at every 2 hours when three consecutive BG values become stable (in target range), etc.; and more details of YIIP can be seen in Appendix A. 1. The primary importance of avoiding hypoglycemia (<60mg/dL) is handled by using of intravenous dextrose, as per protocol when the patient BG value is less than 75mg/dL.

In YIIP, the missing data values are estimated by averaging known BG levels from the hours before and after missing values. The YIIP was successfully implemented in a MICU in which nearly 40% of MICU patients are admitted for primary respiratory failure. This IIP was subsequently validated on 52 patients from the same MICU. In their (Goldberg et al., 2004) study of 5,808 subsequent hourly blood glucose values, only 20 (0.3%) BG values from 12 patients fell below 60mg/dL and only three BG values were less than 40mg/dL. Such hypoglycemic episodes were rapidly corrected by intravenous dextrose infusion. Compared to a group of 47 patients who

received conventional insulin therapy (intravenous or subcutaneous insulin), the patients who received YIIP had better glycemic control. Similar protocols have been developed and used in other hospitals/clinics (see Chant et al, 2005).

Full details of the YIIP (taken from Goldberg et al., 2004) are provided in Appendix A. 1. Note the precautions, the insulin infusion initialization process, rules for adjusting infusion rates, adjustments to BG monitoring frequency etc.

As indicated earlier, one of the goals of the present study is to check how IIP protocols such as the YIIP work on T1D patients. Towards this end, *in silico* patients generated from popular T1D patient models will be utilized for this investigation. The generation of the patient cohort and the results of application of YIIP to this cohort are described next.

3.4 Cohort of Patients

There is natural variability in the physiological behavior of diabetic patients, and this is reflected as variability in parameters of the diabetes patient models. In fact, even in a single patient, the response can vary over time and this can be modeled as gradual or abrupt variations in model parameters over time. Here, it is assumed that the dominant parameters deviate by a certain percent ($\pm$ 20% or $\pm$ 40%) about their nominal values. The combination of these parameter variations results in a cohort of potential patients for each model. The *in silico* patients resulting from this procedure are used to test the control algorithms for robustness and performance.

In the model described in Parker et al. (2000), 8 parameters namely EIPGU-E_Γ, EIPGU-D_Γ, EGHGU-E_Γ, EGHGU-D_Γ, EGHGP-E_Γ, EGHGP-D_Γ, F_{LC} (FHIC), and F_{PC} are chosen as varying from one patient to another. These 8 parameters are perturbed from their nominal values by $\pm$40% (except for FLC that is limited to $\pm$20% to guarantee non-negative glucose concentration as mentioned in Parker et al., 2000). From these 8 parameters, sets of any three parameters are chosen and the chosen parameter set is varied in three levels (max, no change or nominal value, min) resulting in $^8C_3 * 3^3 = 1512$

combinations. Patients with identical values for all eight parameters were removed and a set of 577 unique patients was generated as in Ramprasad et al. (2004). These 577 unique virtual patients are used as test cases in this study.

In Fabietti model, four parameters (namely, K_i, T_{xi}, T_m and K_{is}) are chosen to generate the virtual patients. These four parameters are perturbed by ±40% from their nominal values (see these values in Table 2.3). These parameter variations are within the experimental parameter values of Fabietti et al. (2006). The combination of these parameters results in a cohort of potential patients. The chosen parameter set is varied in three levels (max, no change or nominal value, min) for each parameter, and the combination of these four parameters result in $3^4(= 81)$ simulated patients. These simulated patients are also used to test the performance of the control algorithm.

3.5 Details of the Study

The effectiveness of YIIP is evaluated *in silico* i.e. on the T1D patient cohorts generated. The YIIP algorithm is coded and evaluated on the cohort of patients described in Section 3.4. The computations are done in MATLAB platform using SIMULINK. The effectiveness of the IIP algorithm in terms of disturbance rejection and its robustness are tested on cohorts of virtual T1D patients for a "normal" day with three carbohydrate meal disturbances of breakfast (10 g), lunch (50 g), and dinner (50 g) at the meal times of 7 am, 12 noon, and 6 pm respectively. Both glucose sensing and insulin infusion are administered through intravenous route using portal vein for the advantages of using intravenous route, described in Section 2.5.1. In this study, measurement noise and input constraints (except that insulin infused cannot be negative) are not considered as it is desired to understand the ideal performance of the proposed strategy.

3.5.1 Method I: YIIP

The YIIP was developed for MICU patients, and it is yet to be validated on a broad range of T1D patients. The effectiveness of YIIP on the cohort of T1D patients described in Section 3.4 is studied by subjecting the

"patients" to three meal disturbances for 3 consecutive days. The details of YIIP have been provided in Appendix A. 1; intravenous route is used for insulin infusion and dextrose infusion (the duration for this infusion is simulated as 1 hr generally in this study) is given should there be a hypoglycemic episode. As mentioned, the initial insulin infusion amount is calculated based on the patient BG value, and same dose of bolus insulin is administered at the very start of algorithm.

3.5.2 Method II: Modified YIIP (MODYIIP)

The target of YIIP is conservative (100~139mg/dL) because it is designed to be safe to avoid hypoglycemia as strict blood glucose control (maintaining BG within 81~108mg/dL) has adverse effect on mortality rate (Studer et al., 2010). However, the results from the study of YIIP on chosen diabetic patient models show the amount of initial insulin infusion should be suitably adjusted. Extra glucose infusion is used in YIIP in case of hypoglycemia events but it is burdensome for T1D patients to carry the glucose reservoir, and it would be advantageous if we can modify insulin infusion amount.

To improve its applicability in out-of-ICU settings and especially to avoid hypoglycemia in patients without the use of extra dextrose/glucose reservoir, the initial insulin infusion amount of YIIP will be modified suitably in this work leading to the development of a new modified YIIP algorithm (MODYIIP). The initial insulin infusion for each of the 577 patients (Parker model type) is modified according to their BG response to the original initial amount of insulin (Parker model type patients are chosen here as these type of patients are more sensitive to insulin). If any particular patient exhibits hypoglycemia (BG < 70mg/dL) with original insulin infusion amount, the amount of initial insulin infusion is reduced to 75% of its original value. If it still results in hypoglycemia, the insulin infusion is reduced to 50% of original amount. The procedure is repeated (i.e. to 25% and 0%) until the BG value is in the range of normoglycemic region. A similar procedure is applied by increasing the infusion amount (125%, 150%, 175% and 200%) if any patient shows hyperglycemia (BG > 110mg/dL 3 hours after meals). During the

validation of the modified YIIP on other patient models, insulin infusion is assumed to be via the intravenous route.

Using the "fminsearch" tool (expect in Hovorka model patient where it is infused through the subcutaneous route) available in MATLAB, the idea was tested on the 577 Parker model type patients with initial BG value of around 150mg/dL. The objective was to determine the optimal insulin infusion amount that avoids hyperglycemia in all patients. It was determined that no hypoglycemic episode occurs when the initial infusion limit is set at 50% of original YIIP initial insulin infusion. With this reduced initial insulin amount, the lowest BG value reached was 75mg/dL and the highest BG value attained was 235.94mg/dL. The hyperglycemic episodes are compromised here to avoid dangerous hypoglycemia using 50% of its original values and to make the modified YIIP (MODYIIP) safe for T1D patients. Therefore, the MODYIIP is one in which only 50% of initial insulin infusion as recommended by standard YIIP is chosen. Note that, in MODYIIP, there is no need for glucose infusion to avoid hypoglycemia.

3.6 Results and Discussion: YIIP on T1D Patients

The application of the YIIP protocol is aimed to test its effectiveness and applicability on a broad range of T1D patients constituted from two diabetic patient models (Parker and Fabietti Model) with three meal disturbances and to study how to improve its applicability on T1D patients. Three carbohydrate meal disturbances - breakfast (10 g), lunch (50 g), and dinner (50 g) at the meal times of 7 am, 12 noon, and 6 pm respectively – are considered in this study. The performance of meal disturbance rejection of YIIP on 577 constituted patients using Parker model with three meal disturbances per day over a three day period is presented in Figure 3.1 (with initial blood glucose value of 81. 08mg/dL) and Figure 3.2 (starting from initial hyperglycemic state of BG~150mg/dL). The Lehmann and Deutsch (1992) meal model is used in these simulations.

According to the results on Parker model with hourly BG monitoring (Figure 3.1), 423 patients and 547 patients out of 577 patients record a BG

value in excess of 139mg/dL for normal initial condition and initial hyperglycemic condition respectively. The highest BG peak values for these two cases are 207.99mg/dL and 211.42mg/dL respectively. For the normal initial condition, 15 patients (2.6%) experience hypoglycemia (< 60mg/dL) with lowest BG value being 52.61mg/dL. When the initial condition is hyperglycemic, 12 patients (2.08%) enter into hypoglycemic region (<60mg/dL) with lowest the BG value being 53.99mg/dL. Note that, in these subsets of patients, severe hypoglycemia has been avoided by the use of dextrose infusion administered intravenously. In this subgroup of patients, the low BG value (53.99mg/dL) was observed one hour after initial insulin infusion (plus bolus) was administered; this indicates that the insulin amount suggested by the protocol (initial insulin plus bolus dose) may be higher than required (i.e. overdose). This is perhaps in line with what YIIP intends to achieve - YIIP is initiated when the patient's BG level is above 200mg/dL and the suggested insulin dosage is meant to bring such patients to normoglycemic range.
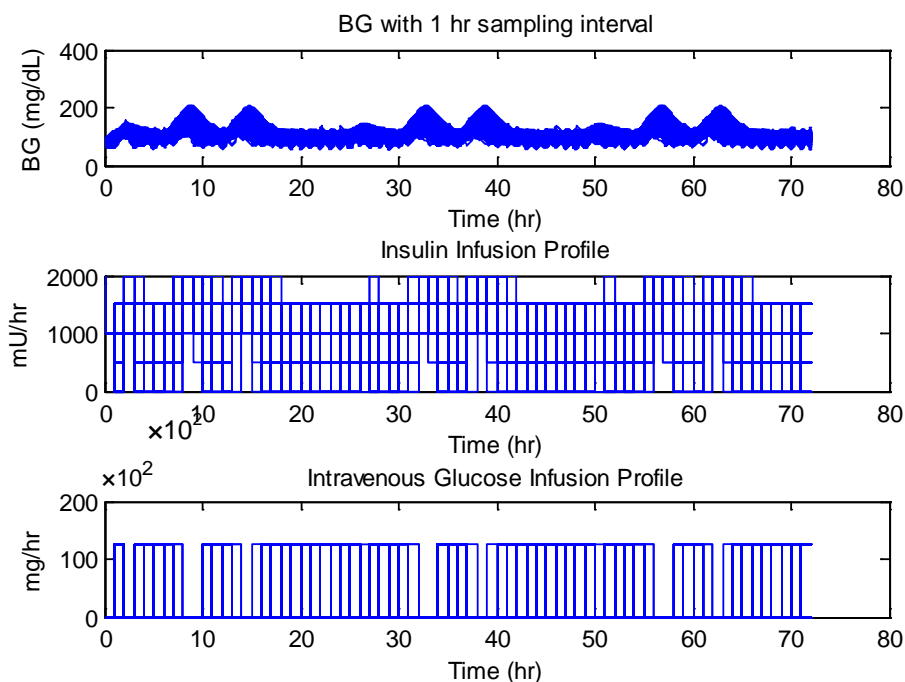
Figure 3.1: Performance of hourly monitoring YIIP on 577 unique patients generated using Parker model (with meal disturbances) with normal initial condition
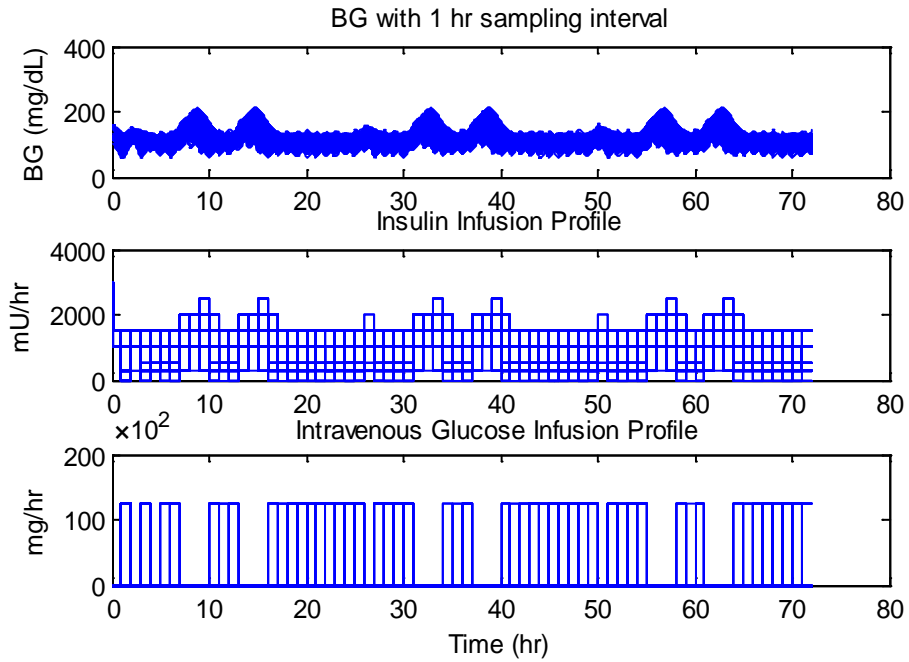
Figure 3.2: Performance of hourly monitoring YIIP on 577 unique patients generated using Parker model (with meal disturbances) with initial hyperglycemia

However, the 577 unique patients considered in this study have an initial BG value of 150mg/dL or less. Therefore, the YIIP should be suitably modified by decreasing the initial bolus for patients who are initially in the hyperglycemic range but with BG values less than 200mg/dL.

The performance of meal disturbance rejection of YIIP on 81 constituted patients using Fabietti model is presented in Figure 3.3.From the results of applying YIIP on Fabietti model type patients (Figure 3.3), we find that all 81 patients have BG peak values in excess of 139mg/dL with the highest value being 289.52mg/dL. The BG values of 7 patients (8.64%) enter into hypoglycemic zone (<60mg/dL) with the lowest BG value reaching 54.13mg/dL. In Fabietti patients, hypoglycemic episodes are not observed after the initial insulin infusion but are seen much later.

Figure 3.3: Performance of hourly monitoring YIIP on 81 constituted patients generated using Fabietti model with meal disturbance

These studies show that YIIP should be tailored if it has to be applied for both Parker and Fabietti type T1D patients. We conclude that the initial insulin infusion (with/without bolus) amount should be optimized for better and safe treatment of a broad range of T1D patients, particularly if dextrose infusion is not practical or intended. This is why the MODYIIP was conceived of. The performance of MODYIIP is tested next.

3.7 Results and Discussion: MODYIIP on T1D Patients

The performance of MODYIIP is studied on the Parker and Fabietti models. The performance of the MODYIIP procedure on the Parker model patients with initial hyperglycemia (around 150 mg/dL) is expected to be good since Parker model patients were used to construct the procedure. The performance of MODYIIP on the entire cohort of Parker model type patients, the nominal patient and the worst-case patient are shown in Figures 3.4, 3.5 and 3.6 respectively.

In order to compare the results of the proposed strategy with those obtained with conventional control, the work of Ramprasad et al. (2004) is

used as the reference. Their work employed PID controller for blood glucose control in T1D patients and employed different tuning methods. They obtained best results with Shen (2002) tuning method, avoiding hypoglycemia (<60mg/dL) in all but 5% of the 577 virtual patients constituted from Parker et al.'s model. Frequent sampling (once every 4 min) was used for glucose measurement according to current glucose sensor technology. In comparison, MODYIIP (without external glucose infusion) with one hour sampling interval is able to avoid hypoglycemia (< 60mg/dL) successfully with a simple rule-based protocol; however, the occurrence of hyperglycemia (> 140mg/dL) could not be avoided.
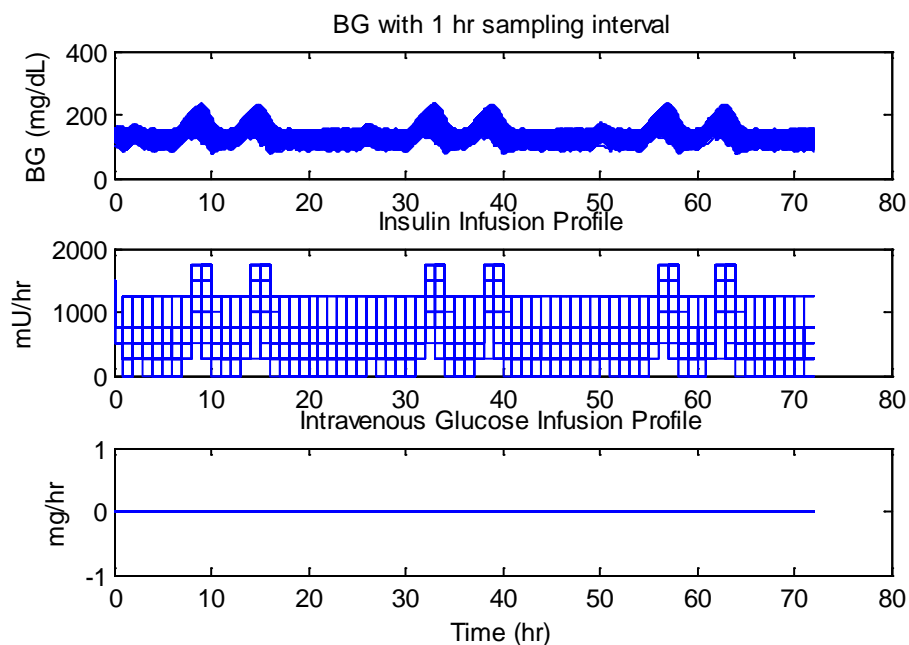
Figure 3.4: Performance of hourly monitoring MODYIIP on 577 unique patients generated using Parker model (with meal disturbances) with initial hyperglycemia

It is seen that hypoglycemia (under 60mg/dL) can be avoided successfully without extra glucose for all Parker model patients as expected. Note that, in Figure 3.4, Parker model patients with initial hyperglycemia is considered while in Figure 3.5 and 3.6, patients with a "normal" initial condition (BG around 81mg/dL) are considered.

Figure 3.5: Comparison of BG profiles of MODYIIP (magenta solid line) and original YIIP (blue dashed line) on nominal patient (Parker model type) with normal initial condition
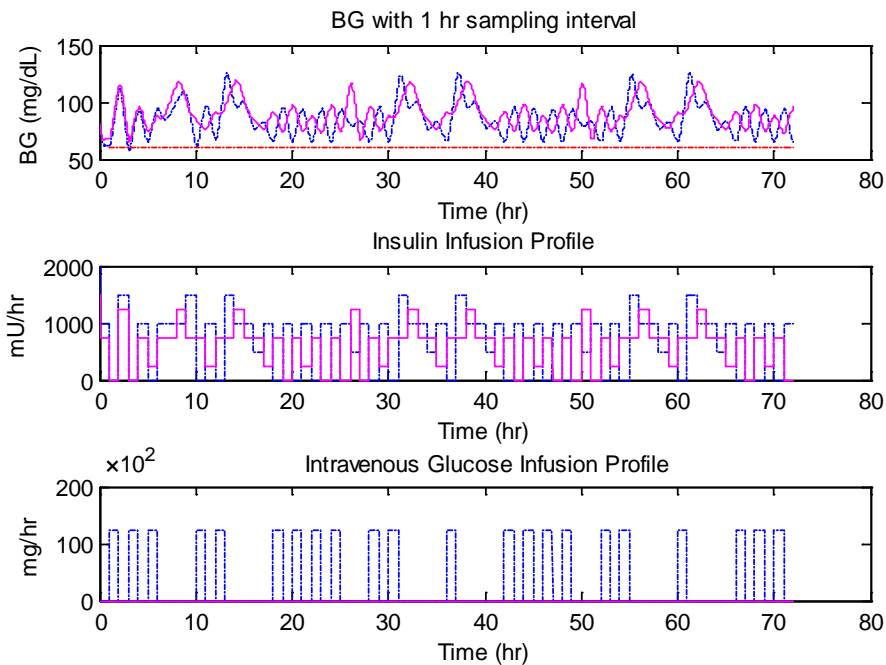
Figure 3.6: Comparison of BG profiles of MODYIIP (magenta solid line) and original YIIP (blue dashed line) on worst case patient (Parker model type) with normal initial condition

It is seen that, for the worst-case patient, the original YIIP requires infusion of glucose to avoid hypoglycemia. Comparable results were obtained for nominal patient and worst-case patient with MODYIIP. For the worst-case patient, hypoglycemia (low BG value = 56.7mg/dL) with original YIIP could be avoided by MODYIIP (lowest BG value = 75.93mg/dL) with less dosage of insulin (50% of original YIIP initial insulin infusion) and no extra glucose. This shows the efficacy of MODYIIP.

The effect of MODYIIP on the cohort of Fabietti model type patients is shown in Figure 3.7. There are no hypoglycemic episodes (lowest BG value is 73.73mg/dL). All 81 patients enter into hyperglycemic zone (> 139mg/dL) with the highest BG peak value turning out to be 317.14 mg/dL.
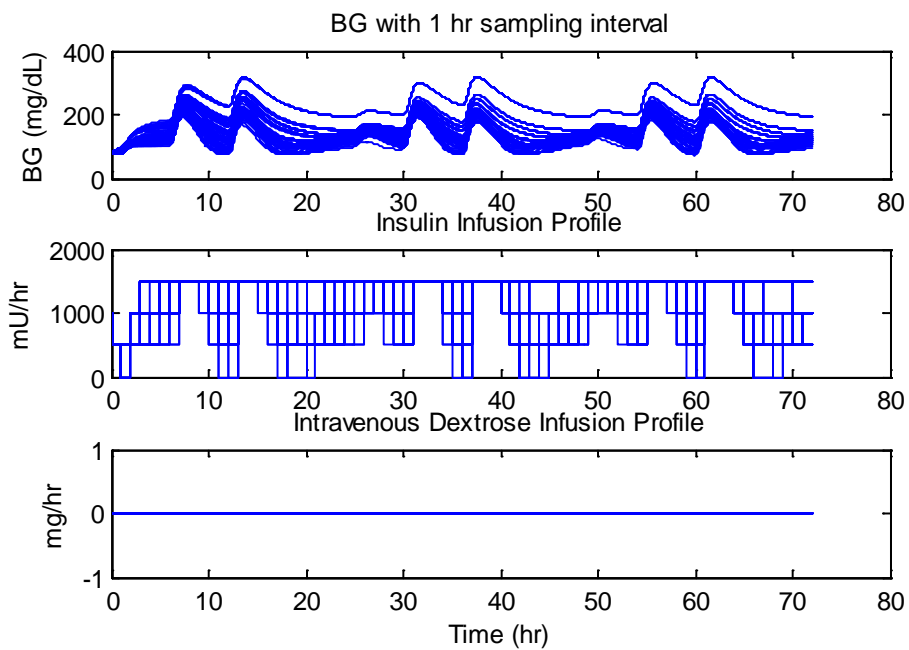
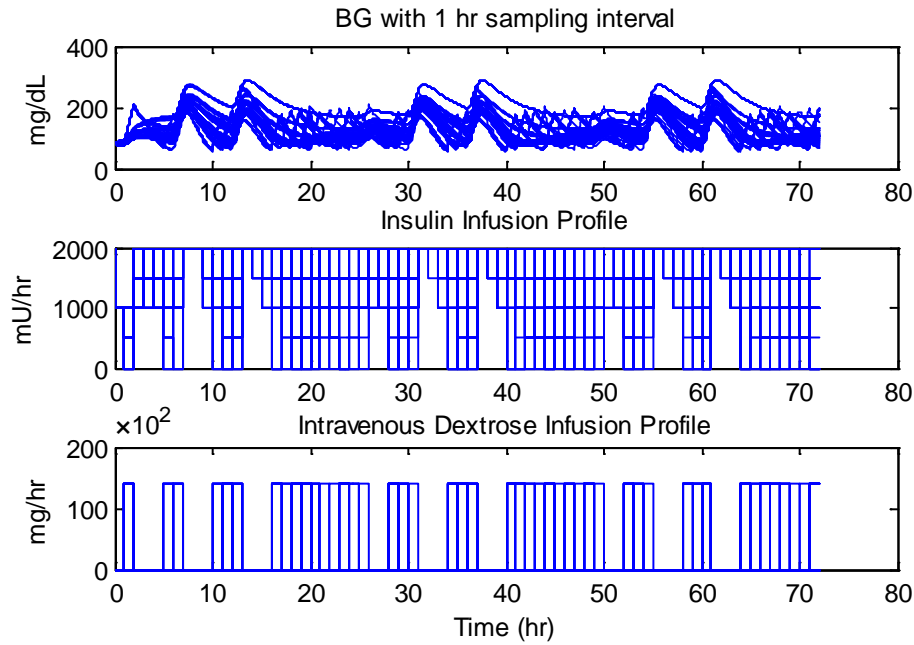Figure 3.7: Performance of MODYIIP on 81 constituted patients generated using Fabietti model with meal disturbance

The performance of modified YIIP on nominal and worst-case patients of Fabietti model type is shown in Figure 3.8 and 3.9 respectively. In both cases, the dangerous hypoglycemia is avoided successfully without external glucose.
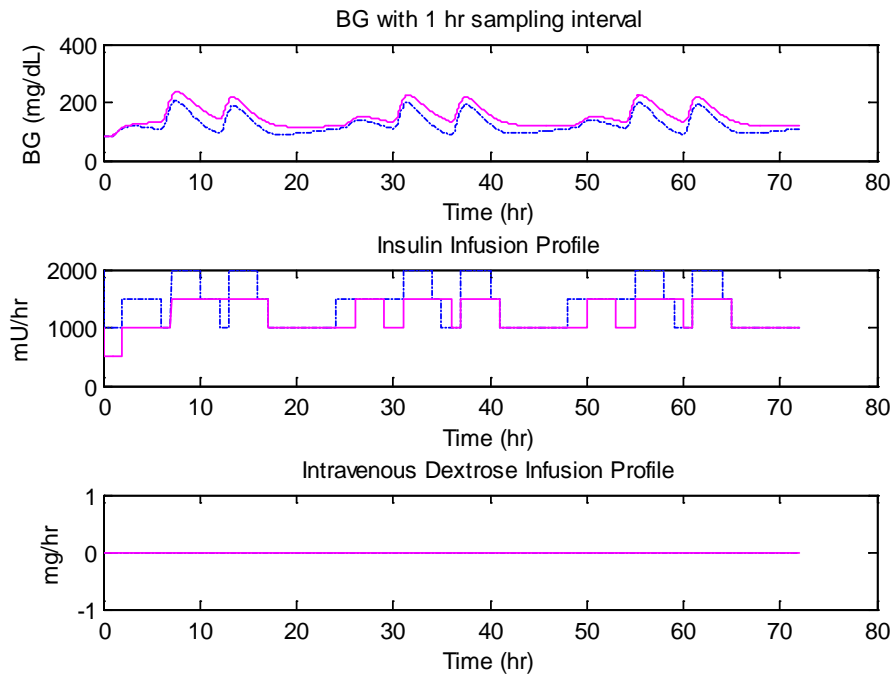
Figure 3.8: Performance of YIIP (blue dashed line) and MODYIIP (magenta solid line) on nominal patient using Fabietti model with meal disturbance
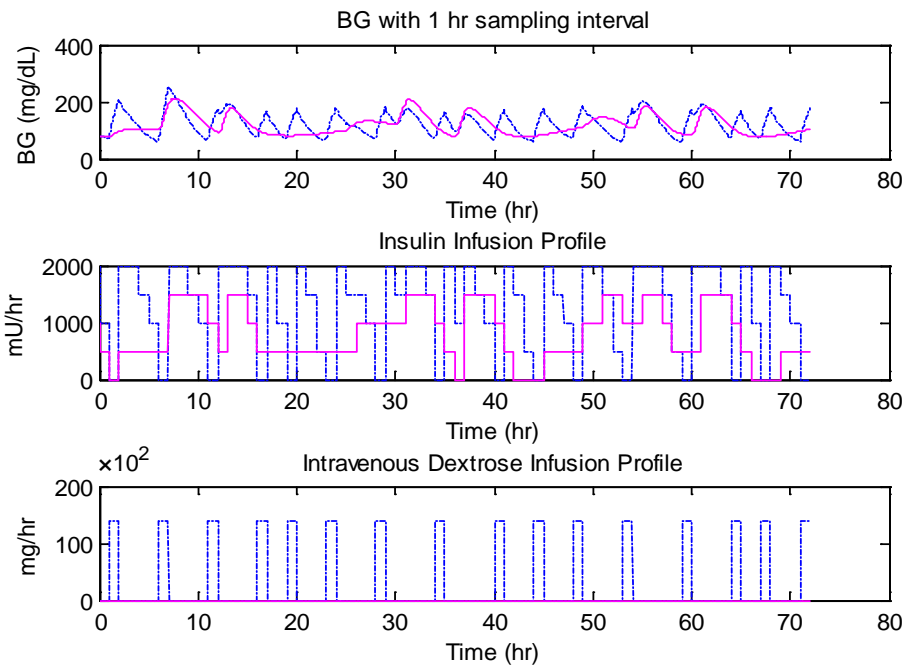
Figure 3.9: Performance of YIIP (blue dashed line) and MODYIIP (magenta solid line) on worst-case patient using Fabietti model with meal disturbance

As can be seen in Figure 3.8, comparable BG profiles are obtained for nominal patient using both YIIP and MODYIIP; however, MODYIIP uses less insulin as compared to YIIP (MODYIIP uses 88.01U while YIIP uses 102.53U of insulin over a period of 72 hours). For the worst-case patient, YIIP uses both insulin and glucose liberally as compared to MODYIIP which uses a moderate amount of insulin but no external glucose.

Canonico et al. (2006) used a PID-type controller named Proportional-Derivative-2nd derivative (PDD2) controller and tested it on virtual patients constituted from T1D patient model of Fabietti et al. (2006). Their work employs frequent measurement of blood glucose concentration but the actual frequency was not mentioned. Compared to their work, the use of MODYIIP shows no hypoglycemia even with infrequent BG sampling interval (1 hr.). These results show that MODYIIP is a simple to implement protocol for the effective control of blood glucose levels in T1D patients; it has the potential to avoid the dangerous hypoglycemia without using external glucose infusion and with relatively infrequent sampling of blood glucose. Some further tailoring of the MODYIIP protocol is still needed to achieve tight glucose control.

3.7.1 Validation of Modified YIIP on Bergman Model

As one other verification of the effectiveness of the MODYIIP protocol, the Bergman model (Lam et al. 2002) with three meal disturbances (20g breakfast, 50g lunch and 40g dinner at 7am, 12 noon and 6pm) was simulated. Different meal amounts are considered here so as to evaluate the disturbance rejection capability on any realistic meal amount (which may vary from time to time for breakfast, lunch and dinner) and also to find out the relative performance of MODYIIP over other similar works conducted by other researchers. The Fisher meal model (Fisher, 1991) was used along with the Bergman model to simulate meal dynamics.

Figure 3.10 compares the BG profiles obtained when one applied MODYIIP and YIIP on the nominal Bergman's diabetic patient model with initial condition characterized by BG being 81mg/dL. The total insulin used by MODYIIP is 72.03U while that of YIIP is 58.01U and total extra glucose

amount used by YIIP is 87.5g for 72 hours Although no dangerous hypoglycemia (<45mg/dL) is observed in both cases, exogenous intravenous dextrose infusion was needed in original YIIP while it is not required in MODYIIP. Interestingly, MODYIIP shows a lowest BG value of 76.04mg/dL with no exogenous intravenous dextrose infusion compared to the lowest BG value of 52.82mg/dL obtained with YIIP which also needs exogenous intravenous dextrose infusion. MODYIIP results in a high BG value of 288.31mg/dL compared to that of 253.73mg/dL obtained with original YIIP.
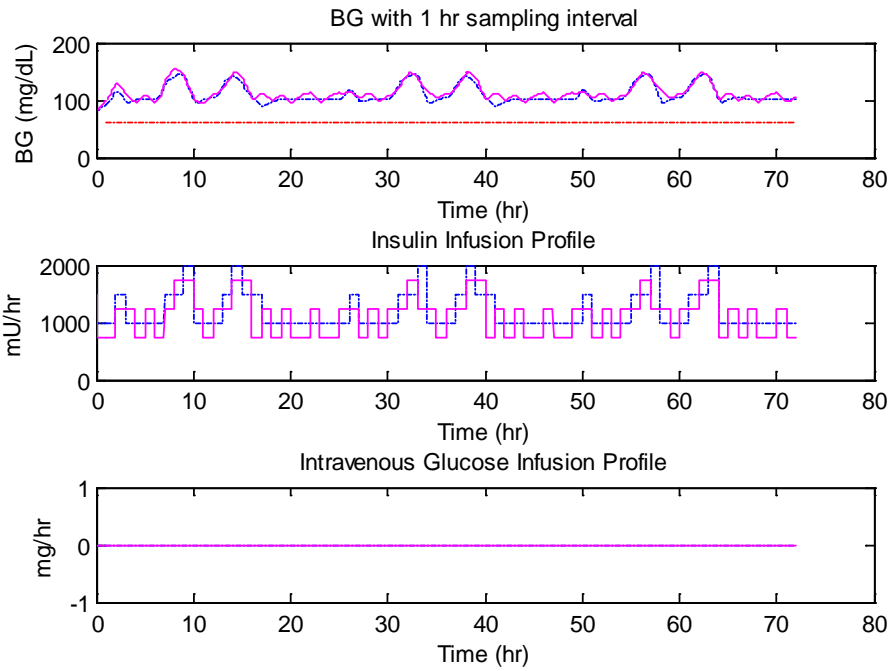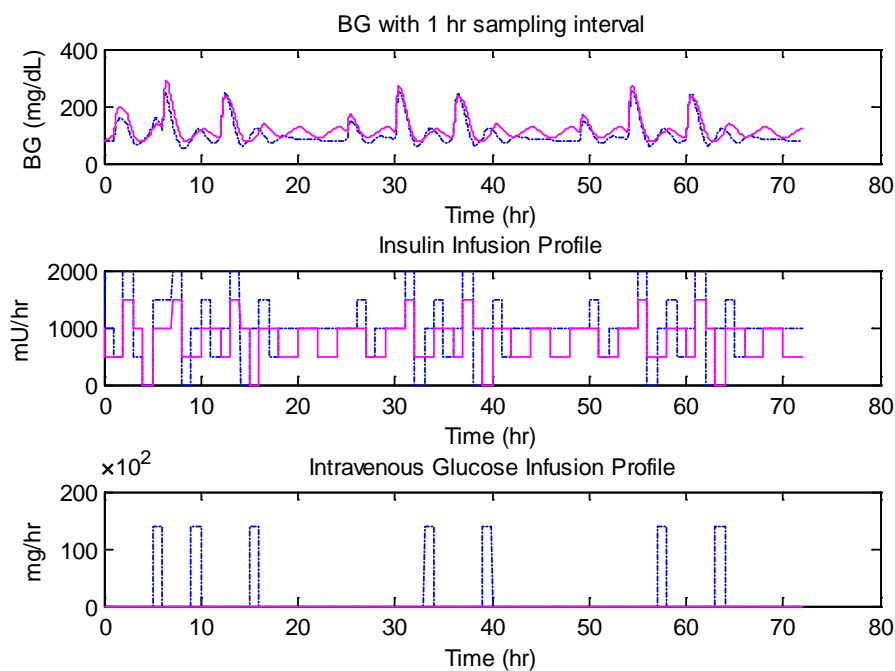

Figure 3.10: Comparison of BG profiles of MODYIIP (magenta solid line) and original YIIP (blue dashed line) on nominal patient (Bergman model type) with normal initial condition

Dua et al. (2004) used the same diabetes patient model to calculate optimal insulin infusion values off-line as an explicit function of the current blood glucose concentration of the patient. This approach has the advantage of using simple function evaluations for calculating insulin infusion and minimal on-line computation. The Bergman 'minimal model' was used as a patient and the sampling time of 5 min (compatible with the then glucose sensor technology) was used. A model predictive controller with the objective function that minimizes a quadratic function of state variables and insulin infusion rate with constraints on glucose concentration (60~120mg/dL) and on

insulin infusion rate (0~100 mU/min) was solved using multi-parametric quadratic programming (mp-QP). In the work of Dua et al. (2004), which uses the same diabetes patient model, meal model and meal amount as in this study, the highest BG value is about 350mg/dL. As noted earlier, MODYIIP shows the highest BG value of only 288.31mg/dL without hypoglycemia employing a simple rule-based strategy. Thus MODYIIP emerges as an effective strategy for BG control in T1D patients. The performance comparison of MODYIIP and YIIP on nominal Bergman model type patient with initial hyperglycemic condition (of about 330mg/dL) is shown in Figure 3.11. The hypoglycemic (<60 mg/dL) episode can be avoided successfully with lowest BG value of 73.11mg/dL but with not much severe postprandial hyperglycemic BG peak of 294.76mg/dL.
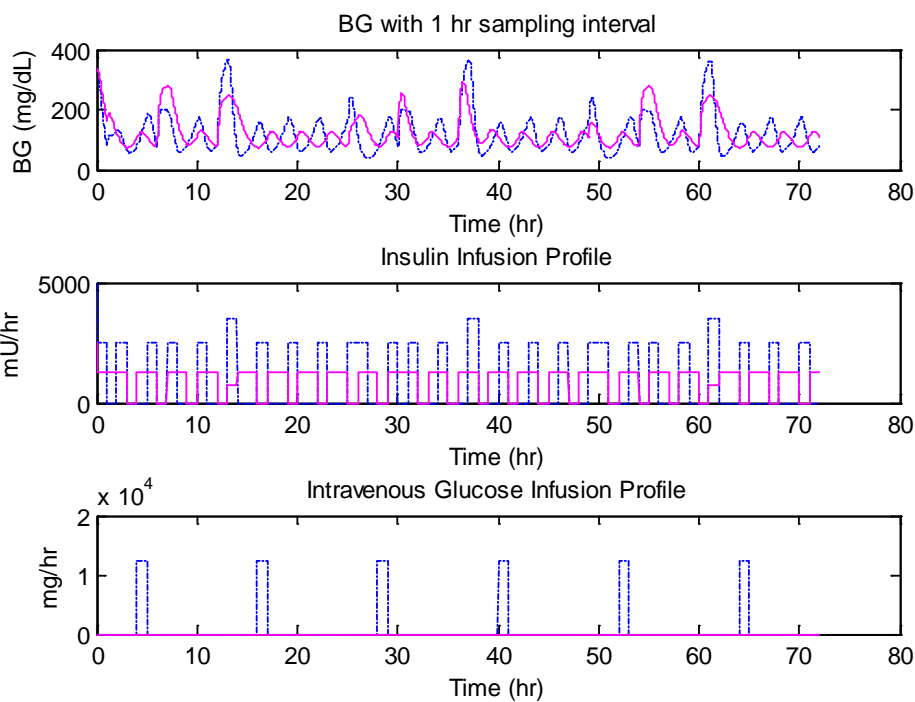
Figure 3.11: Comparison of BG profiles of MODYIIP (magenta solid line) and original YIIP (blue dashed line) on nominal patient (Bergman model type) with initial hyperglycemic condition

The performance of MODYIIP on the worst-case Bergman model patient using Bergman model is shown in Figure 3.12 and 3.13 for normal and hyperglycemic initial condition respectively.
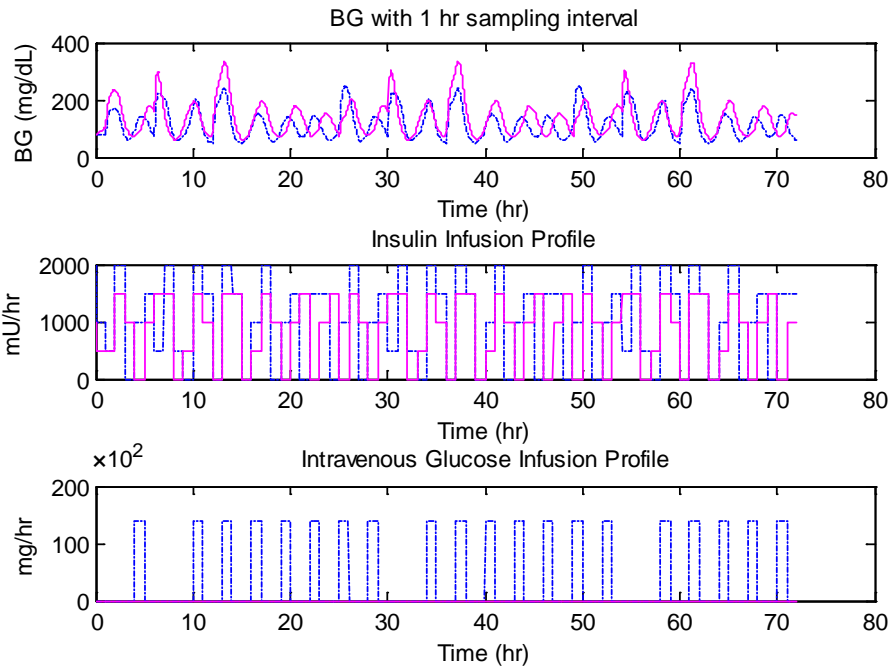
Figure 3.12: Comparison of BG profile of MODYIIP (magenta solid line) and original YIIP (blue dashed line) on worst-case patient (Bergman model type) with normal initial condition
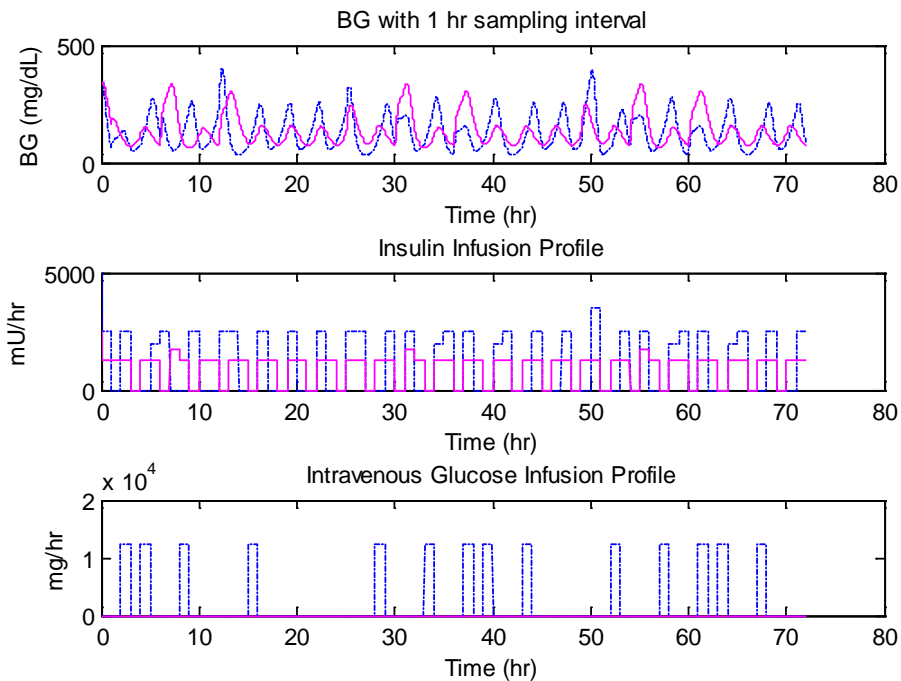
Figure 3.13: Comparison of BG profile of MODYIIP (magenta solid line) and original YIIP (blue dashed line) on worst-case patient (Bergman model type) with initial hyperglycemic condition

The dangerous hypoglycemia (<45mg/dL) is avoided by using MODYIIP, with the lowest BG being 59.39mg/dL and 62.8mg/dL; the total insulin used by MODYIIP is 61.01U and 61.5U while YIIP uses 72.52U and 73.5U for normal and hyperglycemic initial condition respectively. In addition, YIIP uses 200g and 175g of total extra glucose during the 72 hours for normal and hyperglycemic initial conditions respectively.

Thus, the MODYIIP protocol that was developed using Parker's model is effective even on Bergman model type patients proving its robustness and versatility.

3.7.2 Validation of Modified YIIP on Hovorka Model

Next, a simulation study is performed to study the meal disturbance rejection capability of original YIIP and modified YIIP for a 60g carbohydrate meal using nominal Hovorka model (Hovorka et al. 2004 and Wilinska et al. 2005). The 60g meal is given after one hour of the initial insulin infusion. The external insulin is infused through subcutaneous route and BG values are measured at 4 min sampling interval. The result of applying original YIIP on nominal patient of Hovorka type can be seen in Figure 3.14.
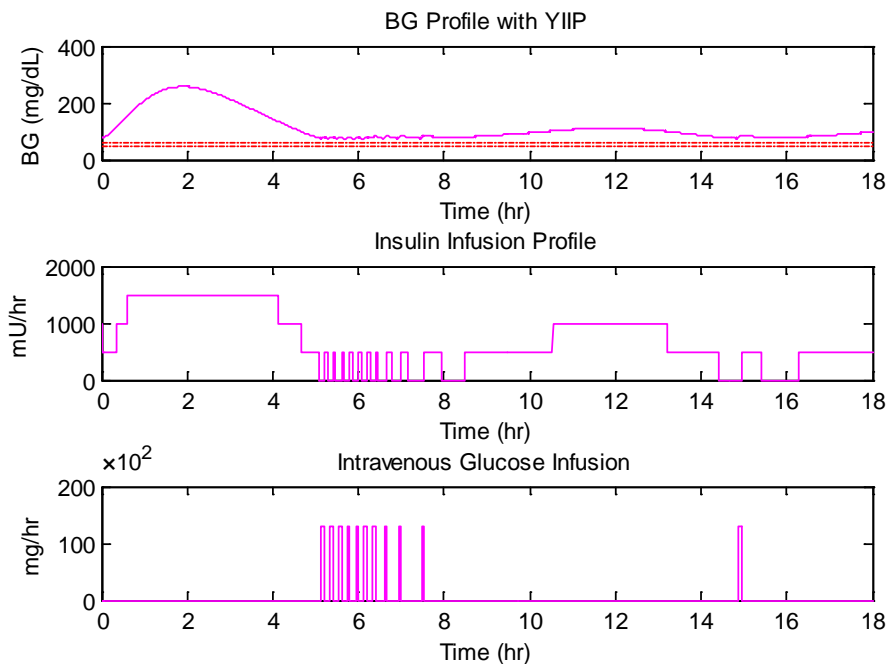
Figure 3.14: BG profile with YIIP on nominal patient (Hovorka model type) with normal initial condition

The YIIP maintains the BG value above 60mg/dL by using frequent intravenous glucose infusion; the total insulin used by MODYIIP is 11.57U while that of YIIP is 12.47U and total extra glucose amount used by YIIP is 137.5g for 18 hours. The maximum BG value is 256.99mg/dL. Thus, the YIIP gives acceptable performance. With MODYIIP, the result is as shown in Figure 3.15; it is seen that BG values can be maintained in the range (45-257mg/dL). The low BG value is definitely a concern although the hypoglycemia (above 45mg/dL) is not considered to be fatal.
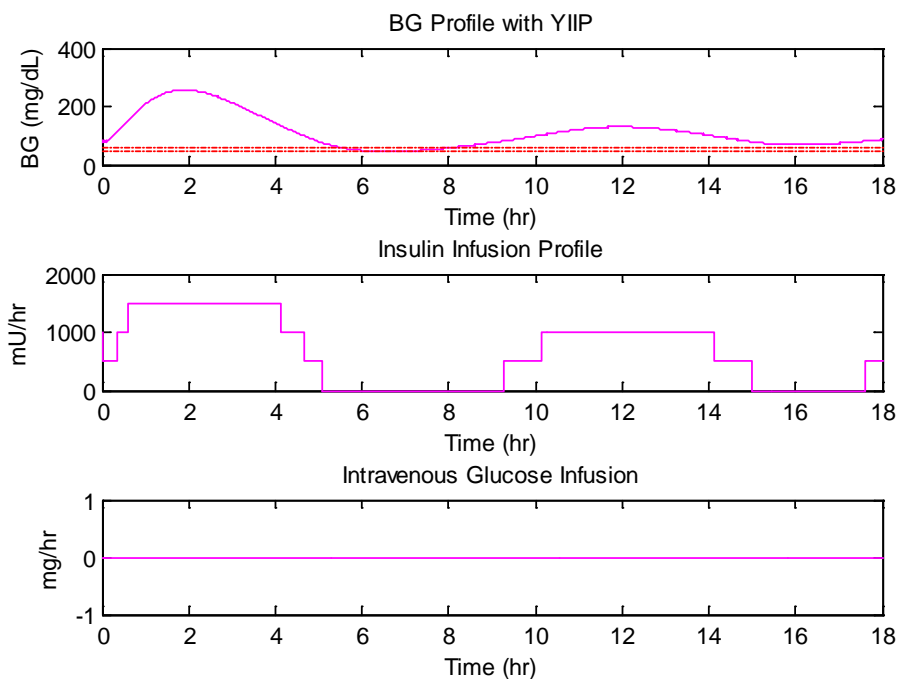
Figure 3.15: BG profile with MODYIIP on nominal patient (Hovorka model type) with normal initial condition

The performances of YIIP and MODYIIP on nominal Hovorka model patient with initial hyperglycemia of about 122mg/dL are shown in Figure 3.16 and 3.17 respectively.

It could be concluded that MODYIIP can cope well with the initial hyperglycemia as per results shown in Figure 3.17 with lowest BG and peak BG being 47.2mg/dL (hypogmic condition above 45mg/dL is not considered to be fatal) and 322.9mg/dL while YIIP resulted in 70.75mg/dL and 285.05mg/dL respectively using extra glucose 100g during 18 hours as shown in Figure 3.16.

58
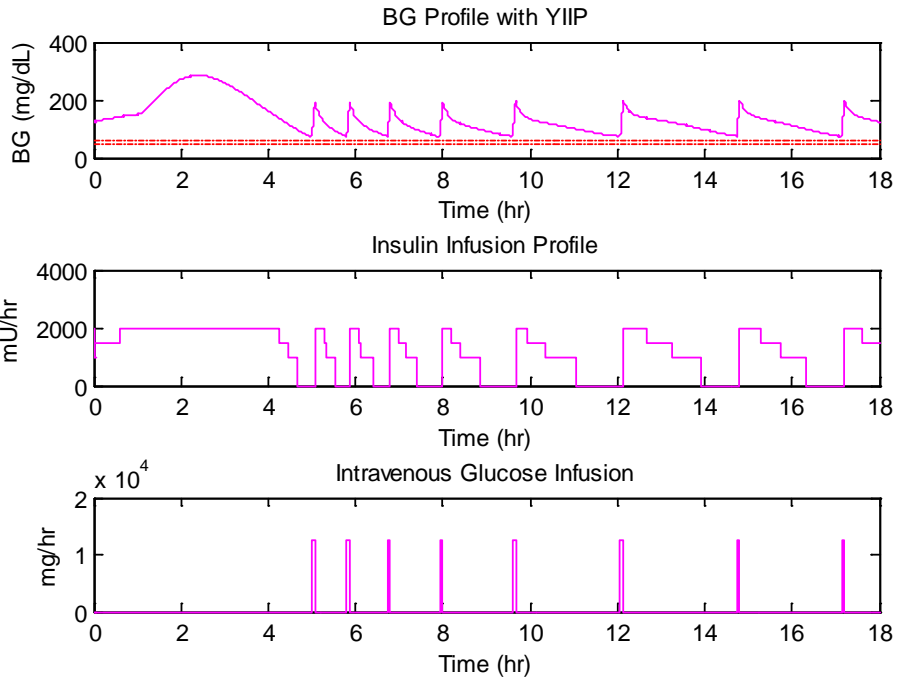
Figure 3.16: BG profile with YIIP on nominal patient (Hovorka model type) with initial hyperglycemic condition
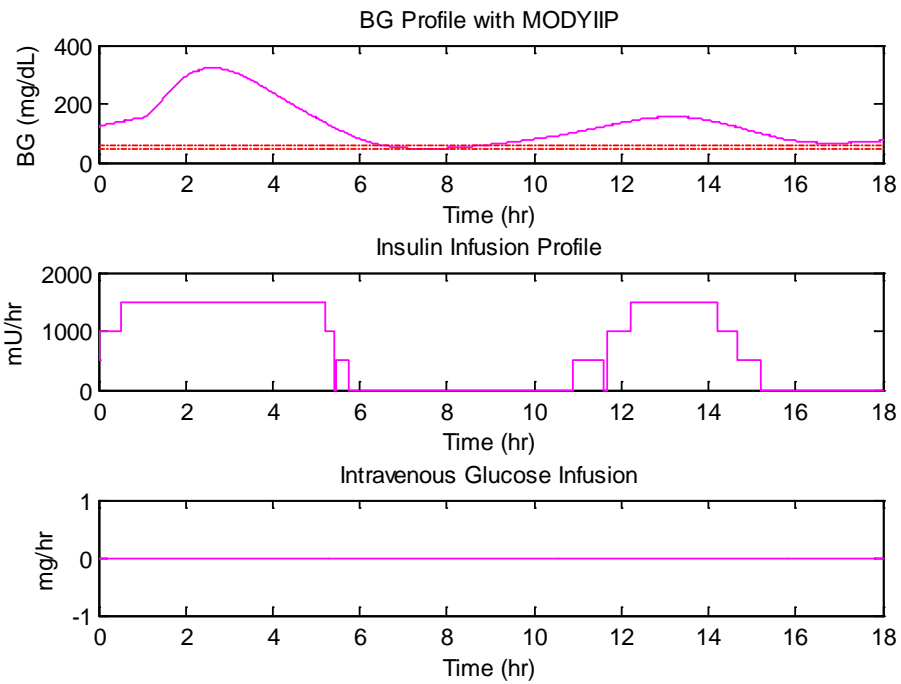
Figure 3.17: BG profile with YIIP on nominal patient (Hovorka model type) with initial hyperglycemic condition

These results show that MODYIIP is a possible candidate in treating T1D with simple and effective protocol.

3.8 Conclusions

The investigation conducted here shows that the YIIP may be modified and employed beneficially for blood glucose control in T1D patients. The original YIIP is tailored by modifying the amount of initial insulin infusion and bolus and by avoiding external glucose infusion – this results in a modified YIIP (MODYIIP) scheme. According to the results presented here, hypoglycemia (under 60mg/dL) can be successfully avoided with MODYIIP for all virtual T1D patients generated using Parker's model and Fabietti's model. On the Hovorka's model based nominal patient, MODYIIP results in a low BG value of 45.1mg/dL with initial BG at 81mg/dL– this is a cause of concern but may not lead to fatal consequences according to medical literature (Alsahli & Gerich, 2010). It is hoped that the MODYIIP scheme which is based on simple rules would be effective for BG control of T1D patients making it easy to implement in micro-implantable devices. Hyperglycemia (>180mg/dL) is tolerated so as to avoid hypoglycemia. Further studies could be performed for the modification of insulin infusion amount in MODYIIP so as to avoid high BG value (>180mg/dL) in T1D patients. Further studies could be performed for the modification of insulin infusion amount in MODYIIP so as to avoid high BG value (>180mg/dL) in T1D patients. In the meantime, to avoid hypoglycemia (that is evident in Hovorka model patient but it is not fatal in this study) could be performed.

Chapter 4

Blood Glucose Regulation in T1D Patients: Classification Using Principal Component Analysis and Treatment Using Tailored Modified YIIP

4.1 Background

The blood glucose (BG) response to insulin and glucose varies from patient to patient (inter-patient variability) and even within a patient from time to time (intra-patient variability). The range of the response can be quite wide when one considers a cohort of patients. This raises the question: would be worthwhile and possible to classify patients into groups and tailor YIIP to each of these groups? In Chapter 3, YIIP was applied to control BG level in T1D patients and a modified YIIP scheme was also suggested with a view to avoid hypoglycemia (< 60mg/dL). The modified YIIP was developed based on the "patients" developed using the model of Parker et al. (2000), and was validated on cohorts of patients generated using Fabietti and Bergman models as well as on the nominal "patient" of the Hovorka model. It was observed that the modified YIIP algorithm was quite successful in avoiding hypoglycemia except in the case of the Hovorka "patient". However, some patients did enter the hyperglycemic zone (> 180mg/dL) in postprandial condition. These results suggest that further modifications to the YIIP scheme are required, to make it effective in regulating BG levels in T1D patients. This objective is taken up in the present chapter where we develop a control strategy that is based on classification of patients into groups using Principal Components Analysis (PCA) followed by tailoring of YIIP to each of these groups. The goal is to regulate BG level in T1D patients in the range 60mg/dL < BG < 120mg/dL (in fasting condition) and 60mg/dL < BG < 180mg/dL (in postprandial condition).

4.2 Motivation and Objectives

As pointed out earlier, developing an algorithm that is effective and yet simple to implement will be helpful to treat T1D patients. YIIP (or its

modified version) is indeed easy to implement but its effectiveness in preventing hypo- and hyperglycemia needs to be improved further. The large uncertainty that one has to deal with in a single algorithm can perhaps be partitioned into smaller chunks of uncertainty via the grouping of patients into different classes and tailoring a control scheme (YIIP) for each of the classes. Such an approach can be expected to result in improved BG regulation in patients.

The patient's classes should be differentiated by their own intrinsic nature i.e. each class of patients should have similar intrinsic response to exogenous glucose and insulin. This information could be extracted from a suitable experiment or test (protocol). The experimental data for classification should be obtained from presently available diagnostic tests and the classification test should be simple for application in a clinical setting. These motivate us to continue our study in which YIIP will be used as the control algorithm but tailored for different classes of patients to achieve tight BG control. Our objective here is: (i) to develop a PCA-based methodology in which patients are classified into different classes based on data collected from a standard clinical protocol and (ii) to tailor YIIP for these different patient classes to meet the requirement of tight BG control (60mg/dL<BG<120mg/dL in fasting condition and 60 mg/dL < BG <180 mg/dL in postprandial condition).

4.3 Clinical Diagnostic Test for Patient Classification

Selection of an appropriate diagnostic test to use for developing the patient classification methodology is important. The chosen test should be simple and applicable in clinical setting. Already, several tests exist for the clinical diagnosis of diabetes – these include: (i) Oral Glucose Tolerance Test (OGTT), (ii) Fasting Plasma Glucose (FPG) test, (iii) Random Blood Glucose (RBG) test, (iv) Intra-Venous Glucose Tolerance Test (IVGTT), and (iv) Modified Intra-Venous Glucose Tolerance Test (MIVGTT). Among them, the MIVGTT is chosen because it is designed to observe both glucose and insulin dynamics with a single test. In MIVGTT, 0.3 g/ (kg body mass) of glucose is given for 1 min at the start and 0.02 U/ (kg body mass) of insulin is infused

after 20 min for a period of 5 min. Though the original MIVGTT needs 2.5 to 3 hours to complete and several BG measurements are taken along the way, we assume that both BG and Plasma Insulin (PI) measurements available once every 20 min during the first hour would be enough for our designed test. The setting of the duration of the test for one hour is to ensure that hypoglycemia (< 60 mg/dL) is avoided during the test. This makes the test very feasible for application in a clinical setting. The fasting condition (after 8 hours of overnight fasting), in which 0.1 mU/L < PI <25 mU/L and 70mg/dL<BG<300mg/dL, is required for our designed test. Note that the fasting PI is lower than 17 mU/L and the fasting BG is 70~99 mg/dL in normal individuals (Esoterix, 2010).

After the test, the patients are offered meal or glucose depending on the last recorded BG value – this is required because the exogenous insulin administered during the test could lower BG to an undesirable level after the test. According to our simulations, the test appears to avoid dangerous hypoglycemia during the test.

4.4 PCA as a Classification Tool

Multivariate statistical tools are efficient for exploratory multivariate data analysis and classification. While several methods exist, PCA is chosen for its simplicity and effective classification efficiency. The application of PCA is well known for fault diagnostics in the chemical and process industries; it has also found applications in several domains of natural and social sciences. The primary application of PCA is as a dimension reduction tool to construct information rich, uncorrelated pseudo-variables (or prominent principal components) from a larger set of correlated variables. The principal components are arranged by their eigenvalues with principal components associated with larger eigenvalues being the most significant. Thus the first principal component is associated with the largest eigenvalue and captures the maximum variation from the data set. Successive principal components capture successively less variance and, by construction, they are orthogonal to the earlier principal components.

Eigenvalue decomposition (EVD) of covariance matrix or singular value decomposition (SVD) of data set can be used to generate the principal components. The data set should be standardized (e.g. auto-scaled i.e. mean-centered and variance-scaled) before the EVD or SVD so that the variables that have large values (based on measurement units) do not dominate the principal components. The PCA calculation (based on SVD of the data matrix) is described briefly below.

- Auto-scaling of Variables

$$Z = X - \mu(X)./std(X) \tag{4.1}$$

- SVD of the auto-scaled data matrix Z

$$[U, \sigma, V] = svd(Z) \tag{4.2}$$

- Score Matrix or Principal Component Matrix can be obtained by

$$[Sc_1, Sc_2, \dots] = Z * V \tag{4.3}$$

The PCA model is characterized by the scores matrix T and the loadings matrix V wherein it is noted that only the first 'k' prominent principal components are retained. Therefore, we may write $Z = T_k V_k T$ where T_k and V_k contains only the first k columns of T and V.

When new data X_{new} arrives, it is first scaled in a manner consistent with the scaling of the original data matrix X.

$$X_{new,s} = \frac{X_{new} - \mu(X)}{std(X)} \tag{4.4}$$

Then PCA projection of the new data can be described by

$$t_{new} = X_{new,S} * V_k \tag{4.5}$$

4.5 Details of the Study

The ability of the control algorithm in meeting the desired control objectives should be tested on a cohort of patients. For our purpose, the model proposed by Fabietti et al. (2006) is chosen and its dominant parameters are perturbed by ± 70% of their nominal values to generate the patient cohort (the same procedure as mentioned in section 3.4 is applied here as well to produce

the cohort of patients). The control algorithm is developed by two steps viz. (1) patient classification using PCA and (2) tailoring of YIIP for each class of patients. The details of both these steps will be described in sections 4.5.1 and 4.5.2 respectively. In all the simulation studies here, measurement noise of about 17% has been added to the true blood glucose values. Input constraint has not been considered in the case studies. However, the lower bound for inputs (meal and insulin) is set to zero so as to keep the simulations physically meaningful.

4.5.1 Patient Classification Using PCA

The PCA model is developed based on the simulated experiments. 81 simulated patients (using Fabietti's Model) who meet the conditions as specified in section 4.3 are given our designed MIVGTT for one hour so as to extract the intrinsic characteristics of each patient. The response of each patient to given intravenous glucose input (given at the start of experiment) and exogenous insulin infusion input (given at the 20th min of experiment) are measured by collecting BG and PI measurements once every 20 min. Similar experiments for this patient cohort are run for 10 times with different random initial values of BG and PI (at the start of the experiment) but within the range of prescribed conditions. This helps to generate a larger patient cohort – thus many patients in the generated database will have similar parameters but, depending on their initial conditions, their response to the MIVGTT will vary considerably. The PCA model is developed based on the collected data.

Then the primary model is developed based on the above mentioned simulated experimental data with the help of PCA using information given by PI measurement data matrix (81 patients ×10 runs and four measurements each). The BG measurements are taken only to ensure that the patient does not experience hypoglycemia but are not used in the PCA model. Pre-processing of the data is performed by removing the linear trends using least squares - this helps to improve the classification efficiency by minimizing the effect of initial BG and PI values. Then, the variance scaling of each column is done so as to provide each variable (column) the same degree of importance in the PCA model. The preprocessed data set is then used to construct the PCA

model. When new patient data is obtained, the data is subject to consistent data pre-treatment and the patient is classified by projecting the data onto the present model (or onto present patient classes). More details on the PCA models will be provided later.

4.5.2 Tailoring YIIP for Patient Classes

Individualization of the treatment protocol for each patient can be very time consuming and such individualized protocols, even if generated, may lack the required robustness when faced with parametric uncertainties and variations. For this reason, the collected MIVGTT data is used to generate specific classes of patients and the YIIP is optimized for each class of patients. The optimized solution for each patient class should provide robust performance for patients within that class.

We seek to modify the YIIP for each patient class in such a way that the initial insulin infusion will be optimized and followed by the original YIIP based insulin infusion. These modified class-based protocols would be generated via the formulation of an optimization problem with suitable cost function and constraints. The optimization problem is set up to find the best initial insulin infusion amount for the YIIP on a "normal" day (with three meals) in which BG is controlled with the following three objectives: (i) BG not to exceed 180mg/dL in postprandial condition, (ii) BG not to enter the dangerous hypoglycemic region (<60mg/dL), and (iii) minimize the maximum value of BG following each meal. The schematic representation of the optimization problem is demonstrated in Figure 4.1 where 'x' represents the initial insulin infusion amount. The need for larger insulin infusion amount to meet objectives (i) and (iii) conflicts with the requirement of objective (ii) which is to use the minimum amount of insulin required to avoid hypoglycemia. The three objective functions are linearly combined with equal weight into a single objective function. Similar optimization problems are set up for each class of patients obtained from the classification process and are solved separately. The optimal solutions obtained from the formulated optimization problems would serve as the initial insulin infusion amount for the patient classes.
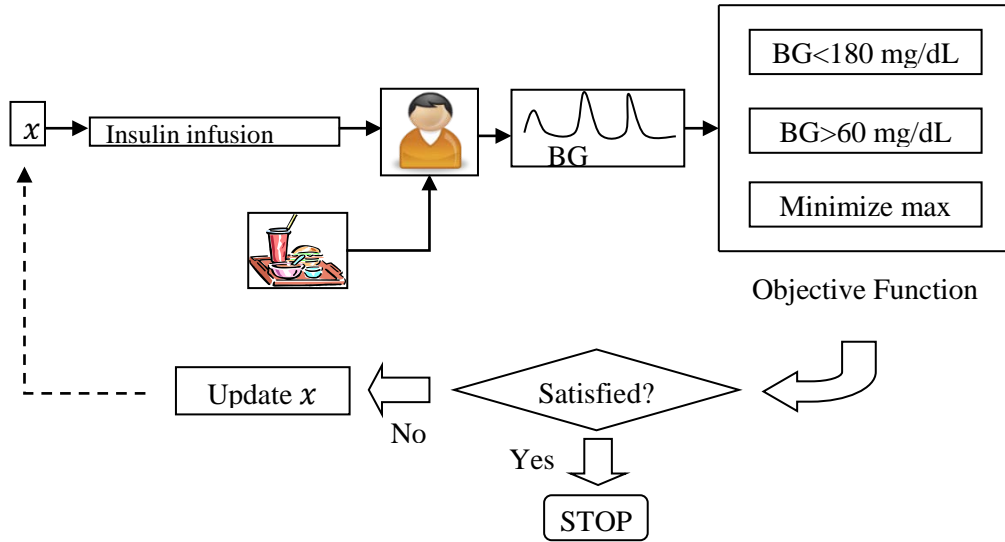
Figure 4.1: Schematic of the Optimization Algorithm

The mathematical description of the optimization problem for a class of patients can be described as follows. The output BG values for patient i over the time t, $BG_i(t)$, which is function of insulin infusion and meal disturbance are described as

$$BG_i(t) = h_i\big(u(t), d(t)\big). \tag{4.6}$$

Where,

t = time interval from 0 to t,

$u(t)$ = the rate of insulin infusion over the time t, $u(t) = f(x, YIIP)$,

x = initial insulin infusion,

$YIIP$ = original YIIP based insulin infusion that followed x,

$d(t)$ = the meal disturbance over the time t, $d(t) = g(M)$,

M = meal (three meals in a normal day).

The highest BG value, $hstBG$ and lowest BG value, $lstBG$ for a class of n patients are:

$$hstBG = \max\left(\big(BG_i(t)\big)_n\right)$$

and
$$lstBG = \min\left(\big(BG_i(t)\big)_n\right).$$

The three objective functions are considered as

$$o(x) = hstBG - 180$$

where, $\qquad o(x) > 0 \tag{4.7}$

$$p(x) = 60 - lstBG$$

where, $\qquad p(x) > 0 \tag{4.8}$

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and
$$q(x) = hstBG. \tag{4.9}$$

These functions are combined into a single objective function with equal weight for a nonlinear optimization problem as

$$\min_{x} (o(x) + p(x) + q(x))^2 \tag{4.10}$$

with constraint $x \geq 0$.

The best value of x for the patient class is found by optimizing the BG values to be in the range 60~180 mg/dL with the objective function (equation 4.10). Note that the initial insulin infusion (x) has significant effect on BG control in YIIP and its requirement for fine tuning (in Chapter 3), and thus x is considered as the decision variable here. The constraint that x is greater than or equal to zero is set in order to avoid negative values. The function $o(x)$ is for BG not to exceed 180 mg/dL in postprandial condition, $p(x)$ is for BG not to enter the dangerous hypoglycemic region ($<$ 60 mg/dL), and $q(x)$ is to minimize the maximum value of BG following each meal.

4.6 Results and Discussion

We present the results and discussion for this study in three parts: (1) PCA results on patient classification (section 4.6.1), (2) tailored YIIP and its results (section 4.6.2) and (3) validation of the developed algorithm on other patient models (section 4.6.3).

4.6.1 PCA Results on Patient Classification

After applying PCA directly onto the (810×4) data set (explained earlier) without removal of linear trends, 9 patient classes are obtained as shown in Figure 4.2. It is confirmed, via matching each point in the PCA score plot with the assigned experiment number (i.e. each patient), that each line represents a single patient group. However, it would be useful to have these groups segregated in the PCA score space if we were to use the scores plot to classify future "patients" into one of these groups.
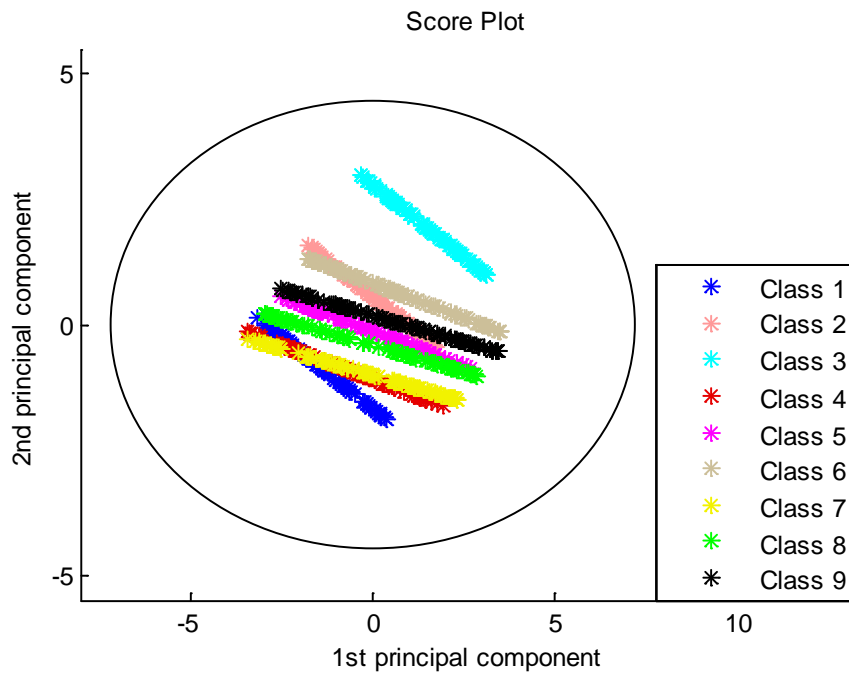
Figure 4.2: Patient classes obtained from PCA without data pretreatment with 99.99% confidence interval
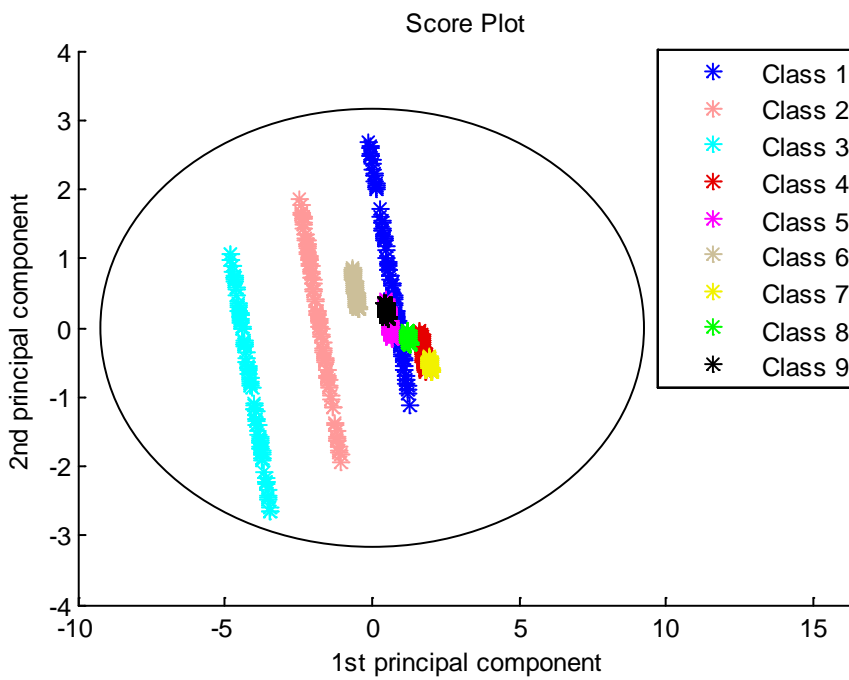
Figure 4.3: Patient classes obtained from PCA with data pretreatment with 99.99% confidence interval

When the linear trend is removed from each data sample and PCA of the resulting data set is performed, the results are as shown in Figure 4.3. It is seen that the segregation is much better now with only classes 5 and 9 overlapping significantly. With the linear trend removed from each data sample, PCA explains 85.25% of the variance in the data set with the 1st principal component and 100% of the variance with the first two principal components. The total of 810 points resulted from 10 runs (different initial BG and PI values for each run) of MIVGTT for each of the 81 patients (mentioned in section 2.6 with 70% variation in patient parameters considered) shows up in Figures as 9 patient classes (each class consists of 90 points).

The loading Plot of PCA without pretreatment and with pretreatment (shown in Figure 4.4 and 4.5 respectively) show the presence of three clusters in the variable space. This indicates that three measurements (one taken out of each of these clusters) may be sufficient information in order to characterize the patients. This insight may be useful in designing measurement protocols for patient classification and treatment.
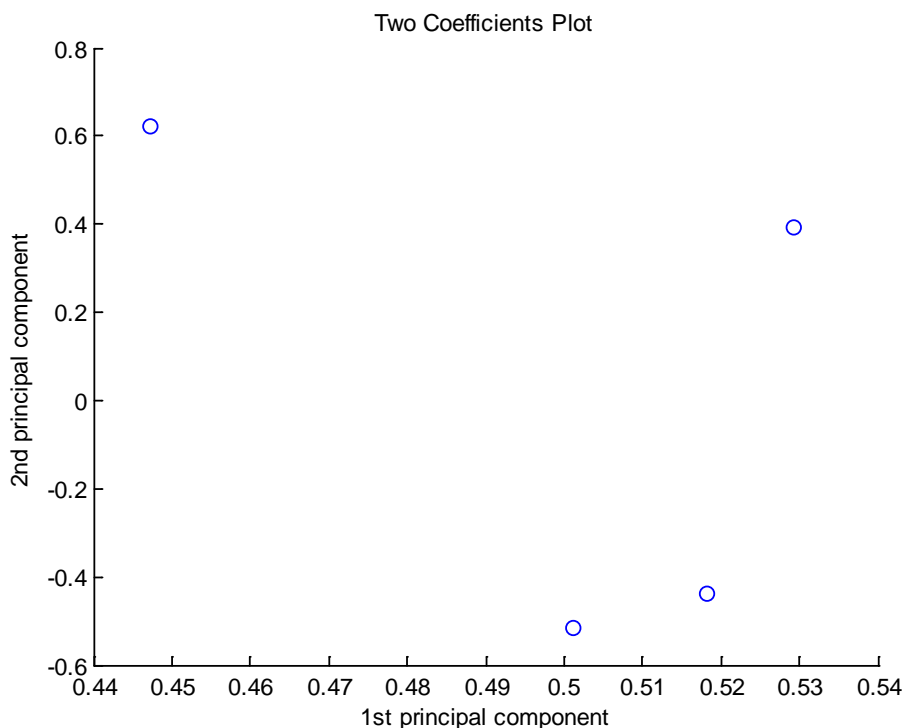
Figure 4.4: Loading Plot obtained from PCA without data pretreatment
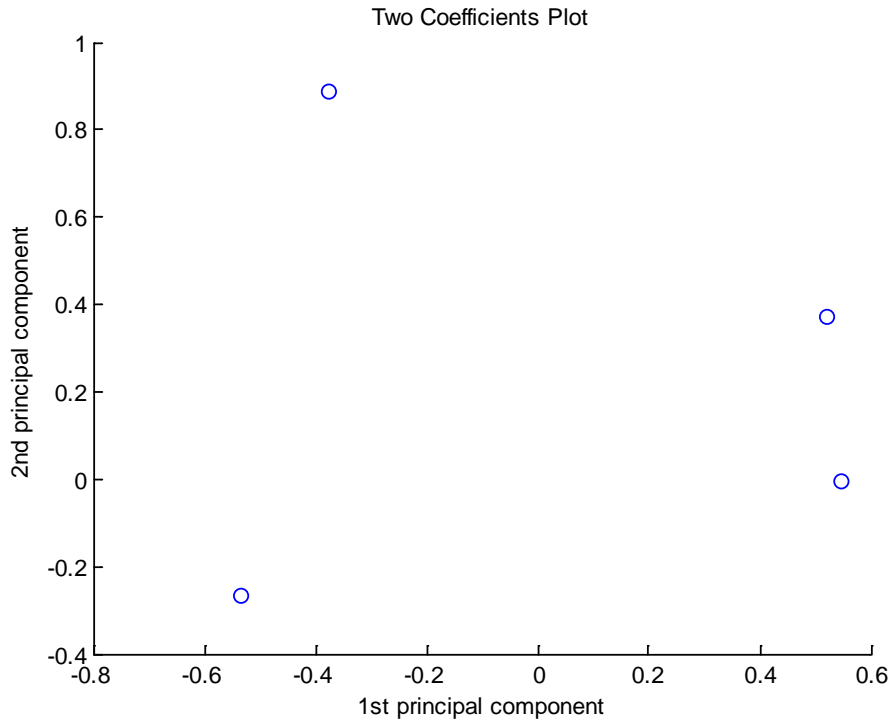
Figure 4.5: Loading Plot obtained from PCA with data pretreatment

4.6.2 Results with the Tailored YIIP

The single variable optimization (SVO) problem of finding out the best initial insulin infusion amount (defined by 'x' in Figure 4.1) for the 9 patient classes is solved by the Nelder-Mead Simplex Search method. For this SVO problem, the simplex search reduces to a line search. MATLAB's (version 7.6, 2008a) built-in algorithm for unconstrained optimization '*fminsearch*' is employed to solve this optimization problem for each patient class.

Positive values between 0 and 10 are provided as initial guess values of 'x'. The algorithm converged to the optimal values in each case for the default tolerance in the '*fminsearch*' algorithm. The $lstBG$ and $hstBG$ values in the functions $o(x)$ and $p(x)$ are changed to 67mg/dL and 177mg/dL (instead of 60mg/dL and 180mg/dL) to avoid hypo- (<60mg/dL) and hyper- (>180mg/dL) glycemic condition. The optimal values of 'x' and the highest & lowest BG values of each of the 9 classes are summarized in Table 4.1.

Table 4.1: Summarized results of tailored YIIP for all patient classes

Class	Initial Insulin Amount (mU/hr.)	Lowest BG (mg/dL)	Highest BG (mg/dL)
1	6.99	67.00	178.86
2	2.05	67.82	178.88
3	1.14	64.83	179.46
4	6.87	61.23	182.64
5	2.03	60.55	182.67
6	1.02	60.10	186.04
7	7.38	60.68	181.04
8	2.21	59.01	180.99
9	1.06	59.31	184.16

Figure 4.6 through 4.14 demonstrate the effectiveness of tailored YIIP on T1D patients on a normal day comprising of three meals (taken at 7 AM, 12 Noon and 6 PM) with 20 g, 50 g & 50 g carbohydrate content respectively. Based on the optimal values of 'x', the 9 classes can be further reduced into 3 groups. The values of 'x' for Group I (Class 1, Class 4 & Class 7) are higher than those of Group II (Class 2, Class 5 & Class 8) which are higher than those for Group III (Class 3, Class 6 & Class 9). Going forward, the results will be discussed based on these three groups.

4.6.2.1 Results of Tailored YIIP for Group I

Group I (Classes 1, 4 and 7) patients have BG values in the range of (60~183mg/dL) - the corresponding illustrations are shown in Figure 4.6, 4.7 and 4.8 respectively. Hypoglycemia (<60mg/dL) is seen to be avoided successfully. Class 7 patients require the highest initial insulin amount among this group.

Analysis of the parameter values reveals that this group has the same insulin diffusion rate value (K_i=3.03e-3mL/hr), which is also the lowest among all groups (nominal K_i=0.0101mL/hr). The time constants of insulin diffusion in the plasma compartment (T_{xi}) are 0.543hr, 1.81hr and 3.077hr for Classes 1, 4 and 7 respectively.
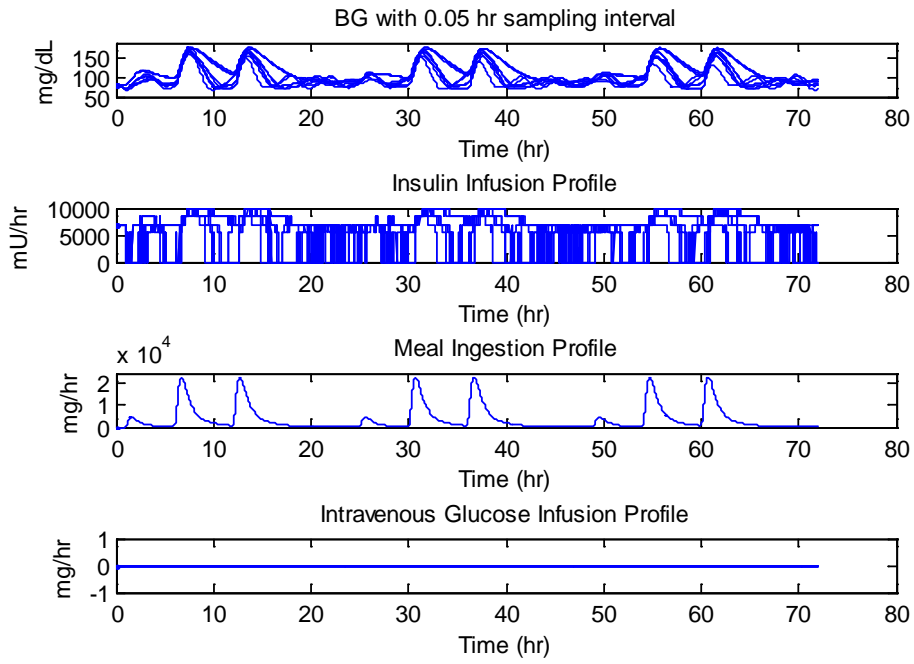
Figure 4.6: Tailored YIIP result for Class 1 Patients
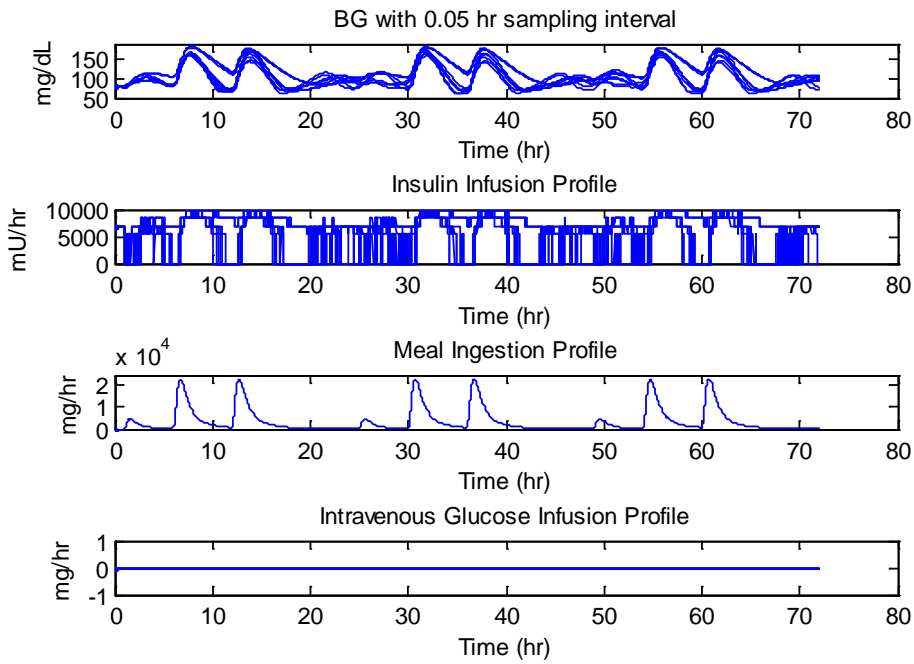
Figure 4.7: Tailored YIIP result for Class 4 Patients
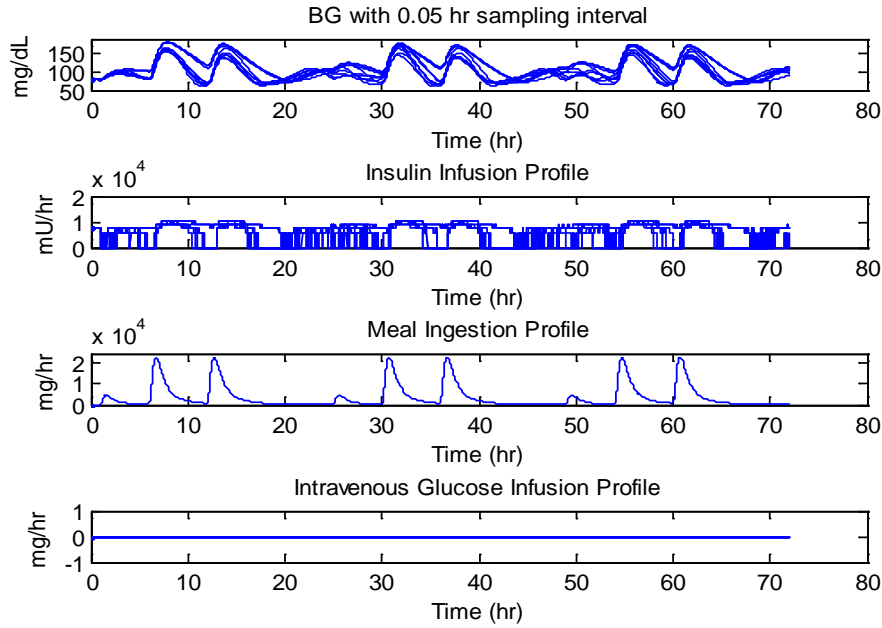
Figure 4.8: Tailored YIIP result for Class 7 Patients

4.6.2.2 Results of Tailored YIIP for Group II

Blood glucose values for Group II (Classes 2, 5 and 8) patients lie in the range between 59mg/dL and 183mg/dL. The profiles of BG, insulin infusion, meal ingestion and intravenous glucose infusion for these three classes are shown in Figure 4.9, 4.10 and 4.11 respectively. Here again, hypoglycemia (BG < 60mg/dL) is avoided for classes 2 and 5 patients and only marginally violated for class 8 patients. Analysis of the parameter values for this patient group reveals that this group has the same insulin diffusion rate (K_i) values. Specifically, K_i (0.0101mL/hr) value for this group can be regarded as medium among the three groups. The time constant of insulin diffusion in the plasma compartment (T_{xi}) for each class of this group is in the ascending order from the lowest to the highest with Class 8 patients having the highest T_{xi} (0.543 hr., 1.81 hr. and 3.077 hr. for Classes 2, 5 and 8 respectively). Class 8 patients require the largest initial insulin amount among this group to maintain BG in the acceptable range (60mg/dL<BG<180mg/dL). Thus it appears that the low time constant (T_{xi}) value results in effective BG control with the tailored YIIP scheme.
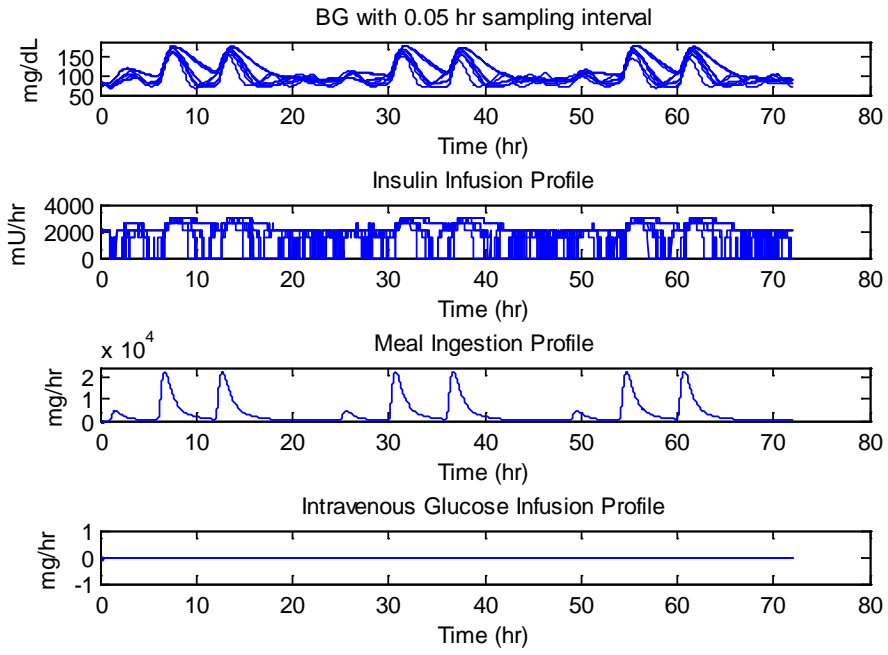
Figure 4.9: Tailored YIIP result for Class 2 Patients
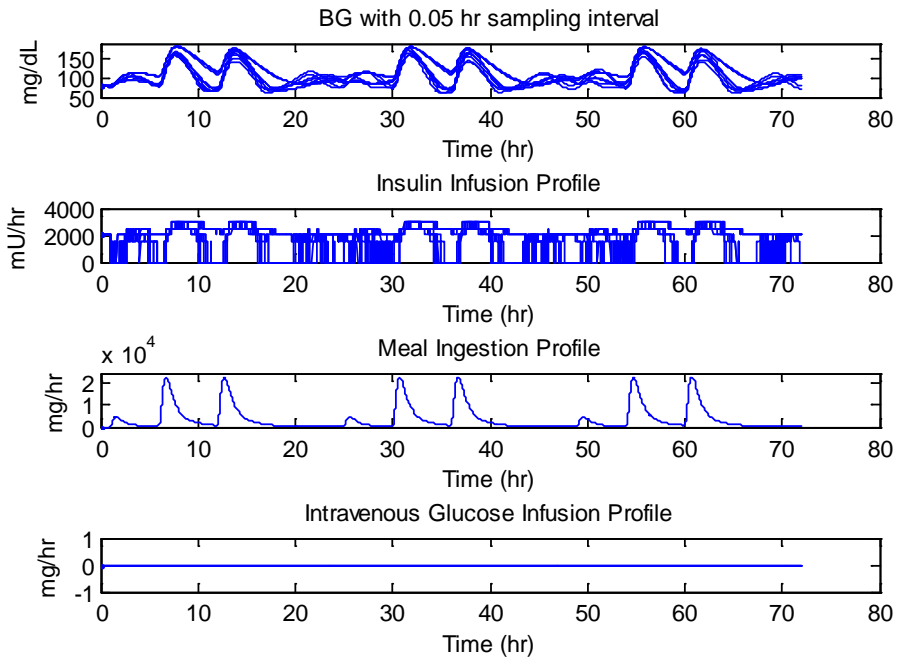
Figure 4.10: Tailored YIIP result for Class 5 Patients
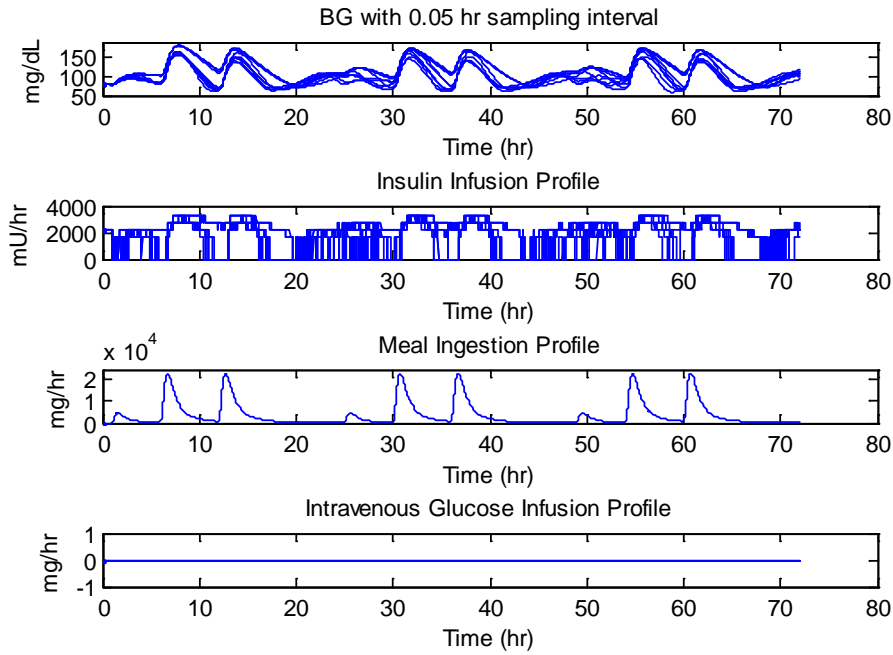
Figure 4.11: Tailored YIIP result for Class 8 Patients

4.6.2.3 Results of Tailored YIIP for Group III

The BG values for patients in Group III (Classes 3, 6 and 9) are between 59mg/dL and 187 mg/dL over the three simulated days - the corresponding plots are in Figure 4.12, 4.13 and 4.14 respectively. There is a tiny violation of the 60mg/dL hypoglycemia limit in the case of Class 9 patients. Hyperglycemia is experienced in Classes 6 and 9 patients with Class 6 patients exceeding the 180mg/dL limit by as much as 6 mg/dL.

Analysis of the parameter values shows that this group has the highest insulin diffusion rate (K_i = 0.01717mL/hr) value among all groups. This group also requires the lowest initial insulin amount among all groups. And the time constant of insulin diffusion in the plasma compartment (T_{xi}) for each class of this group are in the ascending order from the lowest to the highest value with Class 9 patients having the highest T_{xi} value (0.543hr, 1.81hr and 3.077hr for Classes 3, 6 and 9 respectively).
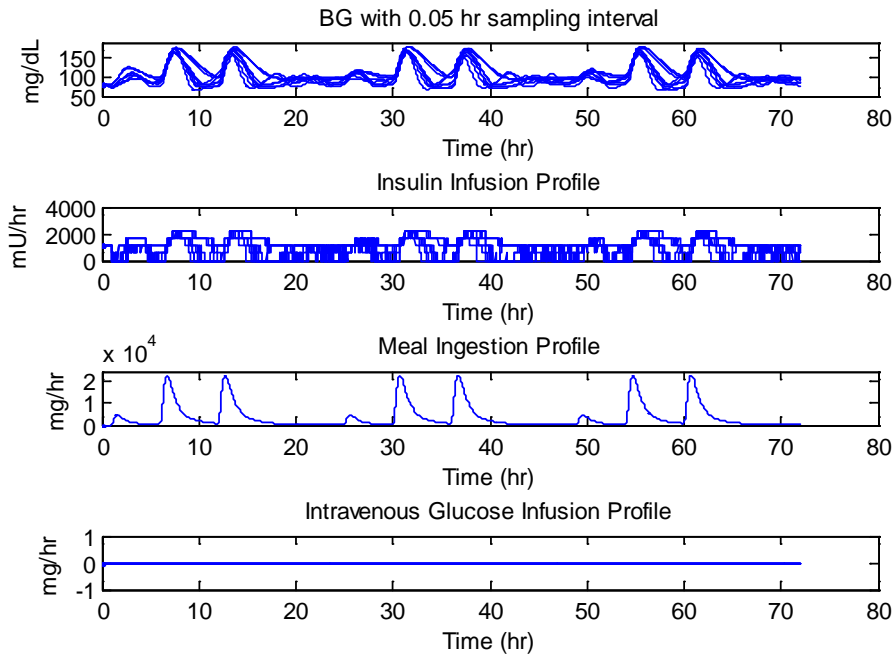
Figure 4.12: Tailored YIIP result for Class 3 Patient
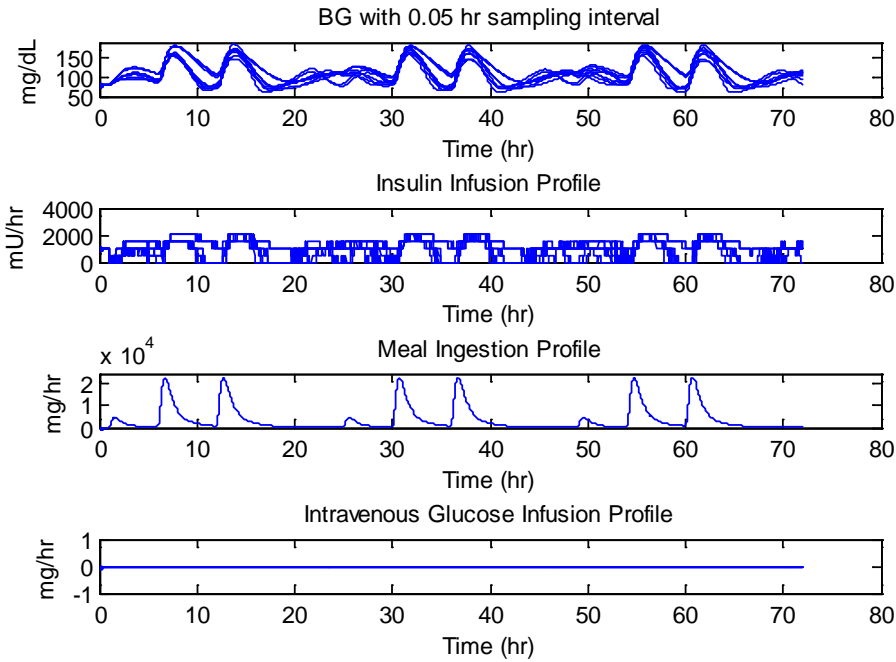
Figure 4.13: Tailored YIIP result for Class 6 Patients
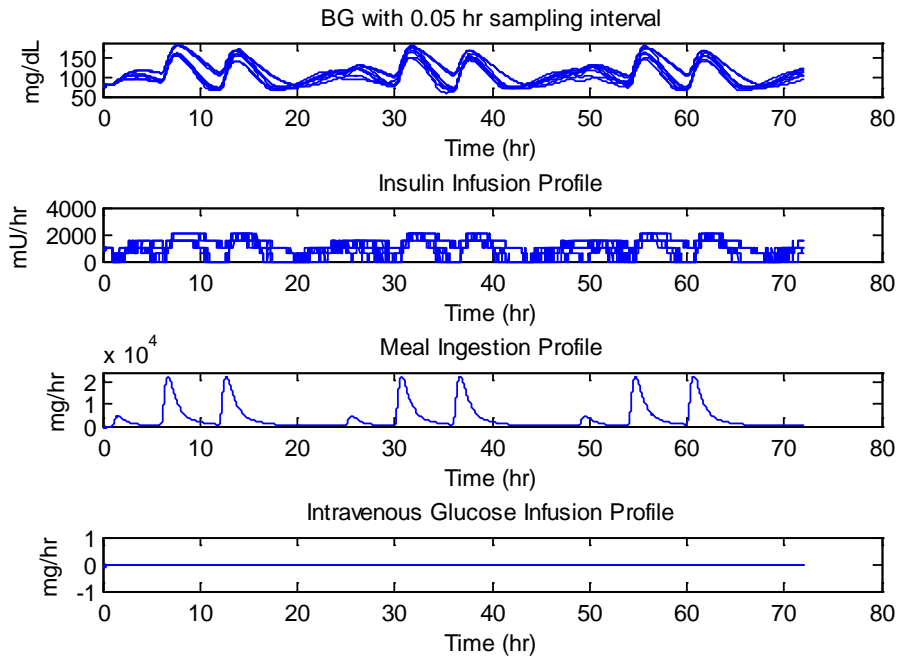
Figure 4.14: Tailored YIIP result for Class 9 Patients

More detailed analysis of patient responses whose BG values exceed 180mg/dL reveals that these patients have very low insulin sensitivity. Thus, insulin sensitivity can be regarded as a significant factor in the quality of BG regulation achieved with tailored YIIP. Class 6 patients require lowest initial insulin amount among all groups to maintain BG in the acceptable range (60mg/dL < BG < 180mg/dL). Overall, low time constant (T_{xi}) value, high value for the plasma insulin distribution volume (K_i) and high insulin sensitivity result in better BG control as expected.

4.6.3 Validation of Developed Algorithm on Other Patient Models

As proof of the appropriateness and effectiveness of the classification based tailored YIIP algorithm, it is tested on patients created from the Parker, Bergman and Hovorka models. Three "patients" using nominal parameter values in the Parker, Bergman and Hovorka models were tested with the classification based tailored YIIP algorithm. The classification test performed on these three patients (after data pretreatment) indicates that all of them are classified as being similar to Class 3 patients (see Figure 4.15). Class 3 patients require less initial insulin infusion amount compared to most other

classes (see Table 4.1). This result is consistent with the low basal insulin requirements of the Parker, Bergman and Hovorka models (with nominal parameters), and demonstrates the validity of the classification algorithm. Averaging of initial insulin infusion amount may be adopted and employed if a "tested patient" happens to fall in between the classes shown in Figure 4.15.
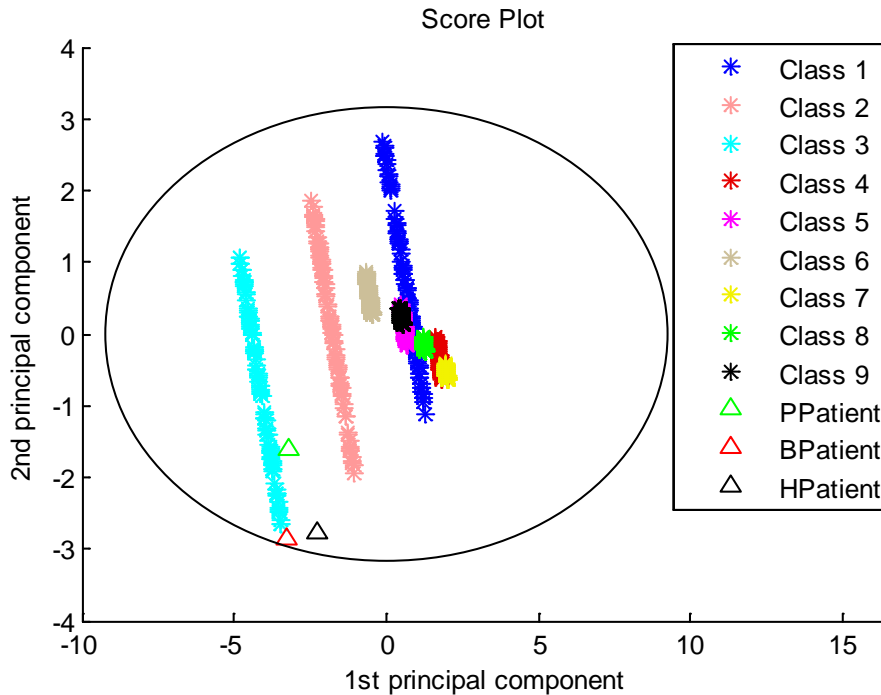
Figure 4.15: PCA based classification of patients obtained from Parker, Bergman and Hovorka models (with data pretreatment) with 99.99% confidence interval

To test the effectiveness of the YIIP algorithm that was tailored for Class 3 patients of the Fabietti model, the three patients (generated from the nominal Parker, Bergman and Hovorka models) are challenged with the same carbohydrate intake over a 3-day period as was done earlier. The obtained results are plotted in Figure 4.16, 4.17 and 4.18 respectively. The resulting BG values are in the range of (50mg/dL < BG < 180mg/dL). For the Parker model, the minimum and maximum BG values were 81.08 mg/dL and 115.48mg/dL respectively. For the Bergman model the minimum and maximum BG values were 69.52mg/dL and 175.8mg/dL respectively while, for the Hovorka model, these values came out to be 51.28mg/dL and 116.16mg/dL respectively. The results indicate that the strategy does not lead to hyperglycemia for any of the patients.
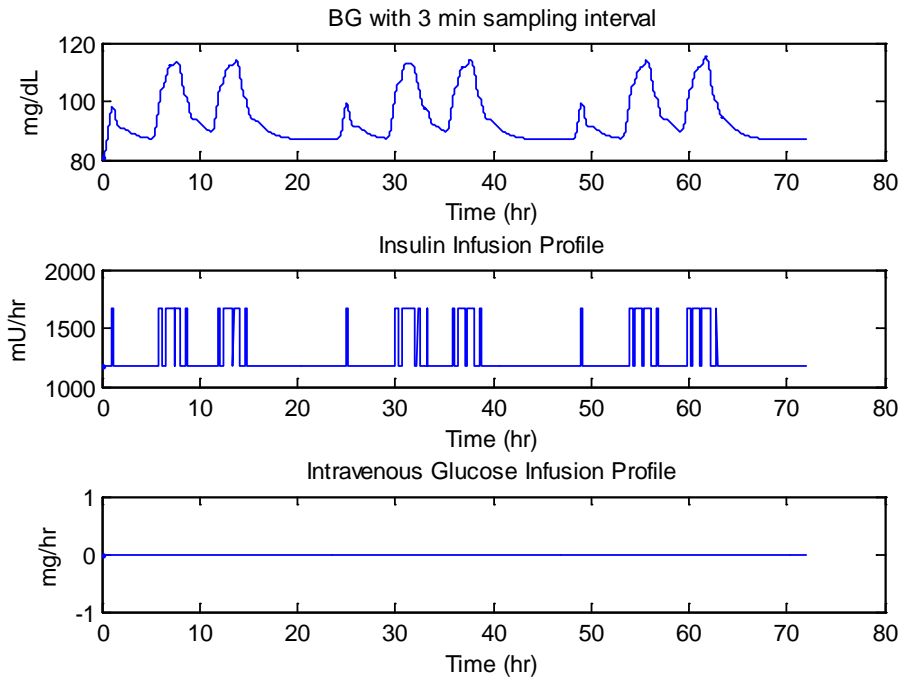
Figure 4.16: Tailored YIIP result for Parker Model nominal Patient
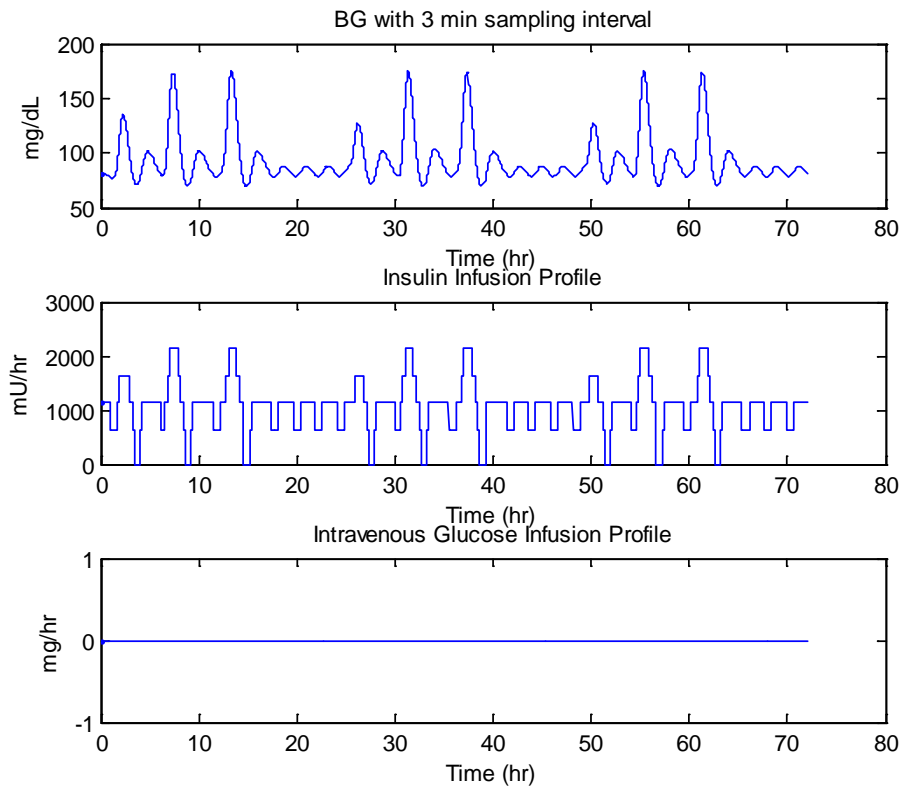
Figure 4.17: Tailored YIIP result for Bergman Model nominal Patient
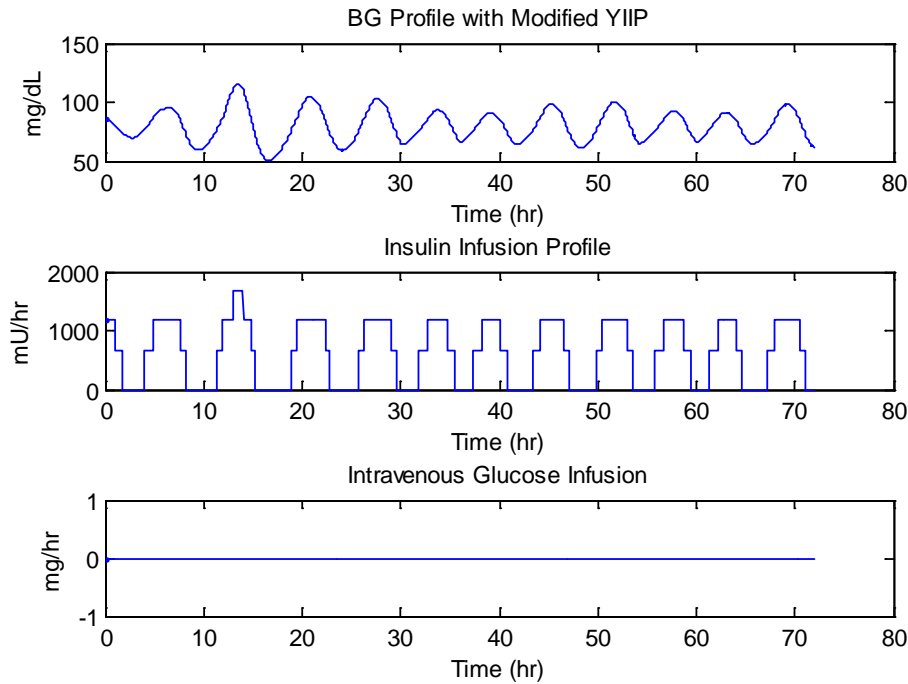
Figure 4.18: Tailored YIIP result for Hovorka Model nominal Patient

The Hovorka patient enters the dangerous hypoglycemia region (BG<60mg/dL) which is a concern. It would appear that the algorithm must be further tuned to avoid hypoglycemia through the intravenous infusion of glucose – this "handle" is not utilized by the algorithm. Also, the BG profile of the Hovorka patient is oscillatory and its amplitude is also significant. The Bergman patients' BG profile is also oscillatory but has a smaller amplitude and therefore not a real concern.

4.7 Conclusions

This chapter demonstrates the development of a novel BG regulation algorithm for T1D patients. It is based on a classification procedure that utilizes PCA to categorize the patient cohort into 9 classes which is further reduced into 3 groups. The YIIP algorithm was tailored for each of the classes through the optimal choice of initial insulin amount. Any new patient would be subjected to the MIVGTT and the test results would be projected on to the PCA scores chart to classify the patient into one of the nine classes. The YIIP

algorithm tailored for that class would be implemented on the patient. This approach showed very promising results on the Parker and Bergman patient but resulted in hypoglycemia on the Hovorka patient. More rigorous tests would be needed on a large cohort of patients generated out of these models to test the robustness of the proposed approach. The proposed approach to classification based BG control, has also identified opportunities to reduce the experiment time of the intravenous glucose tolerance test (IVGTT) as well as indicated that about 3 measurements should suffice during the experimental duration of the IVGTT.

Chapter 5

Control of BG Levels in T1D Patients using the Linear Modeling Error Compensator Approach

5.1 Background

The design of robust controllers is necessary for the model-based control of processes that have significant uncertainties in their structure and/or parameter values. In the context of blood glucose control in diabetes patients, there is a need to design controllers that are robust against the unavoidable model-patient mismatch that arise due to the inter- and intra-patient variability.

In the past, researchers have attempted to handle this problem in several ways; for example, systematic design of robust H_∞ controller based on uncertainty characterization was pursued by Parker et al. (2000), and a simulation-optimization based approach was adopted by Ramprasad et al. (2004b). They established the applicability of their approach by showing how their robust controllers rejected meal disturbances on a cohort of virtual patients taken from within the uncertainty bounds. The positive and negative aspects of these approaches were presented in Chapter 2.

Further studies are needed in developing and testing the effectiveness of robust controllers for blood glucose regulation in T1D patients and reach the goal of attaining fail-proof artificial pancreas. This chapter aims to develop a strategy based on the linear modeling error compensation (LMEC) approach and examine its effectiveness in handling model uncertainties.

5.2 Motivation and Objectives

There is a need to examine alternative approaches that can handle uncertainties in patient models for blood glucose level control in T1D patients. What we need is a simple and yet effective algorithm that can help in this regard – linear robust controllers are therefore prime candidates for the purpose. Among robust controllers, the modeling error compensator has been

found effective in the control of chemical reactors (Alvarez-Ramirez, 2002) and in observer design for estimating bearing internal temperature and pre-load of machine tool spindle (Tu and Stein, 1998). However, these studies involved nonlinear models. Sun et al. (1994) proposed a linear modeling error compensator (LMEC) scheme which could be applied to handle uncertainties in linear models. Here, we wish to study the applicability of the LMEC scheme to regulate blood glucose concentration in T1D patients. Significant levels of uncertainty in patient model parameters for the different T1D models will be considered and LMEC controllers will be developed. The developed LMEC scheme will be tested on cohorts of virtual patients to determine its performance.

5.3 Linear Modeling Error Compensator

In LMEC, a model reference controller is used for primary design and the parameter adaptation is using a compensator instead of on-line identification for estimation of system parameter(s) and tuning of controller parameter(s). The central idea of LMEC is to compensate for the error arising out of parametric uncertainty by determining the modeling error via plant input and output signals with known linear model order and using this information in the design. In addition to nominal feedback, another feedback loop is introduced using the modeling error and this feedback action is explicitly proportional to the parametric error which is the source of uncertainty. When no modeling error is present (i.e. the model parameter is not different from the nominal model), the compensator output becomes zero and the control scheme is then equivalent to the original model reference controller.

5.3.1 Uncertainty Description

The bounds for the uncertainty that represents inherent inter- and intra-patient variability, is incorporated into the parameters of different diabetes patient models. Specific model parameters are perturbed by up to ±40% from their nominal values to obtain patient cohorts. Such an investigation helps to check the robustness of the LMEC and how its performance is when presented

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with the inevitable model mismatch (details including those of the generated patient cohort are mentioned earlier in section 2.4). The controller is based on the linear transfer function approximation of the patient but the "true" patient is the nonlinear model. It is on the true patient that the LMEC based control algorithm will be tested. In this study, the models for controller design are obtained as second order transfer function approximations through a step test on the nonlinear model. The step response(s) are obtained by decreasing insulin infusion by 10% of its nominal value in the particular patient model. The bounds for uncertainty are determined from the parameters of the estimated linear second order transfer functions.

5.3.2 LMEC Controller Design

The plant $G(s)$ (assumed to be strictly proper) is as follows:

$$G(s) = \frac{Y(s)}{U(s)} = \frac{B(s)}{A(s)} = \frac{k_p(s^m + b_{m-1}s^{m-1} + ... + b_0)}{s^n + a_{n-1}s^{n-1} + ... + a_0} \tag{5.1}$$

where $U(s)$ = Laplace transform of the input, $Y(s)$ = Laplace transform of the output.

In this study, we use a second order transfer function to represent the plant.

$$G = \frac{k_P}{(s+\beta)(s+\gamma)}$$

For the nominal model,
$$G_0 = \frac{k_{P0}}{(s+\beta_0)(s+\gamma_0)}$$

Let
$$Y_M(s) = M(s)R(s) \tag{5.2}$$

and
$$Y(s) = G_c(s)R(s) \tag{5.3}$$

where $M(s)$ = reference model which gives the desired behavior of the closed-loop system, $R(s)$ = reference signal, $G_c(s)$ = transfer function representing the closed loop system, $Y_M(s)$ = desired system response, and $Y(s)$ = closed loop system response.

The control objective is to design a feedback controller which uses $R(s)$ and $Y(s)$ to generate $U(s)$ in such a way that $Y(s)$ is as close as

possible to $Y_M(s)$ in the presence of parametric uncertainty in $G(s)$. The reference model can be described as:

$$M(s) = \frac{C_0(s)G_0(s)}{1 + F_0(s)C_0(s)G_0(s)} = \frac{z_M(s)}{p_M(s)} \tag{5.4}$$

in which $G_0(s)$ is the nominal patient model bounded in $G(s)$, and $C_0(s)$ and $F_0(s)$ are conventional adaptive controllers described by:

$$C_0(s) = k\frac{\Lambda(s)}{\Lambda(s) - \theta_1(s)} \tag{5.5}$$

$$F_0(s) = -\frac{1}{k}(\frac{\theta_2(s)}{\Lambda(s)} + \theta_3) \tag{5.6}$$

where $k = \dfrac{k_M}{k_{p0}}$, k_M = leading coefficient of z_M, k_{p0} = nominal value of k_p, $\Lambda(s)$ = a stable monic polynomial of degree $n-1$, (αz_M), α = a stable polynomial, $\theta_1(s), \theta_2(s)$ = polynomials of degree at most $n-2$ and θ_3 = constant.
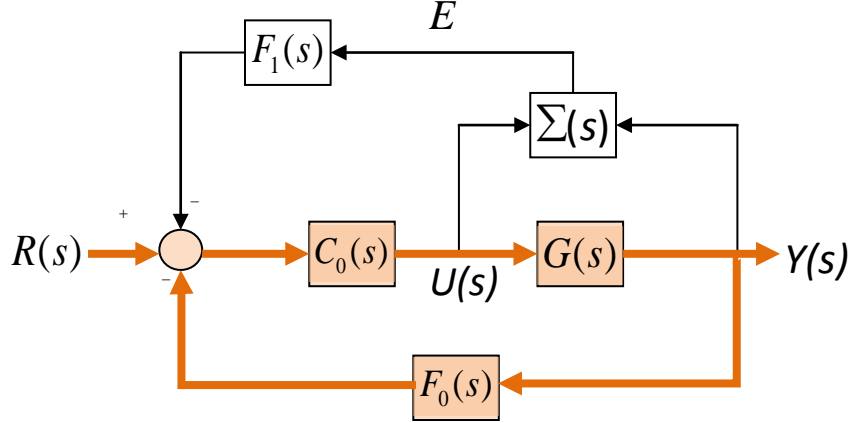
Figure 5.1: Schematic of a feedback control system with modeling error compensation

Equation (5.4) can be deduced from Figure 5.1 using lower loop (bold lines and painted blocks).

For the actual plant, the controller parameters which are varying (i.e $\theta_i = \theta_i^*$ and $k = k^*$) can be solved using the following polynomial identity.

$$(\Lambda - \theta_1^*)A - (\theta_2^* + \Lambda\theta_3^*)B = k^*\alpha p_M B \tag{5.7}$$

Instead of solving equation (5.7), the parameters for the nominal plant are solved by

$$(\Lambda - \theta_1)A_0 - (\theta_2 + \Lambda\theta_3)B_0 = k\alpha p_M B_0 \tag{5.8}$$

By multiplying equation (5.7) with $\left(\frac{M(s)}{\Lambda(s)}\right)Y(s)$ and using the plant equation $B(s)U(s) = A(s)Y(s)$, one obtains

$$MU = k^*Y + M\frac{\theta_1^*}{\Lambda}U + M\frac{\theta_2^*}{\Lambda}Y + \theta_3^*MY. \tag{5.9}$$

With the above scheme, robustness is not guaranteed against uncertainties that are present in the model $G(s)$. To achieve the robustness in the presence of parametric uncertainty, the modeling error signal $E(s)$ is defined by using the plant input and output signals and the information on $M(s)$ and $G_0(s)$. This signal reflects the difference between G and G_0.

$$E(s) = \Sigma(U,Y)$$

$$E = M\frac{\theta_1}{\Lambda}U + M\frac{\theta_2}{\Lambda}Y + \theta_3 MY + kY - MU \tag{5.10}$$

By using equation (5.9) for substitution of MU into equation (5.10), E is related to the controller parameter error as:

$$E = (\theta_1 - \theta_1^*)\frac{M}{\Lambda}U + (\theta_2 - \theta_2^*)\frac{M}{\Lambda}Y + (\theta_3 - \theta_3^*)MY + (k - k^*)Y. \tag{5.11}$$

The proposed control law is $\quad U = C_0(R - F_0Y - F_1E)$. $\tag{5.12}$

Thus, $\qquad\qquad U = \frac{\theta_1}{\Lambda}U + \frac{\theta_2}{\Lambda}Y + \theta_3 Y + kR - kF_1E \tag{5.13}$

The stable transfer function, $F_1(s)$ is chosen as

$$F_1(s) = M^{-1}(s)\frac{1}{k(\tau s + 1)^q} \tag{5.14}$$

where q is an integer not less than $n - m$, and τ is a small positive time constant. τ is chosen for any frequency band $[\omega_l, \omega_u]$ (where ω_l = lower frequency bound (0.00001 rad/s in this study) and ω_u = upper frequency bound (0.1 rad/s in this study)).

$$\tau < \min\{\tau_1, \frac{l_0}{h\omega_u q}\} \tag{5.15}$$

$$\tau < \frac{1 - \dfrac{|\Delta k|}{k^*}}{\overline{h}} \triangleq \tau_1 \qquad (5.16)$$

$$\overline{h} \triangleq \sup_{\omega} \left| q\, j\,\omega\, H(j\omega) \right| \qquad (5.17)$$

$$H \triangleq \frac{M}{k^*} \left(\frac{\Delta\theta_1}{\Lambda} G^{-1} + \frac{\Delta\theta_2}{\Lambda} + \Delta\theta_3 \right) \qquad (5.18)$$

$$\left| H_1(j\omega) \right| < h \qquad (5.19)$$

$$H_1(s) \triangleq M(s) \left(1 + \frac{(k-k^*)}{k^*} k F_1(s) M(s) - \left(1 - k F_1(s) M(s)\right) H(s) \right)^{-1}$$
$$\left(\frac{(k-k^*)}{k^*} + H(s) \right) \qquad (5.20)$$

The bounds for $\theta_1, \theta_2, \theta_3$ and k are determined by using the uncertainty bounds and the general theory of Diophantine polynomial equations.

$$l_0 = \inf\{l(\omega); \omega \in [\omega_l, \omega_u]\} \qquad (5.21)$$

$$l(\omega) > 0 \qquad (5.22)$$

where $\omega_u > \omega_l \geq 0$ are finite.

Thus, $F_0(s), C_0(s),$ *and* $F_1(s)$ are chosen to obtain the robust stability for any finite frequency band $[\omega_l, \omega_u]$ and to achieve the following performance specification:

$$\left| M(j\omega) - G_c(j\omega) \right| < l(\omega), \qquad\qquad \forall \omega \in [\omega_l, \omega_u] \qquad (5.23)$$

5.4 Details of the Study

The effectiveness of LMEC is evaluated *in silico* on a virtual cohort of T1D patients by perturbing the key parameters of the models by 40% i.e. we consider a ±40% uncertainty bound on the parameters. The LMEC controller algorithm is designed and its performance is evaluated on the chosen simulated T1D patient models (Bergman model, Parker model & Fabietti model). For performance evaluation, a normal day (with three meal disturbances: breakfast (10.8 g), lunch (50 g), and dinner (50 g) carbohydrate at meal times 7 am, 12 noon, and 6 pm respectively) was simulated. A bit different meal amount from previous chapters is considered here; again, the

meal amount can be different at any time. The intravenous route is chosen for insulin administration to negotiate these meal disturbances.

5.5 Evaluation of Disturbance Rejection

The performance of LMEC is evaluated on three chosen diabetes patient models (Bergman, Parker, and Fabietti models) by generating virtual patient cohorts based on these models. The desired set point considered in this study is 4.5mmol/L (or 81.1mg/dL). The performance of the proposed controller on the above mentioned three patient models is presented below.

5.5.1 Analysis with the Bergman Model

Uncertainty bounds are determined for the parameters p_1, p_2, p_3 and n of this model. The nominal values of the four model parameters are given in Table 5.1 ($P_2\_basal_{nominal}$). The performance analysis of the LMEC would be evaluated on several patients constituted via model parameter perturbations. The four model parameters (i.e., p_1, p_2, p_3 & n) are perturbed by changing them by ±40 % of their nominal values. Each parameter has three levels (min, nominal, max) and the combination of four parameters resulted in 81 (= 3^4) virtual patients in this study.

The parametric sensitivity analysis for these 81 combinations is done using their BG response to 10% decrease in their basal insulin requirements. Three patients with minimum, nominal, and maximum BG responses from the nominal BG value (81.08mg/dL) are chosen to determine the uncertainty bounds assuming that these three patients could cover the uncertainty bound of all 81 virtual patients. The parameter values of these three patients are presented in Table 5.1. The patient who has nominal basal insulin infusion represents the nominal patient of Bergman model. The nonlinear ODE model with parameter values given in Table 5.1 of these three patients) are perturbed by a 10% decrease in their basal insulin infusion and the corresponding step responses are obtained. Each of the obtained step responses is approximated by a second order transfer function without delay {κ / (τ_1s+1) (τ_2s+1)} and the values are shown in Table 5.2. The uncertainty bounds are obtained from these

three second order transfer functions in the form of $\{\kappa_p/ (s+\beta) (s+\gamma)\}$ and the values of these parameters are shown in Table 5.2 also. The lower, nominal & and upper uncertainty bounds $\{(\kappa_{pl}, \beta_l, \gamma_l), (\kappa_{p0}, \beta_0, \gamma_0)\ \& \ (\kappa_{pu}, \beta_u, \gamma_u)\}$ are marked as in Table 5.3. The reference model (M) is defined to be second order critical damping system of unit gain $\{M(s) = 1/(\tau_M^2 s^2+2\tau_M s+1): \tau_M = \sqrt{\tau_1 \tau_2}/2\}$ using τ_1 & τ_2 of nominal patient from Table 5.2. This model M(s) is converted into unit time constant form and is denoted as $\{M(s) = z_M(s)/p_M(s)\}$. To design the controller $C_0(s)$ and $F_0(s)$, $\{\Lambda(s) = (s+1)\}$, n = 2, m = 0, $k_M = z_M$, and $(k^*=k_M/k_{pu})$ are defined. The $\theta_1(s)$, $\theta_2(s)$ and $\theta_3(s)$ are determined using the general theory of Diophantine polynomial equations and nominal values of uncertainty bounds $(\kappa_{p0}, \beta_0, \gamma_0)$. Similarly, the lower and upper bounds of $\theta_i(s)$ are estimated using lower and upper $\{(\kappa_{pl}, \beta_l, \gamma_l)\ \& \ (\kappa_{pu}, \beta_u, \gamma_u)\}$ uncertainty bounds. The values of θ_i are numeric values and are presented in Table 5.3. To define the $F_1(s)$, the time constant (τ) is estimated by trial and error using equations (5.10) to (5.22) to satisfy the equation (5.23).

Table 5.1: Patient parameter values of nonlinear ODE model for chosen three Bergman model patients

Patient (P_i)	p_1	p_2	p_3	n
$P_1\_basal_{min}$	0.028735×1.4	0.028344×1.4	$5.035e{-}05 \times 0.6$	$5/54 \times 1.4$
$P_2\_basal_{nominal}$	0.028735	0.028344	$5.035e{-}05$	$5/54$
$P_3\_basal_{max}$	0.028735×0.6	0.028344×0.6	$5.035e{-}05 \times 1.4$	$5/54 \times 1.4$

Table 5.2: Parameter values of estimated second order transfer functions for chosen three Bergman model patients

Patient (P_i)	κ	τ_1	τ_2	κ_p	β	γ
$P_1\_basal_{min}$	-1.02	26.54	26.54	-1.44×10^{-3}	3.77×10^{-2}	3.77×10^{-2}
$P_2\_basal_{nominal}$	-4.94	38.74	38.74	-3.29×10^{-3}	2.58×10^{-2}	2.58×10^{-2}
$P_3\_basal_{max}$	-19.39	78.98	78.98	-3.11×10^{-3}	1.27×10^{-2}	1.27×10^{-2}

The meal model proposed by Lam et al. (2002) which gives a more realistic BG response for a given meal compared to Fisher meal model is used as the disturbance model (see Appendix A. 2), and the rate of insulin infusion is bounded between [0, 100] mU/min. The performance results of LMEC controller on the nominal patient and the cohort of 81 patients are illustrated in Figures 5.2 through 5.4.
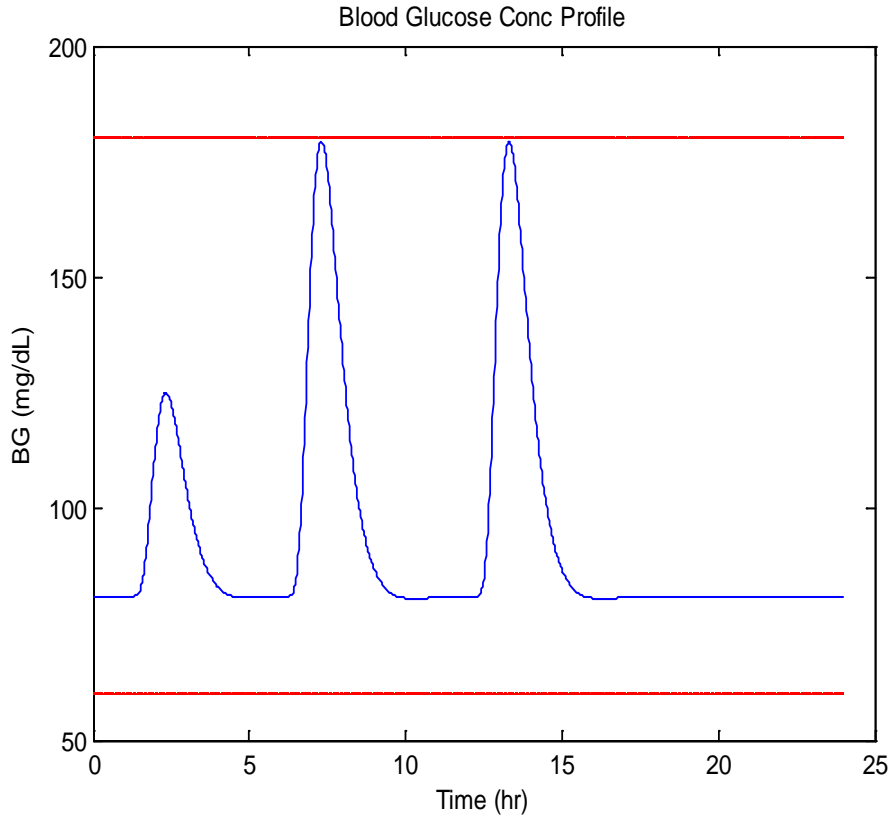
Figure 5.2: Performance of LMEC on Bergman nominal patient model for the three meal disturbances (upper red dash-dot line: 180mg/dL, lower red dash-dot line: 60mg/dL)
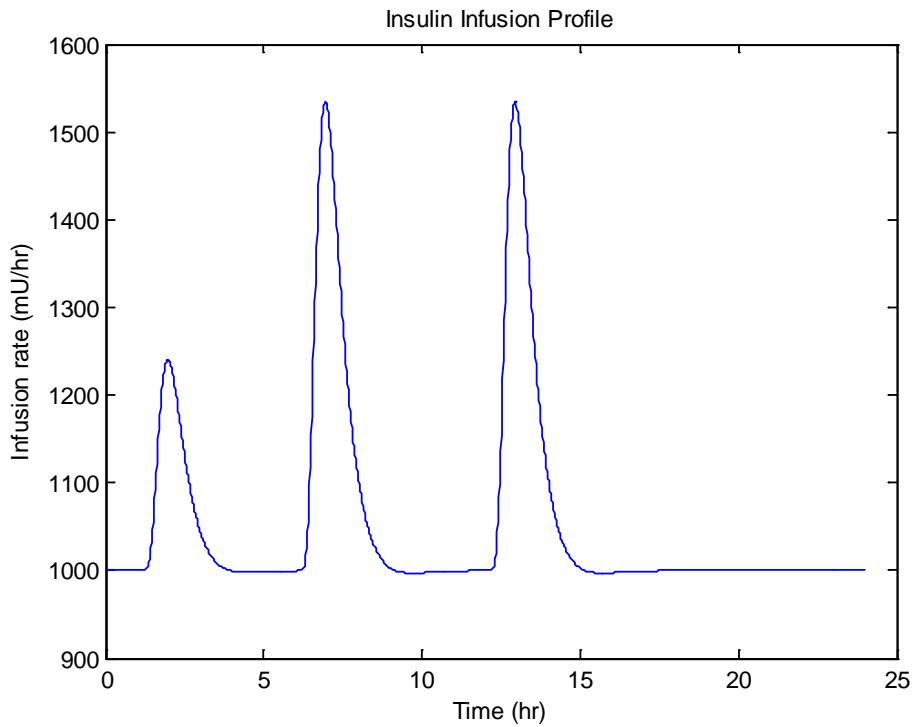
Figure 5.3: Insulin infusion profile obtained with LMEC on Bergman nominal patient model corresponding to the meal disturbances

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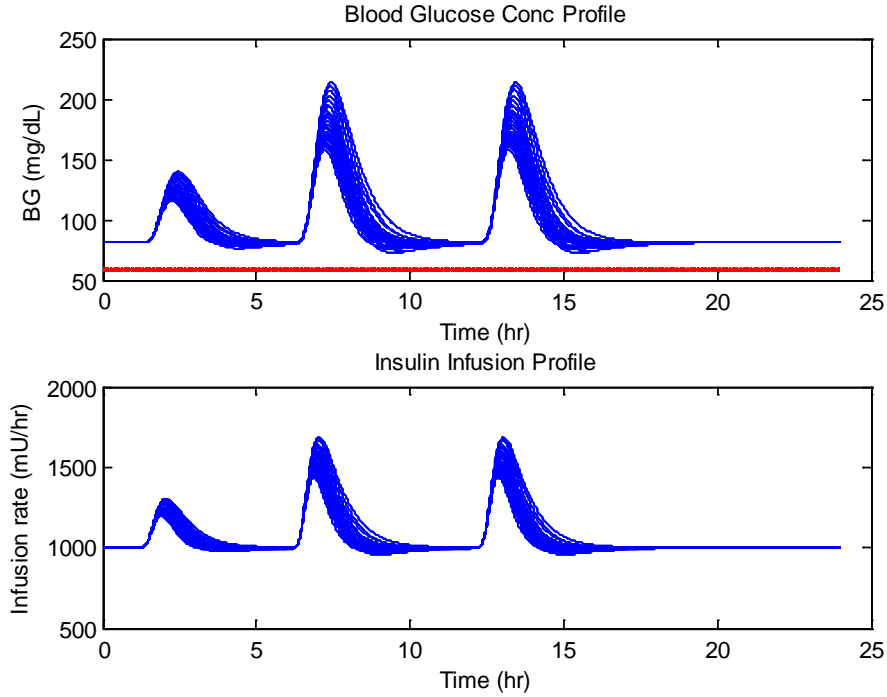
Figure 5.4: Performance of LMEC on a cohort comprising of 81 patients obtained from Bergman model (red dash-dot line: 60 mg/dL)

Table 5.3: Parameter values for designed LMEC controller for Bergman Model

$[\kappa_{pl} \ \kappa_{p0} \ \kappa_{pu}]$	$[-3.29 \ -3.11 \ -1.44] \times 10^{-3}$
$[\beta_l \ \beta_0 \ \beta_u]$	$[1.27 \ 2.58 \ 3.77] \times 10^{-2}$
$[\gamma_l \ \gamma_0 \ \gamma_u]$	$[1.27 \ 2.58 \ 3.77] \times 10^{-2}$
τ	0.51
$z_M(s)$	2.67×10^{-3}
$p_M(s)$	$s^2 + 10.33 \times 10^{-2} s + 2.67 \times 10^{-3}$
$[\theta_1 \ \theta_2 \ \theta_2]$	$[-5.16 \ -1489.30 \ 1549.02] \times 10^{-2}$

The performance of designed LMEC on nominal patient is satisfactory, and BG values are in the range of 80~180mg/dL during the given three meals. The results of using LMEC on the patients generated with the Bergman model show that none of the 81 virtual patients enter the undesirable hypoglycemic region (<60mg/dL) and lowest glucose value reached is 72.81mg/dL. The highest BG value after meal reaches 213.93mg/dL, and is in the acceptable range although higher than 180mg/dL. It can be concluded that the performance of LMEC controller is satisfactory in the sense of avoiding hypoglycemia and maintaining reasonable BG profile through the day. It can also be concluded that defining uncertainty bounds using the deviation from

nominal BG value by 10% decrease in basal insulin is appropriate. In short, the LMEC with the careful specification of the uncertainty bounds is promising for BG control.

5.5.2 Analysis with the Parker Model

Parker et al. (2000) identified the set of eight patient model parameters (EIPGU-E$_\Gamma$, EIPGU-D$_\Gamma$, EGHGU-E$_\Gamma$, EGHGU-D$_\Gamma$, EGHGP-E$_\Gamma$, EGHGP-D$_\Gamma$, FPIC & FHIC) from amongst the 19 parameters by parametric sensitivity analysis. They noted that ±40% deviations in three parameters (EIPGU-E$_\Gamma$, EGHGU-E$_\Gamma$, and EGHGP-E$_\Gamma$) from their nominal values have significant resistance to insulin and glucose dynamics. Thus, these three parameters are assumed that they might almost cover the most uncertainty bounds and are chosen from the set of eight patient-specific parameters to determine the uncertainty bounds for the LMEC controller to avoid extensive numerical analysis. The combination of these three variables with three permutations of each variable (maximum limit, nominal value, minimum limit) results in 27 combinations. The amount of insulin required to maintain the BG of each of these 27 patients at 81.1mg/dL (4.5mmol/L) is calculated.

The "patients" that required the minimum, nominal and maximum insulin amounts to keep BG at 81.1 mg/dL (4.5 mmol/L) are chosen and their step responses by 10% reduction in basal insulin infusion are approximated by second order transfer functions. Similar methods and procedures to define the uncertainty bounds and designing the LMEC controller as in section (5.5.1) are applied here to design the LMEC controller for Parker model type patients. The parameter values for linear second order transfer functions and designed LMEC controller parameter values are provided in Tables 5.4 and 5.5 respectively.

Table 5.4: Parameter values of estimated second order transfer functions for chosen three Parker model patients

Patient (P_i)	κ	τ_1	τ_2	κ_p	β	γ
$P_1\_basal_{min}$	-6.09	53.44	23.52	-0.48×10^{-2}	1.87×10^{-2}	4.25×10^{-2}
$P_2\_basal_{nominal}$	-6.88	52.99	24.45	-0.53×10^{-2}	1.89×10^{-2}	4.09×10^{-2}
$P_3\_basal_{max}$	-7.54	69.19	25.05	-0.43×10^{-2}	1.45×10^{-2}	3.99×10^{-2}

Table 5.5: Parameter values for designed LMEC controller for Parker Model

$[\kappa_{pl}\ \kappa_{p0}\ \kappa_{pu}]$	$[-0.53\quad -0.48\quad -0.43]\times10^{-2}$
$[\beta_l\ \beta_0\ \beta_u]$	$[1.45\quad 1.87\quad 1.89]\times10^{-2}$
$[\gamma_l\ \gamma_0\ \gamma_u]$	$[3.99\quad 4.09\quad 4.25]\times10^{-2}$
τ	6.33
$z_M(s)$	0.31×10^{-2}
$p_M(s)$	$s^2+11.06\times10^{-2}s+0.31\times10^{-2}$
$[\theta_1\ \theta_2\ \theta_2]$	$[-5.10\quad -992.21\quad 1038.82]\times10^{-2}$

The robust performance of the designed LMEC controller is validated on a cohort of 577 virtual patients created from the Parker model (the details of which were presented in section 2.4). The performance of the designed LMEC controller on the nominal patient and on the cohort of 577 patients with three meal disturbances (Lehmann and Deutsch meal model described in section 2.3) are shown in Figures 5.5 to 5.8. The rate of maximum insulin infusion is set to not exceed 100mU/min (6000 mU/hr) taking into account the capability of modern insulin pumps.

Figure 5.5: Performance of LMEC on nominal patient (Parker model) with three meal disturbances (red dash-dot line: 80 mg/dL)

Figure 5.6: Insulin infusion profile of LMEC on nominal patient (Parker model)

Figure 5.7: Blood glucose concentration profiles of 577 constituted patients using Parker model

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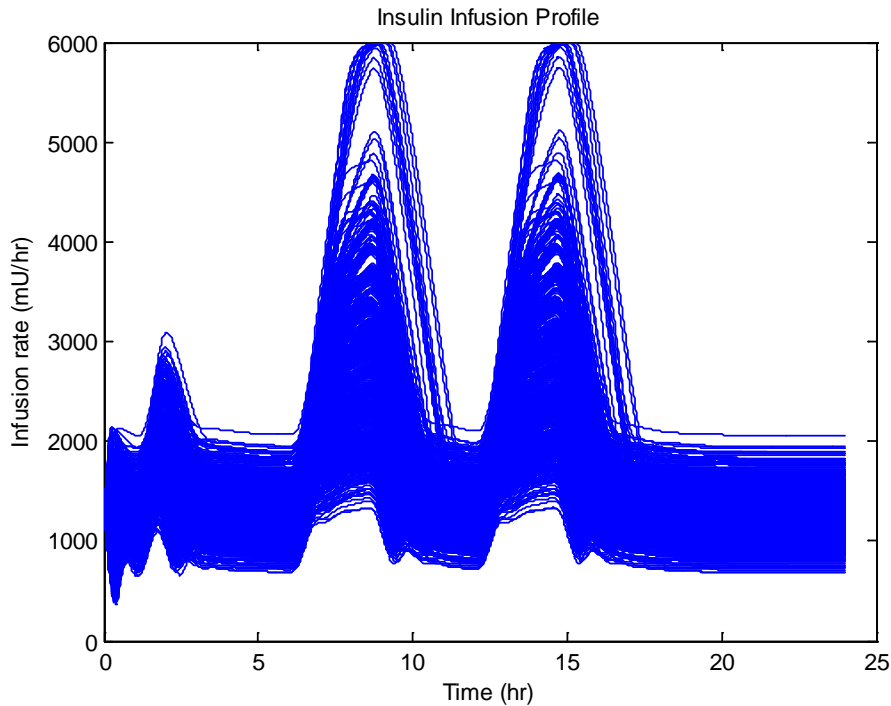
Figure 5.8: Insulin infusion profiles of LMEC on 577 constituted patients
using Parker model

With LMEC, none of the 577 patients generated from the Parker model enter the undesirable hyperglycemic region (>180mg/dL) and none experienced the dangerous hypoglycemia. Thus, all the 577 patients can be kept in BG range of 60~180mg/dL (with minimum and maximum BG values of 62.06mg/dL and 168.32mg/dL respectively). From these results, it can be concluded that the three parameters chosen for determination of uncertainty bounds are appropriate. However, steady state offset (deviation from setpoint) is observed in some of the patients. This may be due to insufficient integral action in the designed LMEC which can be improved with careful determination of uncertainty bounds.

5.5.3 Analysis with the Fabietti Model

The T1D patient model by Fabietti et al. (2006) contains eight patient-dependent parameters. From these, four parameters (T_{xi}, T_i, K_i, and K_{is}) are chosen for producing the simulated patients (circadian insulin sensitivity variation is kept constant at 1). These four parameters were identified as most important in Fabietti et al. (2006). When these parameters were varied at 3

levels, this resulted in a cohort of 81 virtual patients (using ±40% parameter variation from nominal values of the four chosen parameters). Similarly, as in the above models, three patients that required minimum, nominal and maximum basal insulin infusion are chosen. The bounds for uncertainty to design LMEC controller are determined from their step responses produced by 10% reduction in their basal insulin amount. These step responses obtained are fitted to second order transfer functions. Then, the LMEC controller is designed based on the uncertainty bounds generated from three second order transfer function approximations. The same course of determining uncertainty bounds and estimating LMEC controller parameters as in section (5.5.1) are used in designing LMEC controller for this model. The approximated linear second order transfer function parameters and designed parameters for LMEC controller for this patient model are shown in Tables 5.6 and 5.7 respectively.

Table 5.6: Parameter values of estimated second order transfer functions for chosen three Fabietti model patients

Patient (P_i)	κ	τ_1	τ_2	κ_p	β	γ
$P_1\_basal_{min}$	-4.59×10^{-3}	3.81	3.81	-0.32×10^{-3}	2.62×10^{-1}	2.62×10^{-1}
$P_2\_basal_{nominal}$	-9.76×10^{-3}	3.47	2.10	-1.34×10^{-3}	2.88×10^{-1}	4.76×10^{-1}
$P_3\_basal_{max}$	-6.06×10^{-3}	4.45	1.60	-0.85×10^{-3}	2.25×10^{-1}	6.27×10^{-1}

Table 5.7: Parameter values for designed LMEC controller for Fabietti Model

$[\kappa_{pl}\ \kappa_{p0}\ \kappa_{pu}]$	$[-1.34\ -0.85\ -0.32] \times 10^{-3}$
$[\beta_l\ \beta_0\ \beta_u]$	$[2.25\quad 2.62\quad 2.88] \times 10^{-1}$
$[\gamma_l\ \gamma_0\ \gamma_u]$	$[2.62\quad 4.76\quad 6.27] \times 10^{-1}$
τ	0.87
$z_M(s)$	49.95×10^{-2}
$p_M(s)$	$s^2 + 141.36 \times 10^{-2}s + 49.95 \times 10^{-2}$
$[\theta_1\ \theta_2\ \theta_2]$	$[-67.51\ -30571.56\ 64591.80] \times 10^{-2}$

The robust performance of the LMEC controller in rejection of disturbances is evaluated on the 81 patient cohorts that include the nominal patient. The embedded meal model in Fabietti et al. (2006) is used for gut absorption in which meal can be defined as a mixture of sugar, starch, and fiber. The results of the controller performance are shown in Figures 5.9 to 5.11. The infusion rate of insulin pump is bounded by [0, 8000] mU/hr in this case study assuming the future capability of insulin pumps and to show the effectiveness of the controller.
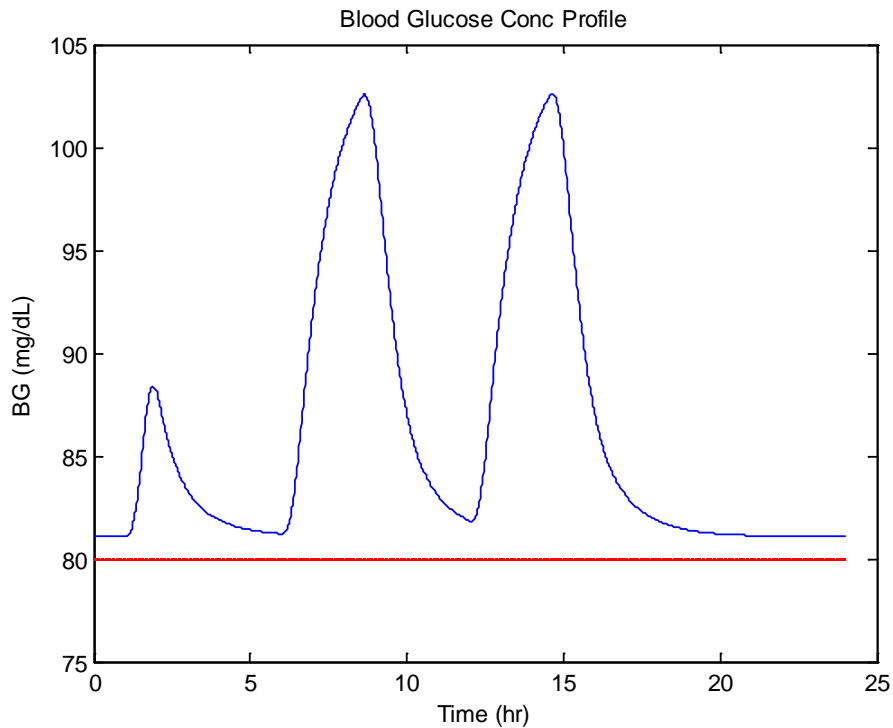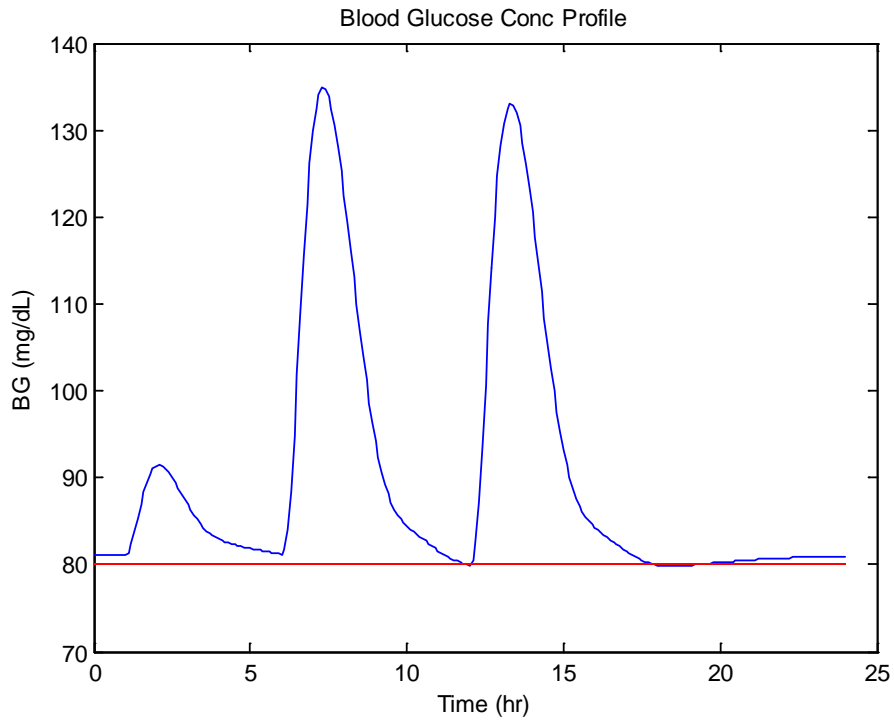
Figure 5.9: Performance of LMEC on nominal patient (Fabietti model) with three meal disturbances (red dash-dot line: 80 mg/dL)

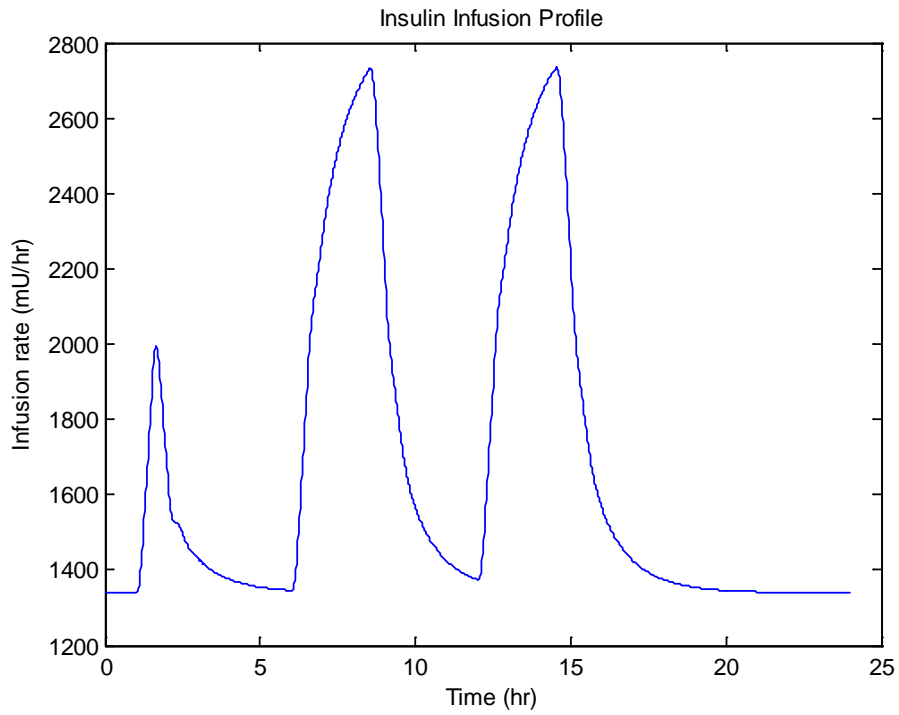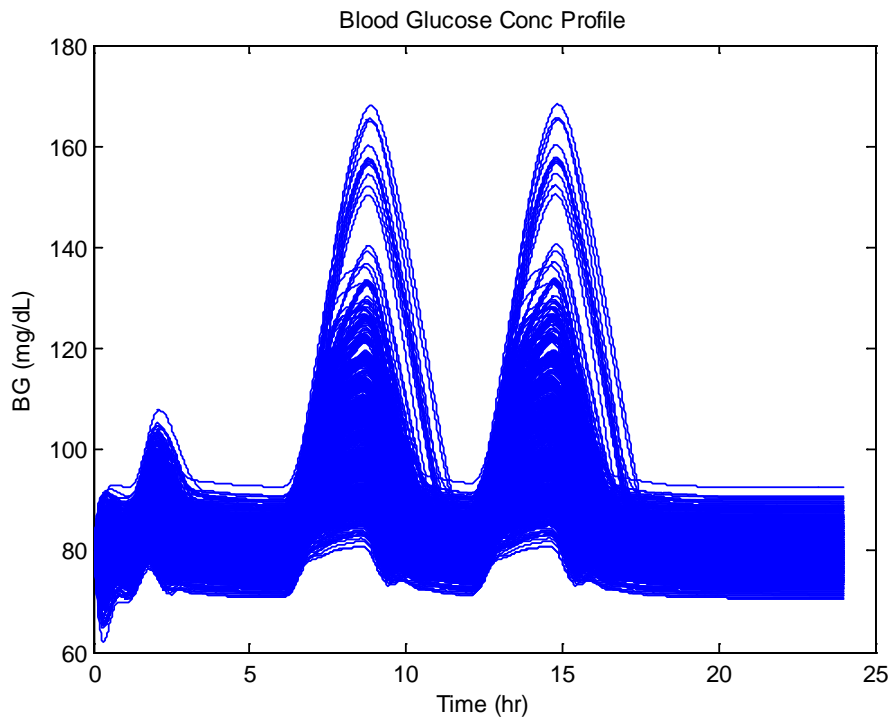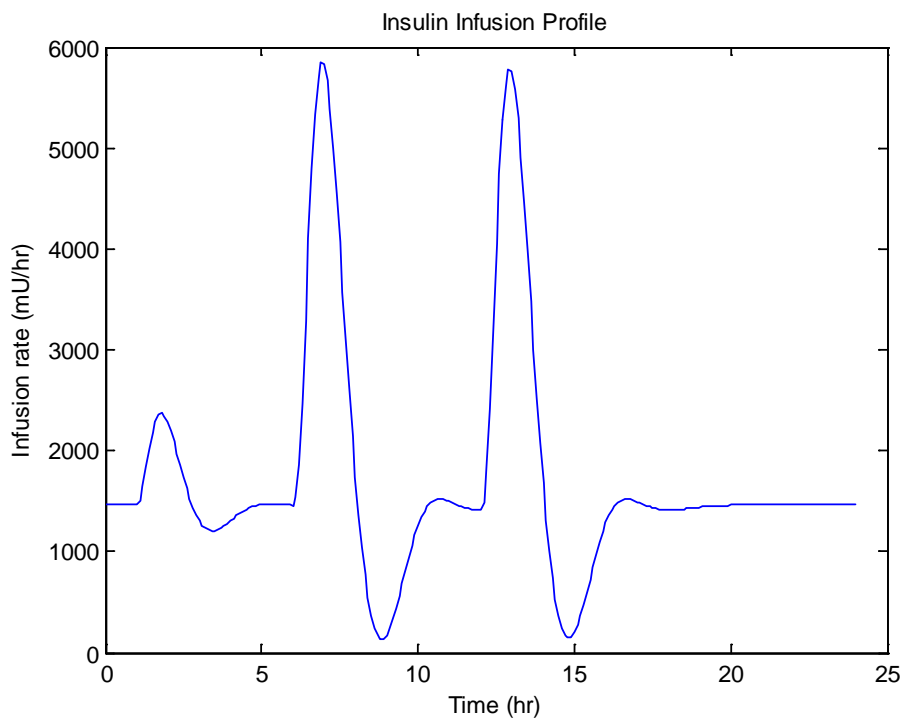Figure 5.10: Insulin infusion profile of LMEC on nominal patient (Fabietti model)

98
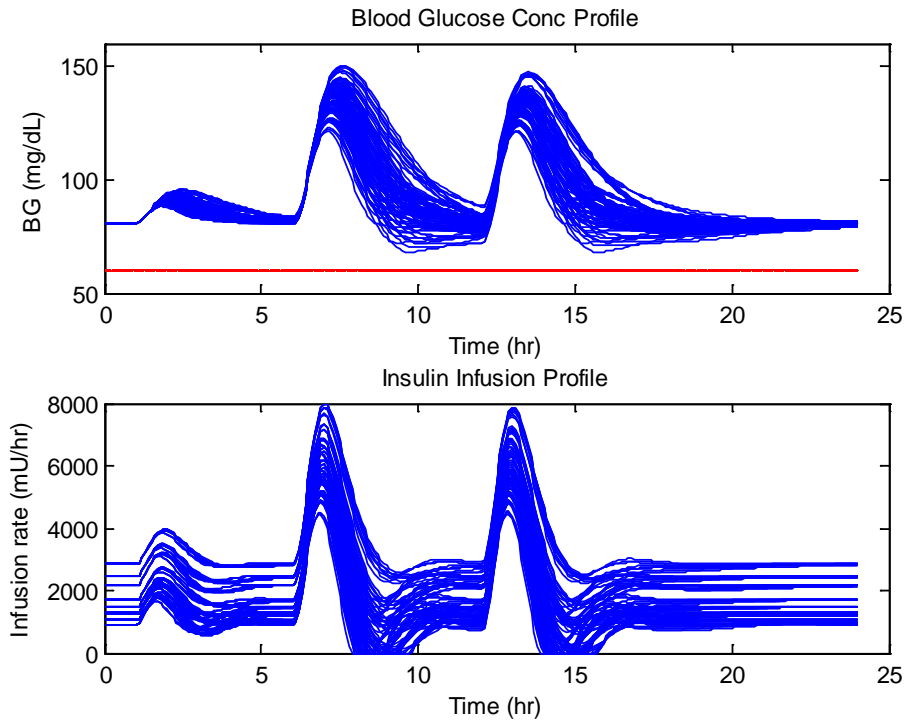
Figure 5.11: Performance of LMEC on the 81 patient cohort generated using the Fabietti model (red dash-dot line: 60 mg/dL)

From the results obtained after applying the LMEC on the 81-patient cohort obtained from the Fabietti model (shown in Figure 5.11), it is seen that all of them are maintained in BG range of 60~180mg/dL. None of the 81 patients enter the dangerous hypoglycemic region (<3.33mmol/L=60mg/dL) or the postprandial hyperglycemic region (>180mg/dL) with minimum and maximum BG values of 67.93mg/dL and 150.32mg/dL respectively.

5.6 Conclusions

From the investigations conducted, it appears that the LMEC controller is a promising candidate for blood glucose control in T1D patients if frequent sampling (1 min interval is used in this study) of BG concentration is possible. LMEC is able to avoid hypoglycemia in a vast majority of virtual Type 1 Diabetic patients. These hypoglycemic episodes can probably be circumvented through a careful specification of the uncertainty bounds. Steady state offset from the target value of 81.1mg/dL (4.5mmol/L) is also found with LMEC in Parker model but this may also be improved with refined uncertainty bounds.

Despite these drawbacks, it could be concluded that LMEC controller is capable of effectively regulating BG levels in T1D patients.

Chapter 6

Glycemic Control for Type 1 Diabetics using Multirate System Identification and Modeling Error Compensator

6.1 Background

A number of mathematical models for diabetics and several control algorithms for blood glucose regulation have been proposed and employed in the literature. Robust control algorithms were shown to cope well the inter- and intra-patient variability by some researchers (Parker et al., 2000 and Ramprasad et al., 2004b). In these studies, the inter- and intra-patient variabilities were represented by certain parametric uncertainty bounds. The LMEC controller introduced by Sun et al. (1994) is one robust controller that was designed to deal with bounded parametric uncertainties. The effectiveness of this controller for treating T1D patients was studied in Chapter 5 from where it appears that LMEC is a possible candidate for BG control in T1D patients. However, the controller depends solely on the mathematical model and further clinical validation would be required to test this control strategy on real patients. Towards this effort, it would be worthwhile to develop the controller based on models developed from patient data using system identification tools. This could pave way for a more personalized diabetic care, and hence it is explored here.

6.2 Motivation and Objective

For the situation in which historical data (BG and rate of insulin infusion amount measurements) is available from patients, the controller would be more effective if it is designed based on these data. Moreover, while frequent sampling of BG will enable better BG control, current glucose sensor technology is still not there. The typical sampling time of current glucose sensors are 3~6 min. Measurement of insulin infusion rates are available more frequently, and meal data are available on a few-hourly basis. This

naturally leads to a multirate data set with less frequent BG measurement, even less frequent meal measurement and fast insulin infusion rate measurement. We assume that the patient is on continuous insulin infusion. Developing a control strategy based on such data will benefit diabetes care. In this chapter, a strategy to utilize multirate patient data for designing robust controllers will be outlined and evaluated.

6.3 Multirate System Identification and Application of Lifting Technique

Multirate systems are periodically time varying systems and so many developed identification methods cannot be directly applied. Lifting technique is a powerful tool which converts linear periodically time varying system (LPTV) to linear time invariant (LTI) system to which most of the system identification techniques can be applied successfully. Applying the lifting technique to the Single Input/ Single Output (SISO) multirate system with input (U) and output (Y) which are sampled with sampling interval ($m \times p$) and ($n \times p$) respectively ($m \prec n, n : m = \gamma$ and $p =$ base time period, both m and n are coprime) can be illustrated as follow:

In Figure 6.1, SISO multirate system (from U to Y) is LPTV system, SISO multirate lifted system (from $\underline{U}_1 \ldots \underline{U}_n$ to Y) is LTI system where $\underline{U}_1 \ldots \underline{U}_n$ represent the lifted input signals, the dash-dot line represents the fast rate sampling (sampling interval mp) and dash-line represents the slow rate sampling (sampling interval np). The lifting the input U can be described in mathematical equation (6.1).
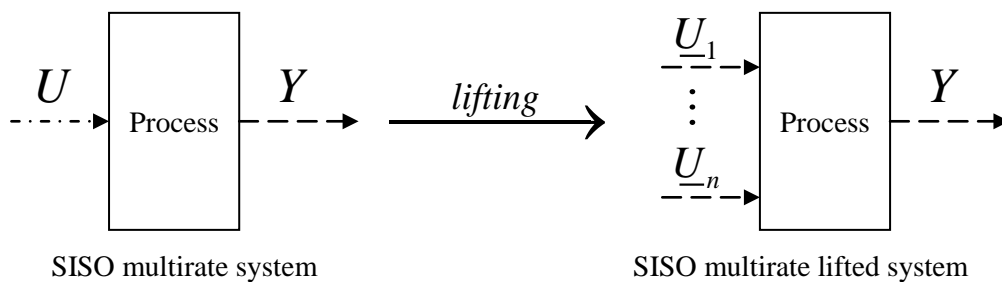
Figure 6.1: Applying the lifting technique to SISO multirate system

$$U \xrightarrow{\quad lifting \quad} \underline{U}_1 \quad,...,\quad \underline{U}_n$$

$$\left\{ u_1, u_2, u_3, ..., u_{fn} \right\} \mapsto \left\{ \begin{bmatrix} u_1 \\ u_{n+1} \\ \vdots \\ u_{(f-1)n+1} \end{bmatrix}, ..., \begin{bmatrix} u_n \\ u_{2n} \\ \vdots \\ u_{fn} \end{bmatrix} \right\} \tag{6.1}$$

It is clear that dimension of $\underline{U}$ is n times that of U and underlying period of $\underline{U}$ is n times that of U again. Thus, now $\underline{U}$ and Y have the same time interval, np and the lifted system becomes single rate system (lifted slow rate system). The details can be found in Khargonekar et al. (1985). A SISO multirate system can be effectively been converted into a MISO/MIMO single rate system. Standard system identification tools can now be applied to identify a model that represents the system dynamics for the slow sampling period. A fast rate model must then be extracted from this slow rate model.

6.4 Details of the Study

The MRID algorithm based on the lifting technique and using state space system identification (SSID) method would be useful in extracting the fast rate model from patient's historical data. Then, an appropriately designed robust controller can be used to deal with unavoidable inter- and intra-patient variability. Previous study (Chapter 5) shows that LMEC is a good candidate for this purpose and we choose it to design the model based controller. LMEC can be implemented using the extracted fast rate model and the current glucose sensor sampling rate and provide frequent controller action (i.e. insulin infusion). Use of the fast rate LMEC is likely to lead to more effective BG control. The details of this algorithm will be presented in the following order: (1) collecting historical data (Section 6.4.1), (2) applying multirate system identification (Section 6.4.2) and (3) designing LMEC controller (Section 6.4.3). The meal amount is estimated based on the scheduled and recommended meal amount for T1D patients (with given three meal glucose amounts: 20 g breakfast, 50 g lunch and 50 g dinner at 7am, 12pm, and 6pm respectively per day). (The measurement noise for meal measurement is not considered here as it is estimated.) Measurement noise on BG (sensor noise) of about 17% is applied throughout this study.

6.4.1 Collecting Patient Data

In the absence of real patient data, we used the data obtained by using the YIIP algorithm (Chapter 4) on patients generated using the model of Fabietti et al. (2006). Without loss of generality, data from patients or other model-treatment method combinations can be utilized. To be realistic, we collect data such that BG concentration is sampled less frequently (3 min sampling) while meal input (that will be transformed into glucose input from meal or meal ingestion profile using a filter described in Fabietti et al. (2006) to meal ingestion rate) and insulin infusion rate are sampled frequently (36 sec sampling).

Note that BG concentration is the controlled variable (output) while the meal input and insulin infusion rate are the input variables. We assume that the "patient" has no initial hyperglycemia and receives external insulin infusion as recommended by the YIIP. Data is collected over a period of 17 days from a cohort of "patients" assuming three meal disturbances (glucose amounts: 20 g breakfast, 50 g lunch and 50 g dinner) per day.

6.4.2 Application of Multirate System Identification

The collected data comprises of BG measurement (one process output) collected at 3 min sampling interval ($n \times p$) and insulin infusion rate & glucose input from meal that is estimated from meal input (two process inputs) collected at 36sec sampling interval ($m \times p$), where $m = 1, n = 5$, and $p = 36$sec. Thus, we have a sampling interval ratio, $\gamma = 5$. A typical illustration of the data can be seen in Section 4.6.2 (glucose input estimated from meal input is illustrated as meal ingestion profile in the figures). The two inputs are lifted according to Li et al. (2001) and Wang et al. (2004).

By applying the lifting technique to the insulin infusion rate, we get the lifted input signals as described in eq. (6.1). After applying the lifting technique to the two process inputs with $\gamma = 5$, the lifted system (slow rate system) has ten lifted inputs and one output with the same sampling interval of ($n \times p$). A state space model of the lifted system can be expressed as follows (Khargonekar et al., 1985):

$$
\underline{G}_p = \left[\begin{array}{c|cccc}
A^{mn} & A^{mn-1}B & A^{mn-2}B & \dots & B \\
\hline
C & D & 0 & \dots & 0 \\
CA & CB & D & \dots & 0 \\
\vdots & \vdots & \vdots & \dots & \vdots \\
CA^{mn-1} & CA^{mn-2}B & CA^{mn-3}B & \dots & D
\end{array} \right]
\qquad (6.2)
$$

To achieve the identifiablity of a state space model, the lifted slow-rate model must be controllable and observable. The lifted slow-rate system is controllable and observable only if the continuous-time system G is observable and controllable. This assumption is valid with the non-pathological sampling interval p; the continuous time delay τ must be in the range of $[0, p]$. We assume that the system time delay is within this limit in this study. Wang et al. (2004) proved that the lifted system can be controllable: (A_i, B_i) is controllable if (A, B) is controllable and A has no eigenvalue on the unit circle (the proof can be seen in Wang et al. (2004)). Here, we use the N4SID method (System Identification Toolbox, Matlab 2008b) to identify the Steady State (SS) model.

Three ways have been proposed by Li et al. (2001) to extract the fast rate model from the lifted slow-rate system. Wang et al. (2004) further developed these methods and demonstrated how one could obtain a fast-rate model with sampling period p for the system with $3p$ hold interval and $2p$ sampling interval. Though theoretically sound, the above methods sometimes present numerical difficulties. An alternate approach by Lakshminarayanan (2000) is a practical solution to the problem. Firstly, he employs model reduction to the slow-rate model to obtain minimal state space form. The reduced-order model is produced with matching DC gain using equivalent steady state step response.

The state or states to be deleted is determined using '*balreal*' command in MATLAB. The '*balreal*' command (The MathWorks, Inc. 1998) is used for producing a balanced realization in state space form reflecting the same controllable and observable properties of the individual states. The elements in the diagonal of the balanced realization form reflect the grammian-based combined controllable and observable properties of the different states.

One can delete those elements of the diagonal (states) with small value so that the most important features of the original system can be captured by retaining the larger values of the diagonal elements. The weak state(s) which are computed from '*balreal*' command were deleted using the '*modred*' command in MATLAB. The remaining model contains the most essential input-output characteristics of the original slow-rate system.

The '*modred*' command (The MathWorks, Inc. 1998) with matching DC gain method works as follows for the discrete-time state space model:
Let the discrete-time state space model be

$$x(k+1) = Ax(k) + Bu(k) \tag{6.3}$$

$$y(k) = Cx(k) + Du(k). \tag{6.4}$$

The state vector is divided into two parts, x_1 (the states that are to be retained) and x_2 (the states that may be eliminated).

$$\begin{bmatrix} x_1(k+1) \\ x_2(k+1) \end{bmatrix} = \begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} x_1(k) \\ x_2(k) \end{bmatrix} + \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} u(k) \tag{6.5}$$

$$y(k) = \begin{bmatrix} C_1 & C_2 \end{bmatrix} x(k) + Du(k) \tag{6.6}$$

Then, x_1 states are calculated by setting the derivative of x_2 to zero and the reduced-order model is as follows:

$$x_1(k+1) = [A_{11} - A_{12}A_{22}^{-1}A_{21}] \quad x_1(k) + [B_1 - A_{12}A_{22}^{-1}B_2] \quad u(k) \tag{6.7}$$

$$y(k) = [C_1 - C_2A_{22}^{-1}A_{21}] \quad x(k) + [D - C_2A_{22}^{-1}B_2] \quad u(k) \tag{6.8}$$

Then, the fast rate model G_f with p sampling interval is extracted from resulting low order slow-rate discrete-time model using '*d2d*' MATLAB command which can transform discrete-time model with particular sampling interval into discrete-time model with required sampling interval. This method operates in state space domain and the resulting fast-rate model is also in discrete-time state space form valid for sampling interval p.

In this work, a new approach, shown in Figure 6.2, is proposed to obtain the fast rate model. The gain of the SS model obtained from slow rate identification has discrepancies due to loss of information resulting from lifting the system. Thus, the best possible system gain is found using a best lifted insulin input and a best lifted meal input (the lifted input signals which have "proper response" and are best representatives of original manipulated

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variables are chosen from the bundle of lifted input signals) by optimization approach that can give best fit to the output variable (here, "proper response" means that the signal grasps the negative sign of process gain for insulin model and positive sign of process gain for meal model). The nonlinear least squares (NLLS) fit is applied here as a quick start. The '*lsqnonlin*' command in MATLAB can be used for this method; desired bounds on the optimized variables can be given to ensure proper values for the adjusted gain. The NLLS optimization method gives quick and best solution to the objective function. The SS model with adjusted gain is then approximated by a second order transfer function (SOTF). The optimization approach with direct search method ('*fminsearch*' function in MATLAB) is applied here. The new continuous SOTF with adjusted model gain and time constants can be converted into discrete model with sampling interval p by using "*c2d*" command in MATLAB. This discrete model is referred to as the MRID model in this work.
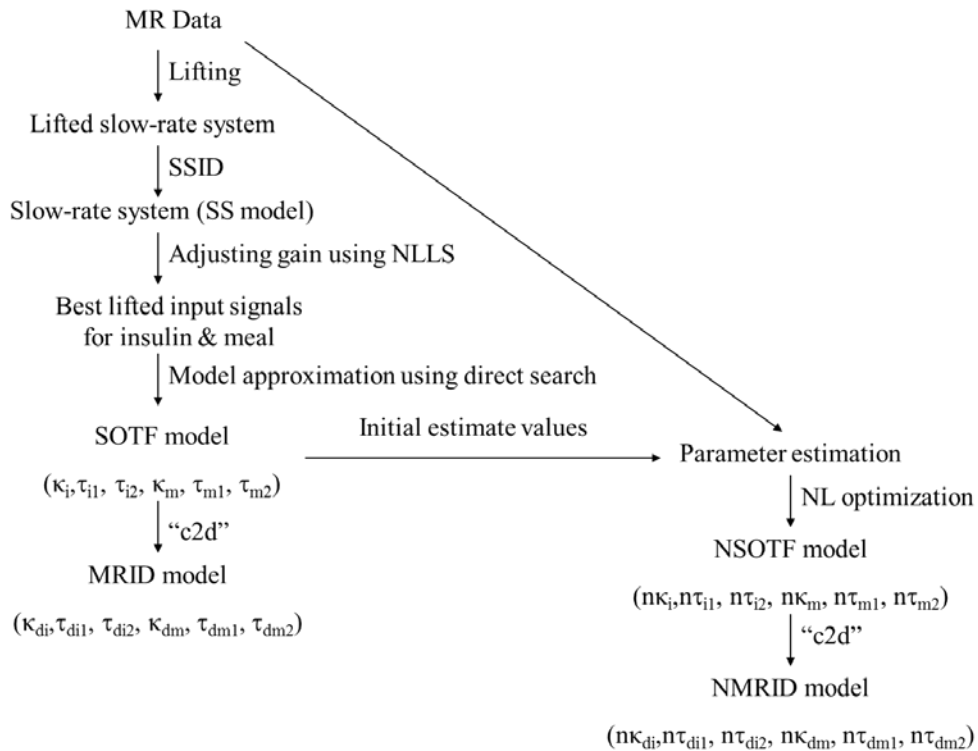
Figure 6.2: Diagram for "New MRID" (NMRID) approach

The SOTF parameters are used as the initial estimates for the nonlinear optimization using pattern search method in MATLAB in which new

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continuous SOTF model (referred to as NSOTF) parameters are found for the cost function to give the best fit to the BG output using a best lifted insulin input and a best lifted meal input. The pattern search engine gives the best possible local minimum of the objective function with specified bounds on the optimization variables. The obtained NSOTF model can be converted into discrete fast rate model with the sampling interval p and the resulting model is referred to as the "New MRID" (NMRID) model in this work. Note that the fast rate model obtained from the NMRID procedure is employed to obtain the inter-sample BG estimates for each of the patients. The LMEC-MRID controller (to be described next) will use these estimates to determine insulin infusion rates at time instants where the measured BG values are not available. In addition, note that the parameters of NSOTF model will be used in LMEC-MRID controller development.

6.4.3 Design of Linear Modeling Error Compensator

The LMEC controller is designed based on the BG responses of selected patients to changes in insulin infusion rate. LMEC is developed for two scenarios based on the linearized models and the uncertainty description derived from them. LMEC is designed based on: (1) unit step response of linear models (NSOTF model) obtained from MRID of 7 selected "patients" (LMEC-MRID I) and (2) linear models obtained from the response of the nonlinear models (unit step response at nominal insulin infusion rate is approximated by second order linear transfer function model) of 12 selected "patients" (including 5 more patients to the chosen 7 MRID patients) (LMEC-MRID II). LMEC-MRID II is developed to act as performance benchmark to LMEC-MRID I.

The responses of the nominal "patient" from both scenarios provide us the nominal model parameters. The bounds for uncertainty are determined from the parameters of the estimated linear second order transfer functions of the selected patients. The smallest and largest parameter values are defined as lower and upper bound. These bounds for the uncertainty (assuming that they represent inherent inter- and intra-patient variability) are incorporated in the controller design. The uncertainty bound of LMEC-MRID II was found to be

wider than that of LMEC-MRID I. The details of LMEC-MRID controller design has already been described in Section 5.3.2.

6.5 MRID Results and Discussion

Seven specific patients are chosen from the cohort of 81 patients (Fabietti model). These chosen patients consist of nominal patient, and the patients who have lowest and highest BG from each of the three groups (as described in Section 4.6.3). The proposed NMRID is applied to obtain the fast rate model from the multirate historical data (where patients were treated using YIIP) of the 7 patients. The parameter values of the NSOTF model for the 7 patients are given in Table 6.1. The NSOTF model parameters are compared with those of actual (NL) model approximated by a second order transfer function and that of SOTF models.

Table 6.1: Details of the NSOTF models

Patient	Model	κ_i	τ_{i1}	τ_{i2}	κ_m	τ_{m1}	τ_{m2}	MAE
Nominal	NL	-0.16	2.77	2.77	2.08	1.29	1.29	-
	SOTF	-0.07	1.27	1.27	2.47	1.16	1.16	7.21
	NSOTF	-0.09	2.89	2.89	1.64	1.91	1.91	1.51
G1L (C4p3)	NL	-0.02	2.56	2.56	1.73	1.05	1.05	-
	SOTF	-0.23×10^{-2}	0.47	0.47	0.88	0.44	0.44	16.25
	NSOTF	-0.026	2.45	2.45	1.29	1.24	1.24	3.56
G1H (C7p7)	NL	-0.05	5	5	4.59	3.04	3.04	-
	SOTF	-0.92×10^{-2}	1.11	1.11	2.19	1.10	1.10	15.84
	NSOTF	-0.03	4.64	4.64	2.44	3.41	3.41	2.45
G2L (C5p3)	NL	-0.06	2.57	2.57	1.73	1.05	1.05	-
	SOTF	-0.45×10^{-2}	0.44	0.44	0.76	0.46	0.46	15.76
	NSOTF	-0.09	2.50	2.50	1.36	1.43	1.43	3.50
G2H (C8p4)	NL	-0.07	4.12	4.12	4.59	3.04	3.04	-
	SOTF	-0.76×10^{-2}	1.05	1.05	1.77	0.73	0.73	11.40
	NSOTF	-0.10	5.39	5.39	2.27	3.12	3.12	2.14
G3L (C6p3)	NL	-0.11	2.57	2.57	1.73	1.05	1.05	-
	SOTF	-0.02	1.15	1.15	0.08	0.89	0.89	22.42
	NSOTF	-0.23	2.95	2.84	1.57	1.74	1.74	2.69
G3H (C9p7)	NL	-0.27	5	5	4.59	3.04	3.04	-
	SOTF	-0.02	1.40	1.40	1.79	1.39	1.39	17.99
	NSOTF	-0.18	4.87	4.87	2.43	3.40	3.40	2.63

The model fits using SOTF and NSOTF models are displayed in Figure 6.3 for nominal patient and compared with the YIIP data. For the nominal patient, the mean absolute error (MAE) between actual data (YIIP) and NSOTF model prediction is 1.51mg/dL which is rather good. The gain of unit step response for insulin using NSOTF model is closer to that of NL model than that of SOTF model even though the NSOTF model gain shows a gain mismatch with the actual NL model (values are provided in Table 6.1). The model fit to the actual BG response is better with the NSOTF model than with the SOTF model. The NSOTF model seems more acceptable compared to the SOTF model.
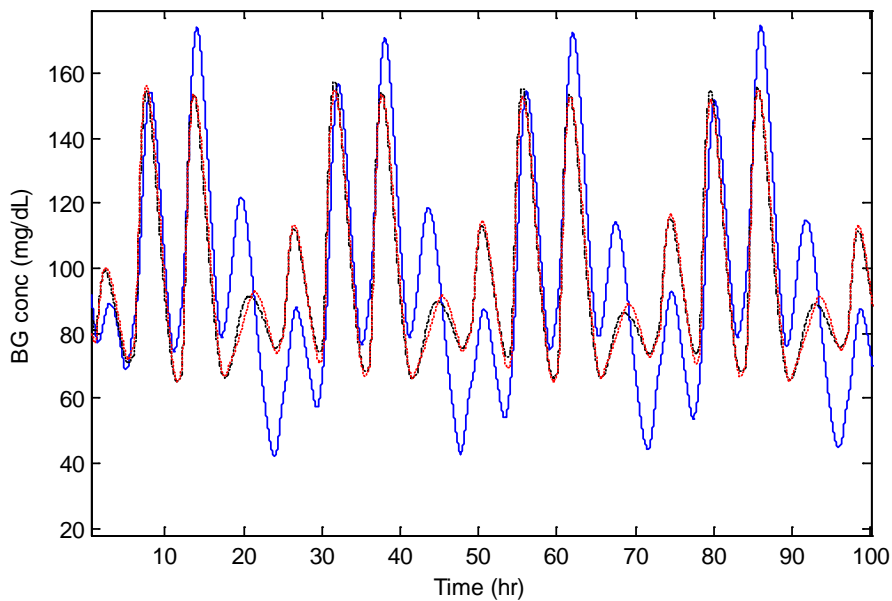
Figure 6.3: Model fit for nominal patients (solid line: SOTF model, dash-dot line: NSOTF model, dotted line: actual BG response)

The second chosen patient is from Class 4 (Group I) whose BG is the lowest in the group. The model fits to the actual BG response are compared in Figure 6.4 and MAE of NSOTF model is 3.56mg/dL (given in Table 6.1). The NSOTF model gains for both insulin and meal are much better than those obtained from SOTF model (values are provided in Table 6.1). The model fit of NSOTF model is not good as it does not match with the actual BG response trend at several places (e.g. between 15hr and 25hr) but is acceptable. The MAE of NSOTF model is higher compared to that obtained for the nominal patient but the difference is not significant to be of any concern.

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Figure 6.4: Model fit for a patient from Class 4, Group I (solid line: SOTF model, dash-dot line: NSOTF model, dotted line: actual BG response)

Figure 6.5: Model fit for a patient from Class 7, Group I (solid blue line: SOTF model, dash-dot black line: NSOTF model, dotted red line: actual BG response)

The third chosen patient is from Class 7 (Group I) whose BG is highest in the group. The model fit of identified models are compared with the actual BG response in Figure 6.5. The MAE of NSOTF model fit is 2.45mg/dL. The gains of NSOTF model for insulin and meal are better than that of the SOTF model in terms of closeness to the gains obtained with the NL model. However, the gains of NSOTF model are about half of the actual response indicating significant mismatch to the actual BG response. Therefore, the response of NSOTF model is about 20mg/dL to 30mg/dL higher at the start (first 5 hours in Figure 6.5). These features might lead to over infusion of insulin and subsequently to lower BG in patients. However, this deficiency in the model can be compensated by bias updating.

The fourth patient is chosen from Group II, Class 5. This patient has the lowest BG response in the group, and the MRID and NMRID results are demonstrated in Figure 6.6 for the resulting model fit. Again the NSOTF model gains are much better than that of the fast-rate model. The NSOTF model gain of insulin is higher than actual response, and that of meal is slightly lower than actual response (values are provided in Table 6.1). The NSOTF model has a MAE of 3.50 mg/dL. The estimated values for the model parameters indicate that use of this model in a control algorithm for computing insulin infusion can lead to lower insulin infusion than the actual required amount which may lead to hyperglycemia. This, though not optimal, is not life threatening in most cases. The performance of the SOTF model is not acceptable.

The fifth patient is chosen from Group II, Class 8 to represent the patient with highest BG in this group. The MRID and NMRID results are presented in Figure 6.7 showing the model fit to the YIIP data. The NSOTF model gain for insulin is much better than the corresponding gain of the SOTF model. The gain for meal input is slightly better than SOTF model gain (values are described in Table 6.1). The NSOTF model gain for meal is lower than actual model gain, that for insulin is higher than actual model gain and time constants are greater than the actual model. These will lead to the lesser insulin infusion and will lead to similar effect and conclusion as in above case (the fourth patient). The model fit is quite good with MAE equal to 2.14mg/dL

for the NSOTF model. There is a mismatch of about 10mg/dL at the very start (0-5 hours in Figure 6.7) for the NSOTF model but the model fit for the later times is very acceptable.
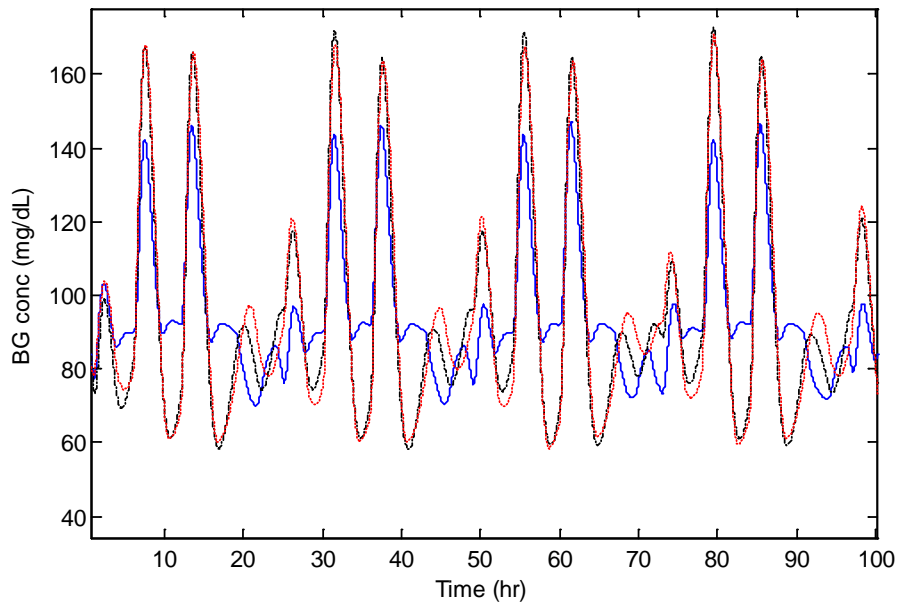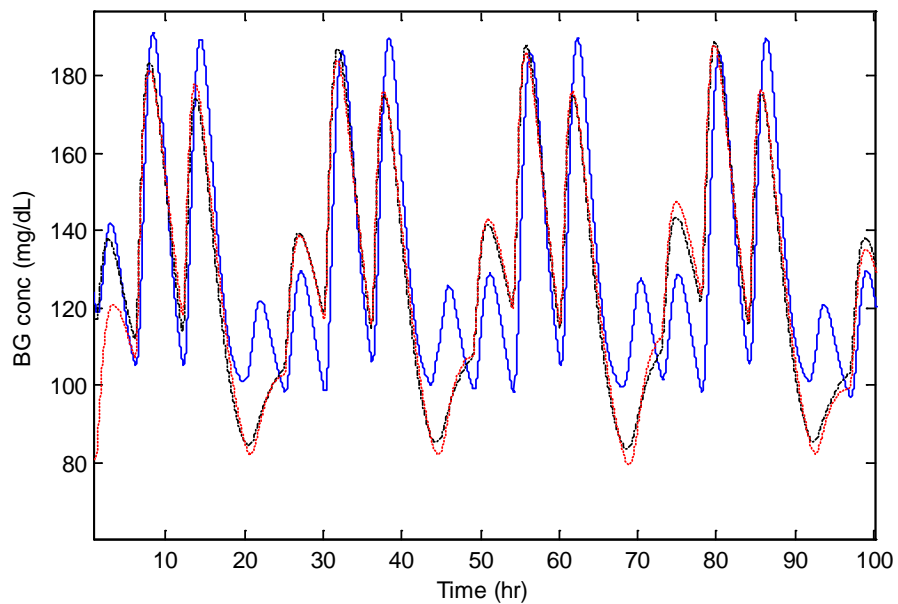

Figure 6.6: Model fit for a patient from Class 5, Group II (solid line: SOTF model, dash-dot line: NSOTF model, dotted line: actual BG response)

Figure 6.7: Model fit for a patient from Class 8, Group II (solid line: SOTF model, dash-dot line: NSOTF model, dotted line: actual BG response)

The sixth patient is from Class 6, Group III with the lowest BG in the group. The MRID and NMRID model fits for this patient are shown in Figure 6.8. The gain of insulin in the NSOTF model is about two times the true gain and that of meal input and is close to the actual model gain. These gains are much better than the gains indicated by the SOTF model (see values in Table 6.1). The time constant values in the NSOTF model are similar to the actual values. For this patient, the NSOTF model has an MAE value equal to 2.69mg/dL. Because of much lower gain values, the SOTF model is not acceptable at all. (In the SOTF model identified, the time constants are also smaller than the true values.) Significant discrepancy is exhibited during the first 5 hours by the NSOTF model with higher estimated BG values than the actual BG response but the model fit for the later times is quite acceptable.
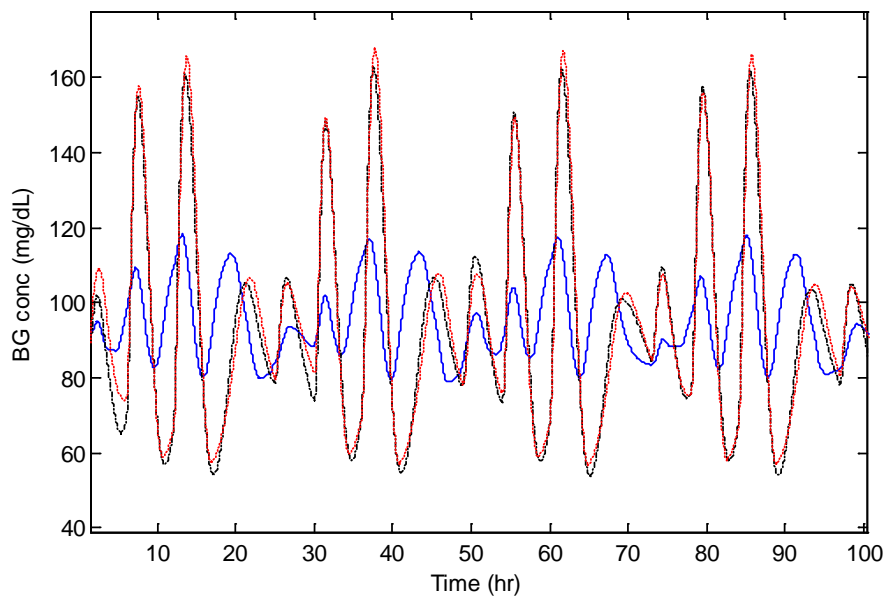
Figure 6.8: Model fit for a patient from Class 6, Group III (solid line: SOTF model, dash-dot line: NSOTF model, dotted line: actual BG response)

The last (seventh) patient is from Class 9, Group III with highest BG values in its group. The model fits for SOTF and NSOTF are compared to the YIIP data in Figure 6.9. In the NSOTF model identified, the absolute value of gains for insulin and meal inputs are lesser than actual model gains. The overall model fit (for NSOTF model) exhibits a MAE value of 2.63mg/dL.

Significant discrepancy is exhibited during the first 5 hours by the NSOTF model with higher estimated BG values than the actual BG response but the model fit for the later times is acceptable.
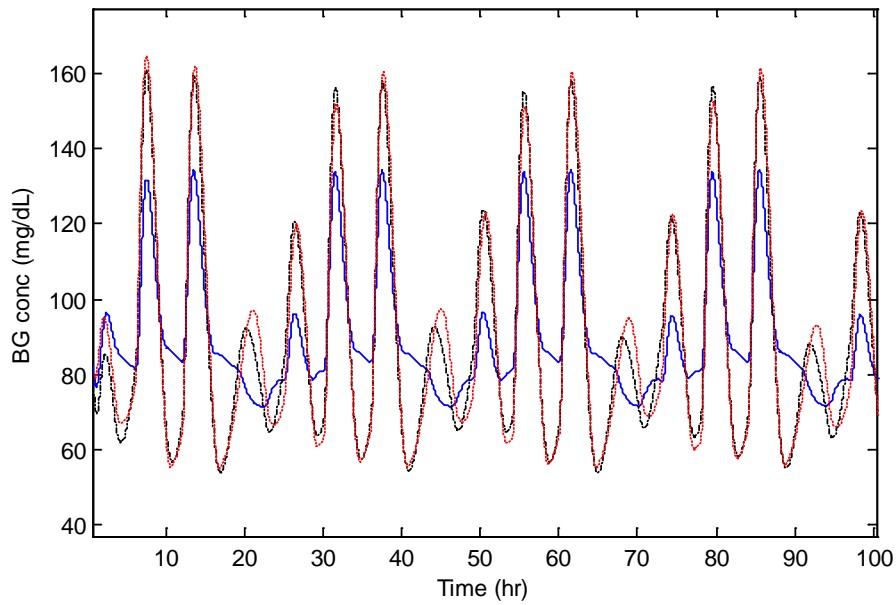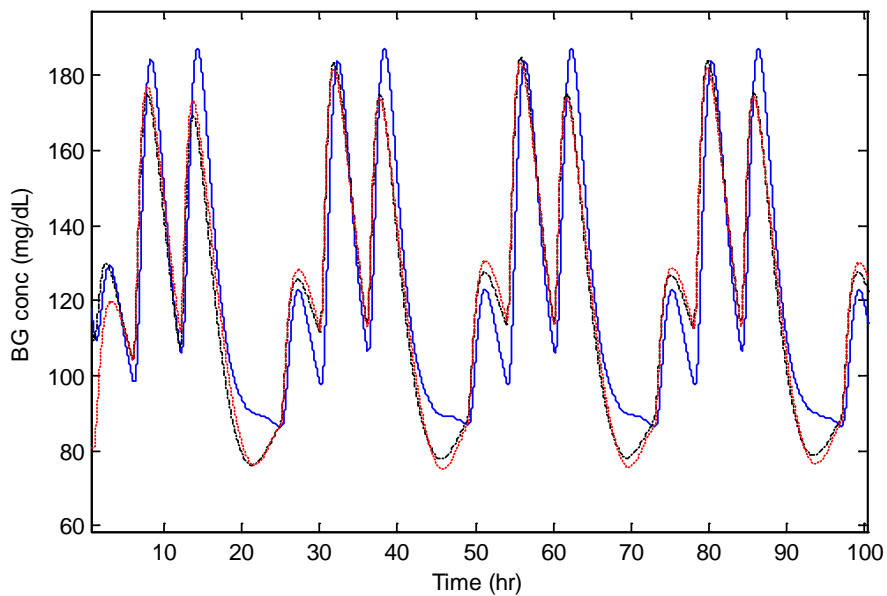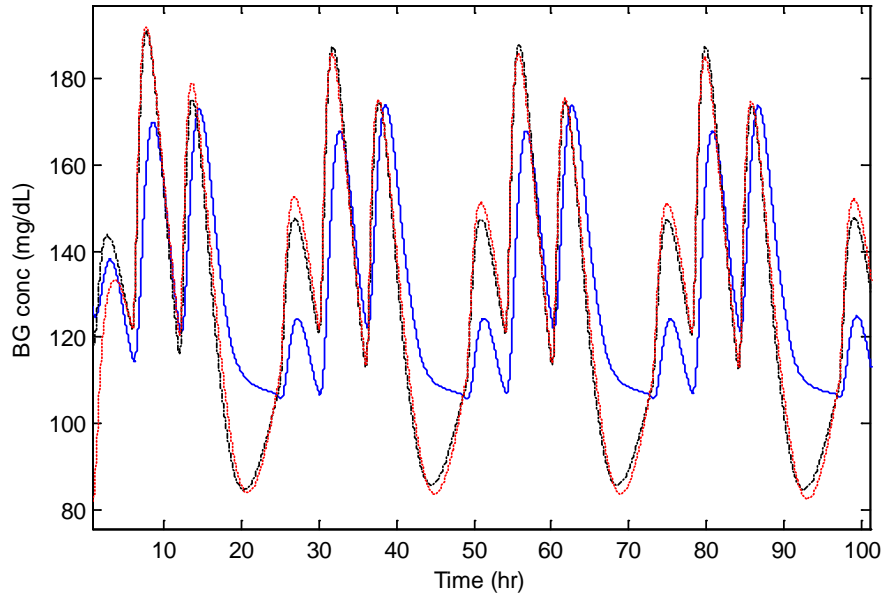

Figure 6.9: Model fit for a patient from Class 9, Group III (solid line: SOTF model, dash-dot line: NSOTF model, dotted line: actual BG response)

The pattern search used for NSOTF model converges for all 7 patients chosen. All the above results demonstrate that the NSOTF model is better than the SOTF model and is closer to the actual model responses. Values of time constants of NSOTF model are much closer to actual model values. Likewise, the gain values of NSOTF models are closer to actual model gain values and much better than the SOTF model values. The experience with SOTF and NSOTF models indicate that NSOTF models can be used for controller design. The LMEC implementation is presented in the next section.

6.6 LMEC-MRID, Results and Discussion

LMEC-MRID implementation is described in Section 6.6.1 and the results are shown and discussed in Section 6.6.2.

6.6.1 LMEC-MRID Implementation

We developed two LMEC-MRID controllers: (1) LMEC-MRID I is developed based on NMRID results of the 7 selected patients discussed above and (2) LMEC-MRID II developed based on second order transfer function approximation of NL model response of 12 chosen patients (7 patients described above and additional 5 more patients chosen randomly to obtain more accurate uncertainty bounds than LMEC-MRID I. LMEC-MRID II is designed also as benchmark controller for LMEC-MRID I and to check if discrepancy exists in defined uncertainty bounds by LMEC-MRID I using their performance comparison.

LMEC-MRID I: The NSOTF models (insulin and meal model) obtained from MRID are used to design the LMEC I controller (as outlined in Section 6.4.3). The models can also help in the estimation of BG inter-sample measurements based on the frequently available data on meal and insulin inputs. Bias updating is performed at every sampling interval when the actual measurement is available from the BG sensor. To overcome the spikes in the controller outputs, a first order filter with time constant of 1 unit in simulation time (1hr in actual time) is applied. The initial state of the filter is set to basal insulin amount for each patient. The rate limiter is also applied for maximum input constraint and to avoid negative input.

LMEC-MRID II: LMEC II (as described in section 6.4.3) is implemented along with the NMRID insulin and meal models which can help to estimate BG inter-sample measurements. The same first order filter setting is applied to remove input insulin infusion spikes. The same rate limiter setting as in LMEC-MRID I is used.

6.6.2 LMEC-MRID Results and Discussion

For the comparison LMEC-MRID performances, three patients are chosen (nominal patient from Group II and two patients with highest and the lowest BG from Group I and Group III respectively). For testing the disturbance rejection capability, meals containing 10 g, 50 g and 50 g of

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carbohydrates are provided at 7 am, 12 noon and 6 pm respectively. The set point is one of the target values of 81mg/dL, 90mg/dL and 100mg/dL to investigate the proper set point to be ensure the proper BG control. The disturbance rejection capability will be demonstrated at each of these three set points.

6.6.2.1 LMEC-MRID for Group II Patients

Firstly, the LMEC-MRID controller settings are tuned for the nominal patient. The input constraint (insulin infusion rate $<=$ 4000 mU/hr) is implemented for ensuring safe performance. The disturbance rejection performance of the two LMEC-MRID controllers for nominal patient at three set points (81.08mg/dL, 90mg/dL & 100mg/dL) are shown in Figure 6.10, 6.11 and 6.12 respectively.

Figure 6.10: Performance of LMEC-MRID controllers for nominal patient (Group II) with set point equal to 81 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)

Figure 6.11: Performance of LMEC-MRID controllers for nominal patient (Group II) with set point equal to 90 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)
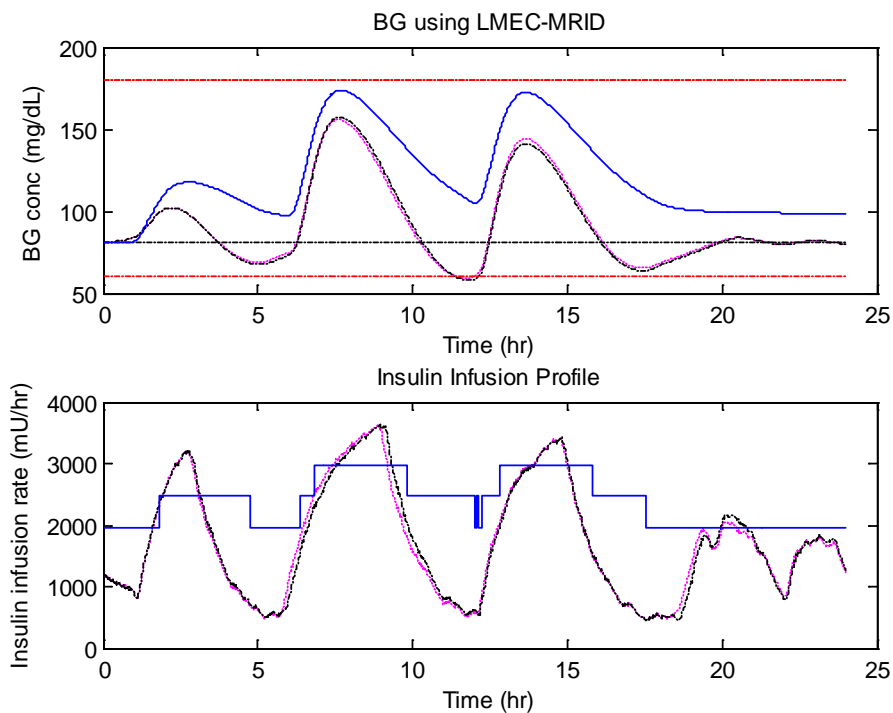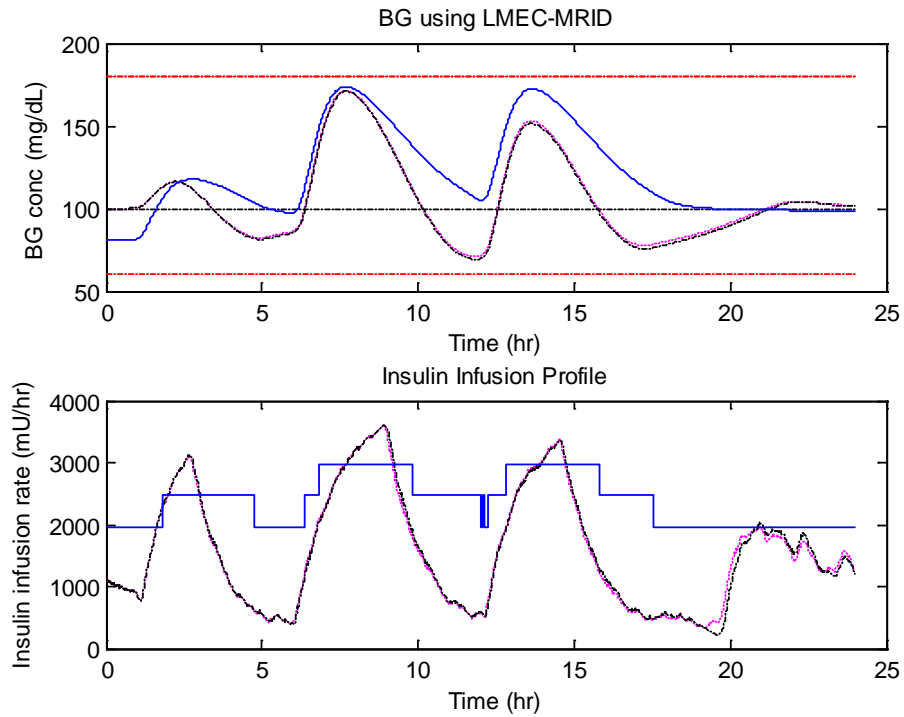

Figure 6.12: Performance of LMEC-MRID controllers for nominal patient (Group II) with set point equal to 100 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)

As shown in Figure 6.10 to 6.12, the performances of LMEC-MRID I and LMEC-MRID II are comparable. The BG results are in acceptable range (55mg/dL~180mg/dL). The controllers take about 3 to 5 hr for the set point to be reached after dinner. The controller output displays a proper trend to counteract the meal disturbance, and the resulting BG peak values are lower than tailored YIIP results, with lesser total insulin infusion amount and without hypoglycemic (BG < 50mg/dL) events. The total insulin amounts used by controllers for three set points for normal day (with three meals) are compared in Table 6.2.

Table 6.2: Comparison of Insulin Infusion Amount for a Group II patient
(nominal patient)

Set point value	LMEC-MRID I	LMEC-MRID II	YIIP
81 mg/dL	4.14×10^1 U	4.15×10^1 U	6.84×10^2 U
90 mg/dL	3.95×10^1 U	3.96×10^1 U	6.84×10^2 U
100 mg/dL	3.76×10^1 U	3.77×10^1 U	6.84×10^2 U

The total insulin amount used by YIIP is highest and that by LMEC-MRID I is the lowest among the three controllers. The LMEC-MRID I uses lesser insulin amount and has comparable performance to the LMEC-MRID II. The BG trajectory goes below 60mg/dL in Figure 6.10 (for set point equal to 81mg/dL) but the patient's BG values stay above 60mg/dL for the other two set point values (90mg/dL and 100mg/dL). As expected, the set point value 100mg/dL provides the best performance (normoglycemic region of 70mg/dL<BG<180mg/dL) compared to the other two set point values, in the prospect of avoiding possible hypoglycemia. According to these results, to avoid possible hypoglycemia, a set point value of 100mg/dL seems to be better.

6.6.2.2 LMEC-MRID for Group I Patients

The LMEC-MRID controller output constraint is tuned for Group I patients who have highest basal insulin requirements among the cohort of patients. The patient from Class 7 (Group I) who exhibited highest BG values when subject to tailored YIIP treatment is selected as a representative member of this group. The corresponding LMEC-MRID results are shown in Figure 6.13 to 6.15 for the three set points considered here.

Figure 6.13: Performance of LMEC-MRID controllers for a patient from Class 7 (Group I) with set point equal to 81 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)
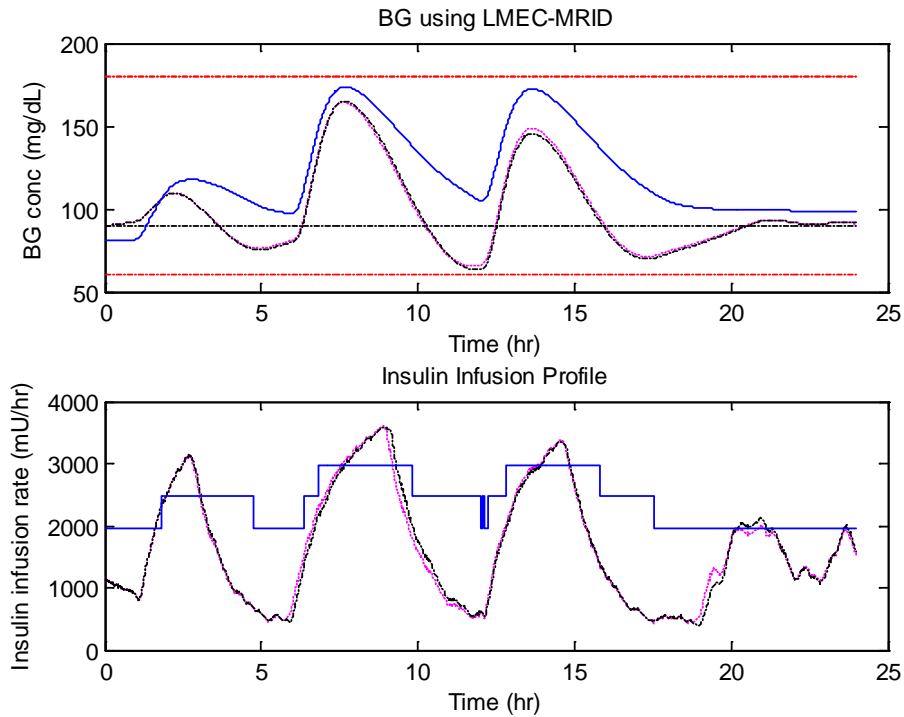

Figure 6.14: Performance of LMEC-MRID controllers for a patient from Class 7 (Group I) with set point equal to 90 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)

Figure 6.15: Performance of LMEC-MRID controllers for a patient from Class 7 (Group I) with set point equal to 100 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)

The total infusion amount of insulin for each of the set points for each controller (LMEC-MRID I, LMEC-MRID II & YIIP) in a normal day with three meals is given in Table 6.3. Similarly as in the above nominal patient, the total insulin amount used by YIIP is highest and that by LMEC-MRID I is lowest among the three controllers. Likewise in the above nominal patient case, LMEC-MRID I has economic advantages with lesser insulin amount used and has comparable performance to LMEC-MRID II.

Table 6.3: Comparison of Insulin Infusion Amounts for a Group I patient

Set point value	LMEC-MRID I	LMEC-MRID II	YIIP
81 mg/dL	2.19×10^2 U	2.21×10^2 U	3.21×10^3 U
90 mg/dL	2.12×10^2 U	2.13×10^2 U	3.21×10^3 U
100 mg/dL	2.05×10^2 U	2.06×10^2 U	3.21×10^3 U

The controller output is constrained so as not to exceed 20000mU/hr. (20U/hr.), to achieve good BG control for this group, which requires higher insulin amount. The process input (the controller output) has an acceptable

trend without any spikes and the BG profile following each meal is quite good with BG values above 55mg/dL. There are no hypoglycemic events. However, the results show that the set point is not reached between meal inputs. Similar to the previous case, a BG target of 100mg/dL has better performance than other two tested BG targets in successfully staying away from the hypoglycemic limit but its BG peak value hits the upper limit of 180mg/dL which is acceptable. The overall controller performance given the constraints on BG is quite satisfactory. The BG can be maintained in acceptable range with BG around its target value between meals though more insulin is infused than the tailored YIIP.

6.6.2.3 LMEC-MRID for Group III patients

The patient from Class 6 who exhibits lowest BG values in tailored YIIP treatment, is chosen from Group III. Patients from this group need low basal insulin amount when compared to other patients in the cohort. This patient is selected in order to test the ability of the controller in preventing hypoglycemic events. The results of BG regulation using the two LMEC-MRIDs are demonstrated and compared with tailored YIIP treatment results in Figures 6.16 to 6.18 for three BG target values.

The LMEC-MRID controllers are implemented with a constraint on the insulin infusion amount (upper limit of 2000 mU/hr). This setting satisfied the objective that no BG value should go under 50 mg/dL or over 180 mg/dL with acceptable return to set point within a 3 to 5 hr period.

Similar to previous cases, the BG target value of 100 mg/dL is better for patient safety compared to the other two set point values in that it avoids possible hypoglycemia. The total insulin infusion amounts utilized by the controllers for a normal day with three meals are tabulated in Table 6.4. The total insulin infusion amount used by LMEC-MRID is rather less than that by tailored YIIP and thus LMEC-MRID is advantageous economically. Likewise in the above cases, the total insulin used by YIIP is the highest and that by LMEC-MRID I is the lowest among the three controllers.
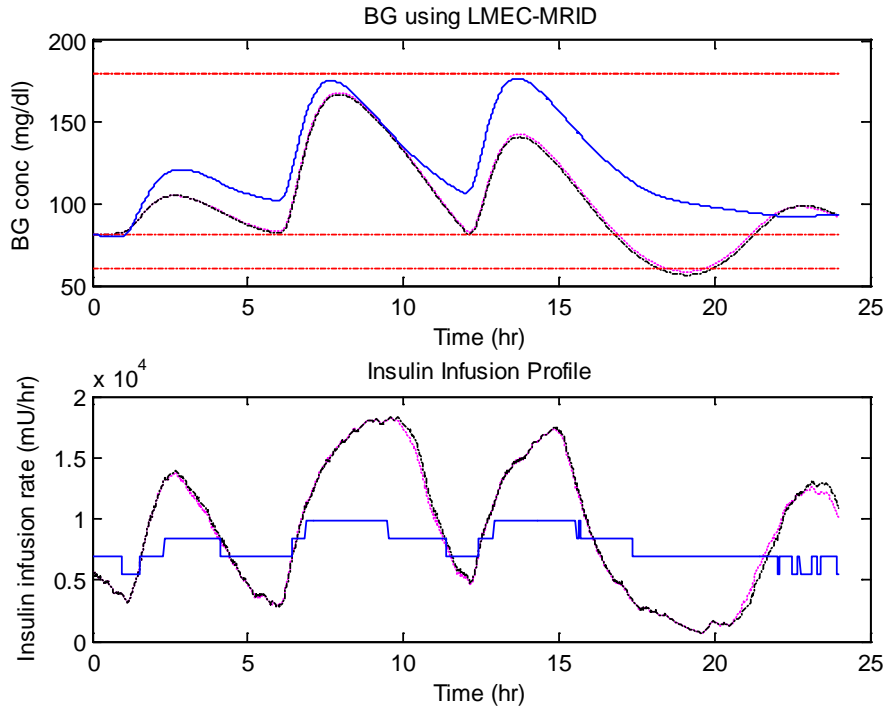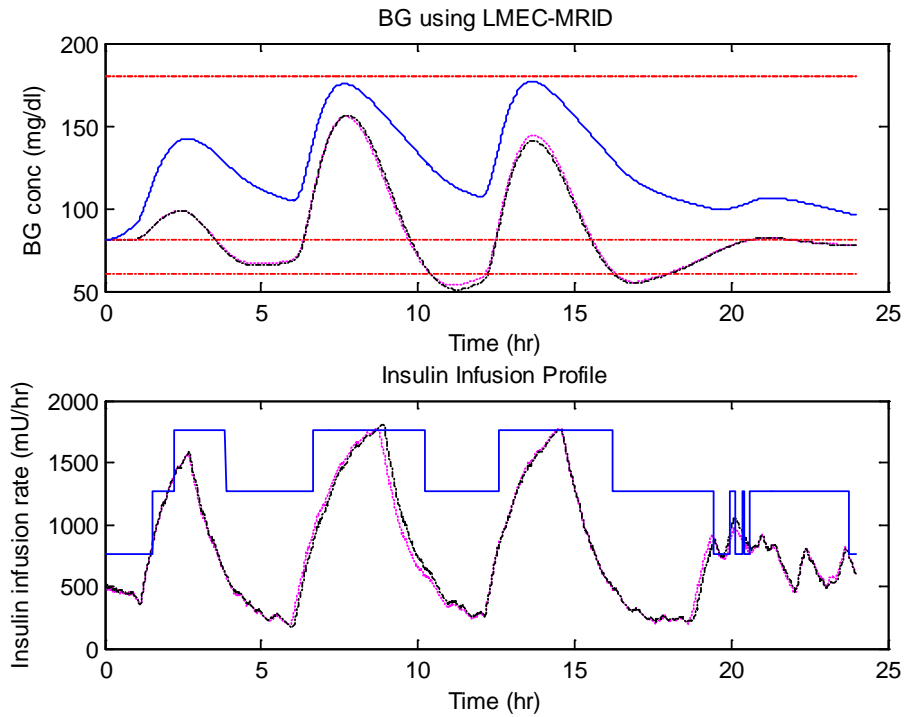
Figure 6.16: Performance of LMEC-MRID controllers for a patient from Class 6 (Group III) with set point equal to 81 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)
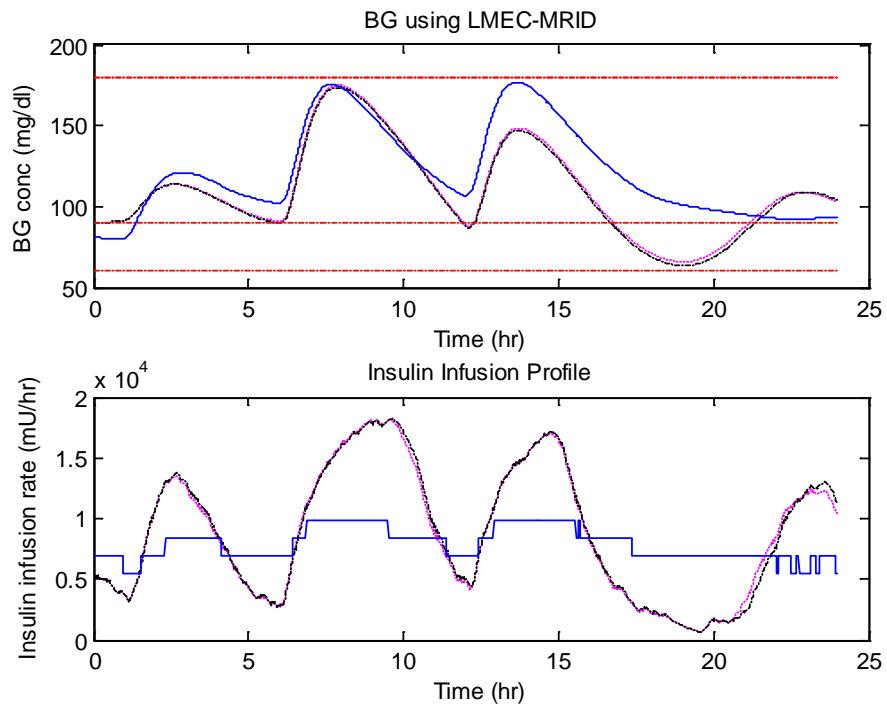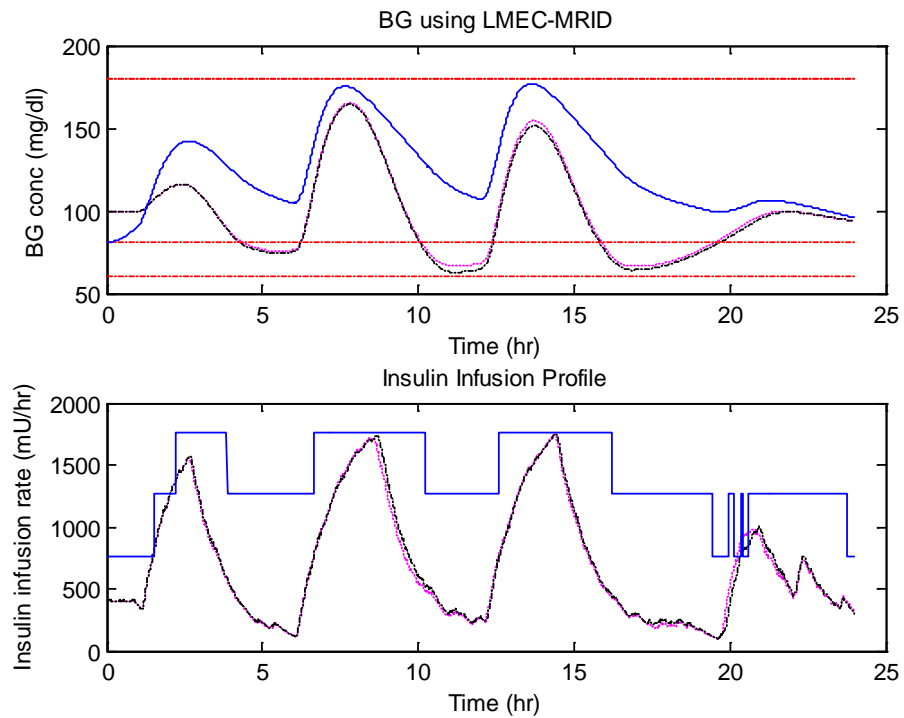

Figure 6.17: Performance of LMEC-MRID controllers for a patient from Class 6 (Group III) with set point equal to 90 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)
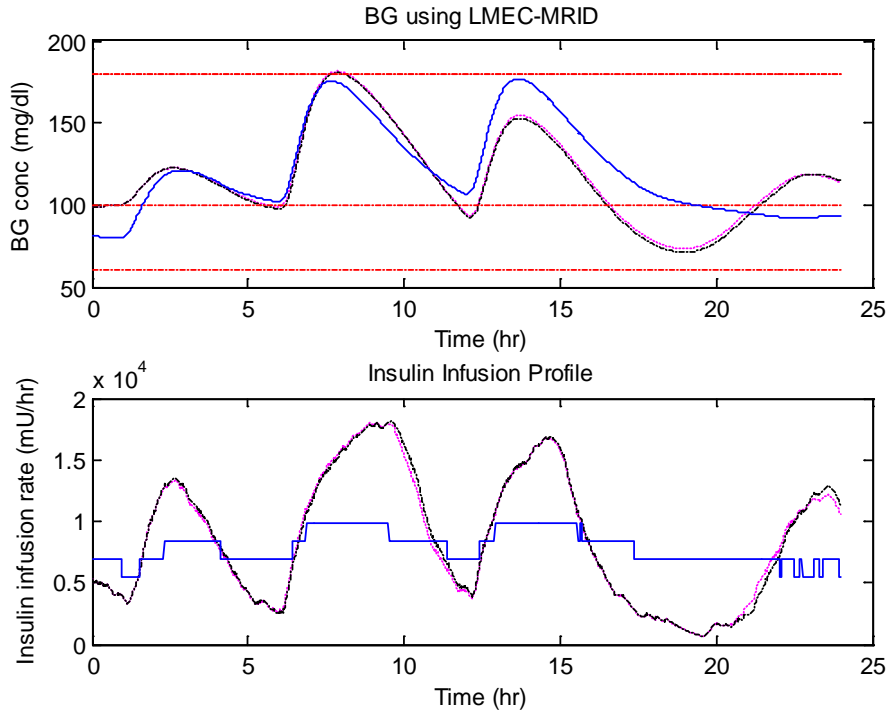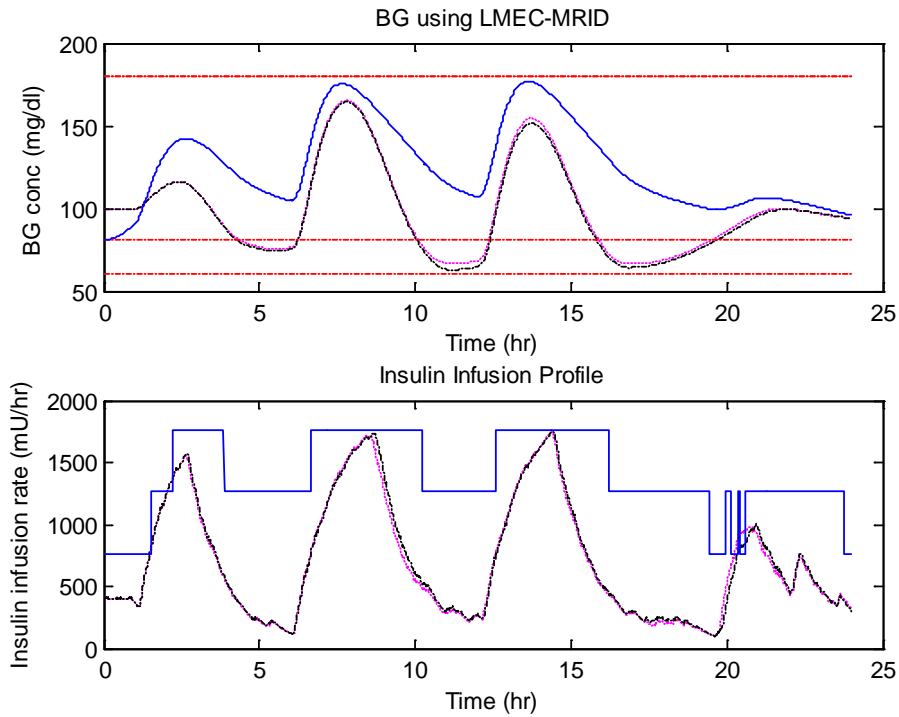
Figure 6.18: Performance of LMEC-MRID controllers for a patient from Class 6 (Group III) with set point equal to 100 mg/dL (dashed line: LMEC-MRID I, dash-dot line: LMEC-MRID II, solid line: tailored YIIP)

Table 6.4: Comparison of Insulin Infusion Amounts for a Group III patient

Set point value	LMEC-MRID I	LMEC-MRID II	YIIP
81 mg/dL	1.90×10^1 U	1.92×10^1 U	3.02×10^2 U
90 mg/dL	1.79×10^1 U	1.80×10^1 U	3.02×10^2 U
100 mg/dL	1.68×10^1 U	1.68×10^1 U	3.02×10^2 U

The two LMEC-MRIDs have comparable performance. They are better to the tailored YIIP treatment outcomes since less insulin is used with the LMEC scheme. Similarly as in above cases, LMEC-MRID I outperforms economically with lesser insulin amount used and comparable performance to LMEC-MRID II.

6.6.3 LMEC-MRID Validation on Parker Model Patient Cohort

The LMEC-MRID I controller was developed based on Fabietti model patient cohort. To test the effectiveness of the controller on patients generated

from other models, the 577 patient cohort of Parker model is chosen here. The disturbance rejection scenario of the controller is tested using the more favorable set point of 100mg/dL (5.5mmol/L).

Firstly, the 577 patients are categorized into respective patient classes using MIVGTT data as mentioned in sections 4.3 and 4.4. The test data are pretreated and then projected onto the PCA model constructed in section 4.6.1. The results are shown in Figure 6.19. Categorizing the 577 patients based on the closeness to the nearby patient classes using t-squared values as the basis, the 577 patients are classified into Class 2 (86 patients out of 577 patients) – belonging to Group II, and Class 3 (the remaining 491 patients out of 577 patients) – belonging to Group III. The respective LMEC-MRID I for Group II and Group III are administered those two patient classes (with the set constraints) and the results are shown in Figure 6.20 and Figure 6.21 respectively.
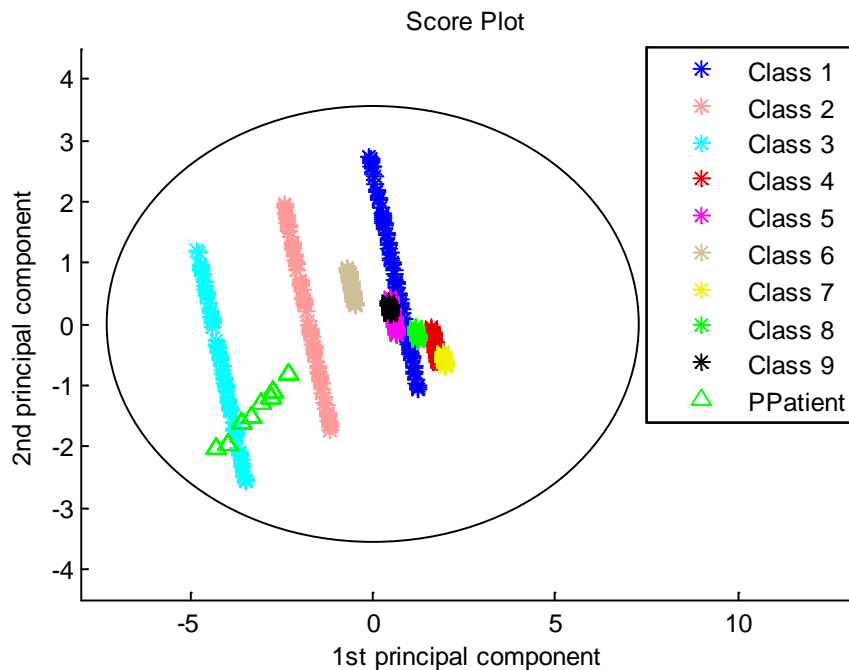
Figure 6.19: PCA based classification of the cohort of 577 patients obtained from Parker models (with data pretreatment) with 99.99% confidence interval
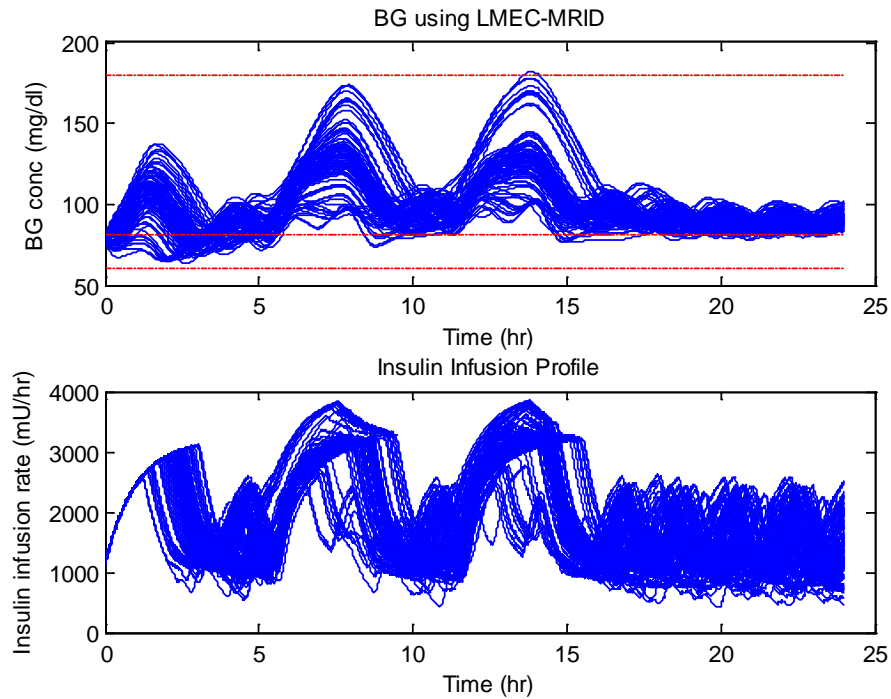
Figure 6.20: Performance of LMEC-MRID I for Group II controller on Class 2 patients - 86 patients out of 577 Parker patients
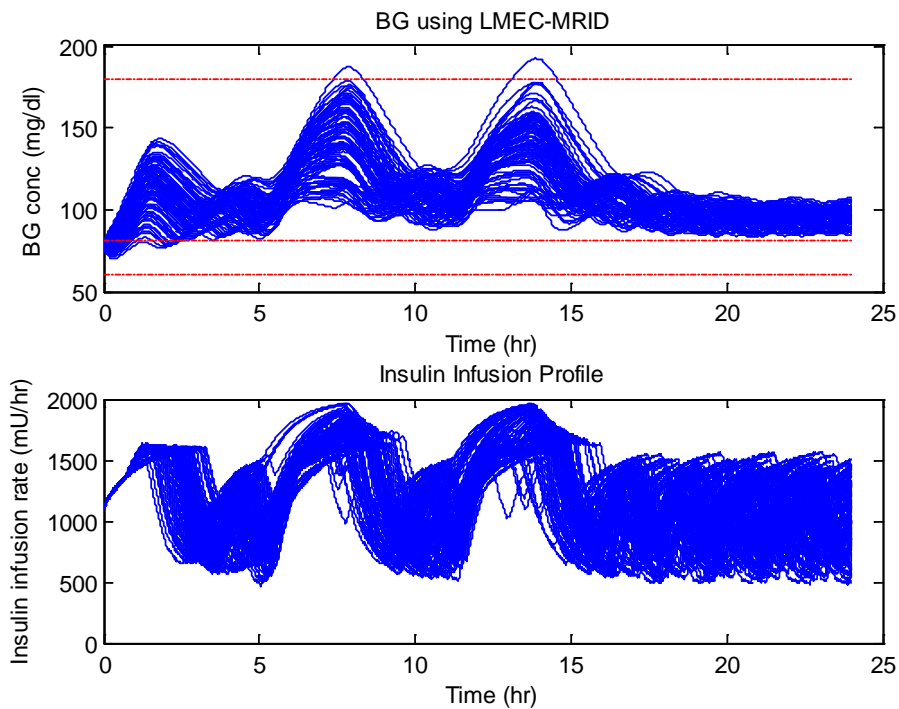
Figure 6.21: Performance of LMEC-MRID I for Group III controller on Class 3 patients - 491 patients out of 577 Parker patients

As shown in Figure 6.20, the LMEC-MRID I for Group II controller can maintain BG of Class 2 patients – 86 patients almost in the range 60~180mg/dL with the highest BG being 181.92mg/dL. The hypoglycemia (<60mg/dL) can be avoided successfully with the lowest BG being 63.47mg/dL. Likewise, the result shown in Figure 6.21 reveals the fact that LMEC-MRID I for Group III controller (on Class 3 – 491 patients) maintained almost all BG values in the range of 60~180mg/dL with only one patient's BG violating the range (highest BG for this patient being 192.37mg/dL) without hypoglycemia (with lowest BG being 69.78mg/dL).

These results highlight the fact that LMEC-MRID I controller could be a promising candidate for T1D patients managing BG within the acceptable range and circumventing hypoglycemia efficaciously.

6.7 Conclusions

The proposed NMRID algorithm (NSOTF method) is quite reliable in providing acceptable inter-sample BG measurement estimation. The identified models lead to acceptable controller performance when augmented with bias updating mechanism, filter and constraints on the insulin infusion rate to controller. LMEC-MRID I is designed based on the NMRID results and LMEC-MRID II is designed based on the response of the NL model. Different LMEC-MRID settings for three groups (classified by the method proposed in Section 4.6.2) are proposed. The performances of LMEC-MRID I and LMEC-MRID II for disturbance rejection at three target values are quite comparable. A BG target of 100 mg/dL appears to be most effective in avoiding possible hypoglycemic events. The LMEC-MRID controllers are seen to outperform tailored YIIP in keeping BG values within practical limits while using less insulin. The LMEC-MRID I controller performance evaluation on a cohort of 577 patients generated with the Parker model also substantiates that LMEC-MRID I controller is a promising candidate for blood glucose regulation inT1D patients. Particularly, LMEC-MRID is economically beneficial with lesser insulin amount used and with performance comparable to LMEC-MRID II – all these indicate that NMRID approach is quite acceptable.

Chapter 7

Conclusions and Recommendations

7.1 Conclusions

Treating T1D in a timely and effective manner is an important problem for which a complete, reliable solution is not yet available. In diabetic patients, it is crucial to keep the fasting blood glucose concentration in normoglycemic range (70-126mg/dL) and a postprandial BG value of under 180 mg/dL (but over 55mg/dL). This can be achieved using exogenous insulin infusion in a manner that avoids both hyperglycemia and hypoglycemia. However, the unavoidable inter- and intra-patient variability makes BG control very challenging. To obtain effective BG regulation in Type 1 diabetics, efficient and practically implementable control algorithms are needed. This thesis proposed simple, implementable and effective control algorithms that work on a broad range of patients. Due to the cost and safety issues that are associated in testing the developed algorithms on human subjects, this thesis used state-of-the-art T1D mathematical models as virtual patients and tested the various control algorithms via simulations using MATLAB.

The rule based control algorithms that are currently practiced in ICUs have had significant positive effect in reducing mortality and morbidity. These algorithms are built based on experience and practical knowledge of the physicians. Among them, the YIIP is most popular. This protocol was modified to develop a strategy to treat a broad range of virtual T1D patients, and the effectiveness of this modified YIIP was studied in Chapter 3. The performance of the proposed rule based control algorithm, MODYIIP, on cohorts of simulated virtual patents demonstrate that MODYIIP is a potential candidate for treating T1D patients. However, the results show that MODYIIP needs to be tailored to avoid possible hyperglycemia in different patients. On the positive side, the proposed MODYIIP was successful in avoiding dangerous hypoglycemia.

To obtain effective BG regulation in T1D patients, an efficient and practically implementable "class-specific" control algorithm was proposed in

Chapter 4. In the absence of real patients, a state-of-the-art mathematical model that adequately simulates BG dynamics in diabetics was employed to develop a classification-based approach that groups "patients" into different classes and to demonstrate the success of tailored, "class-specific" algorithms. The novel approach consists of a diabetes diagnostic test (Modified Intravenous Glucose Tolerance Test, MIVGTT), and a multivariate statistical tool (Principal Component Analysis, PCA) was used for classification. Then, YIIP was tailored and applied to different patient classes. Applicability of this approach through validation on different patient models was also investigated.

The results indicated that T1D patients can be classified into nine classes. Using the tailored YIIP-based treatment on a "normal day" (with three meals), it was observed that hypoglycemia ($< 50mg/dL$) can be successfully avoided for the entire cohort of the *in silico* patients without the need to administer any extra glucose. For any *in silico* patient, the MIVGTT can be conducted and the patient class determined. Then, the tailored YIIP for the particular class can be used to treat the patient. This work has investigated the robustness of the approach for certain intra-patient variability within the same patient class and obtained acceptable results. The developed algorithm appears to be simple, effective and practical for treating real T1D patients. Clinical validation of the classification approach and the control algorithm would be the subsequent step in this work.

Robust controllers are other potential candidates for treatment of T1D patients because they can handle predefined uncertainty in model parameters. LMEC (linear modeling error compensator) was chosen for investigation here because it is a linear controller and capable of providing good performance with less complexity than, say, a nonlinear controller. The central idea of LMEC is to compensate the error arising out of parametric uncertainty by determining the modeling error using plant input and output signals and employing a linear model of known order. In addition to nominal feedback, another feedback loop is introduced using the modeling error and this feedback action is explicitly proportional to error which is induced by parametric uncertainty. The uncertainty bounds are determined from the transfer functions of virtual patients and incorporated into the controller

design. Effectiveness of LMEC was demonstrated on a large set of virtual patients embedding as much as 50% parametric uncertainty (Chapter 5). The results showed that LMEC is a good candidate for BG control in T1D patients when frequent BG sampling is possible. Clinical test of this technique is one possible area for future work.

Sometimes, data on BG and insulin infusion amount can be obtained from medical records or from patients. These data are often available as multirate measurements because variable such as insulin infusion amount are more frequently measurable than the BG values. To handle such data and to develop a control strategy subsequently, the thesis proposed a LMEC-MRID strategy in Chapter 6. The required transfer function parameters for LMEC controller were estimated from multirate data using MRID. This model helped in the estimation of intersample BG values to be used by the LMEC controllers. The estimated BG values from the model were updated whenever an actual BG measurement became available (bias updating). The required uncertainty bounds were incorporated into the LMEC controller from MRID of patient data. This controller was named LMEC-MRID I. The benchmark controller, LMEC-MRID II was designed based on the linear approximation of original NL model. Both LMEC-MRID I & LMEC-MRID II provided similar control performance and were able to keep the BG values within safe limits. The performance validation of developed controller on different patient cohort also attests the acceptable performance. This shows that the control strategy based on model developed from multirate patient data is a promising strategy for BG control in T1D patients.

7.2 Recommendations for Future Works

In the following sections, the recommended future works are summarized.

7.2.1 Classification Methods

The classification of patient classes using PCA with data pretreatment is simple and quite effective. However, more efficient classification methods

such as Dynamic PCA (DPCA) would be worth exploring. Patient data from MIVGTT is dynamic in nature so that DPCA would be the right choice to handle the classification problem. Other classification approaches such as Qualitative Trend Analysis can also be employed.

7.2.2 Incorporation of Recursive Identification Scheme into LMEC-MRID

The existing bias updating scheme suggested for our LMEC-MRID implementation is simple suggesting that the performance would be better if a more efficient updating scheme can be implemented. Moreover, the intra-patient variability that exists in T1D patients owing to different situations such as changing insulin sensitivity, stress and lifestyle should be identified as parametric variations and utilized in the LMEC-MRID algorithm. Recursive identification methods could be employed to handle such parameter variations leading to an adaptive-LMEC algorithm.

7.2.3 Association of Exercise and Other Effects into Modeling

The exercise effect cannot be neglected in real patients and has been taken into account by some researchers (e.g. Roy and Parker, 2006). These models need to be modified to handle the intensity and duration of exercise. Anxiety and stress can also affect BG dynamics. Anxiety and stress are known to cause hypertension which is correlated to hyperglycemia (Mancia, 2007). These issues should be dealt with in modeling of diabetics, and applied control strategies for BG regulation in T1D patients should also take these aspects into consideration. More comprehensive models of diabetes need to be developed and employed in artificial closed loop pancreas systems.

7.2.4 Nonlinear Control Strategy

The LMEC is effective in avoiding severe hypoglycemia for given uncertainty bounds. If an adequate nonlinear model is available, one could try employing a nonlinear modeling error compensator based on the fundamental nonlinear model and the uncertainty associated with its parameters. This

extension of MEC to biomedical process control can be an excellent avenue for research.

7.2.5 Diabetes Control in ICU patients

Critically ill patients or patients in ICU experience stress induced hyperglycemia even if they do not have any past history of diabetes. Other factors such as presence of hypertension, cortisone and pancreatic disease may also results in hyperglycemia. From the extensive literature review, it is clear that intensive insulin therapy (IIT) can reduce morbidity, mortality and duration of patients stay in ICU. According to Leuven study, an IIT that maintains BG in the 80-110 mg/dL range can reduce: ICU mortality by 42%, bloodstream infections, the incidence of acute renal failure, the need for prolonged ventilatory support, and the duration of ICU stay (Goldberg et al., 2004). Many IIP protocols have been developed for glycemic control in ICU - some protocols have been developed for medical ICU (MICU) and some others have been proposed for use in surgical ICUs (SICU). These protocols are currently based on physicians' expertise and experience; however, they can be further optimized and personalized to provide tight BG control. Avoiding hypoglycemia is the primary intention in ICU patients. Developing a protocol that can avoid hypoglycemia, provide tight glycemic control for the different conditions of patients with minimal physician intervention, and is easy to use by ICU nursing staff would be worth the effort. Developing a patient model that takes into account conditions such as hypertension, corticosteroid, and administration through enteral or parenteral routes would be worthwhile efforts to pursue in order to develop more effective IIP strategies for use in ICUs.

References

Ackerman, E., L.C. Gatewood, J.W. Rosevear and G.D. Molnar, "Model Studies of Blood-Glucose Regulation", The Bulletin of Mathematical Biophysics, 27, pp. 21-37, 1965.

Albisser, A.M., B.S. Leibel, T.G. Ewart, Z. Davidovac, C.K. Botz and W. Zingg, "An artificial endocrine pancreas", Diabetes, 23, pp. 389-396, 1974.

Alsahli, M. and J.E. Gerich, "Hypoglycemia in Diabetes Mellitus", Principles of Diabetes Mellitus, 2nd Ed, Chapter 19, ed by L. Poretsky, Springer Press, New York, pp. 297–312, 2010.

Alvarez-Ramirez, J., J. Alvarez and A. Morales, "An adaptive cascade control for a class of chemical reactors", Int. J. Adapt. Control Signal Process., 16, pp. 681–701 (DOI: 10.1002/acs.717), 2002.

American Diabetes Association, "Standards of Medical Care-Table 6 and Table 7, Correlation between A1C level and Mean Plasma Glucose Levels on Multiple Testing over 2-3 months", Diabetes Care, 29(Suppl. 1), pp. 51-580, 2006.

Arleth, T., S. Andreassen, M. Orsini-Federici and M. Massi-Benedetti, "A model of the endogenous glucose balance incorporating the characteristics of glucose transporters", Comput. Methods Programs Biomed., 62(3), pp. 219–234, 2000a.

Arleth T., S. Andreassen, M. Orsini-Federici, A. Timi and M. Massi-Benedetti, "A model of glucose absorption from mixed meals", In Proc. 4th IFAC Symposium on Modeling and Control in Biomedical Systems 2000, March 2000, Karlsburg/Greifswald, Germany, pp. 307–312, 2000b.

Aye, T., J. Block and B. Buckingham," Toward Closing the Loop: An Update on Insulin Pumps and Continuous Glucose Monitoring Systems", Endocrinology & Metabolism Clinics of North America, 39(3), pp. 609-624, September 2010.

Bellomo, G., P. Brunetti, G. Calabrese, D. Mazzotti, E. Sarti and A. Vincenzi, "Optimal feedback glycaemia regulation in diabetics", Med. & Biol. Eng. & Comput., 20, pp. 329-335, 1982.

Bequette, B.W., "A Critical Assessment of Algorithms and Challenges in the development of a Closed-Loop Artificial Pancreas", Diabetes Technology Therapeutics, 7(1), pp. 28-47, 2005.

Berghe, V.D., "Intensive Insulin Therapy in the ICU", Indian J. Crit. Med., 7, pp. 106-111, 2003.

Bergman, R.N., L.S. Phillips and C. Cobelli, "Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man", J. Clin. Invest., 68(6), pp. 1456-1467, 1981.

Bolie, V.W., "Coefficients of Normal Blood Glucose Regulation", Journal of Applied Physiology, 16(5), pp. 783-788, 1961.

Botz, C.K., "An improved control algorithm for an artificial β-cell", IEEE Trans. Biomed. Eng., BME-23, pp. 252-255, 1976.

Boutayeb, A. and A. Chetouani, "A Critical Review of Mathematical Models and Data used in Diabetology", BioMedical Engineering OnLine, 5(43), (DOI: 10.1186/1475-925X-5-43), 2006.

Broekhuyse, H.M., J.D. Nelson, B. Zinman and A.M. Albisser, "Comparison of algorithms for the closed-loop control of blood glucose using the artificial beta cell", IEEE Trans. Biomed. Eng., BME-28, pp. 678-687, 1981.

Camelia, O.L. and F.J. Doyle III, "Performance Monitoring of Diabetic Patient Systems", 2001 Proceedings of the 23rd Annual EMBS International Conference, Istanbul, Turkey, 2001.

Canonico, V., P.G. Fabietti, M.M. Benedetti, M.O. Federici and E. Sarti, "Virtual type 1 diabetic patient for feedback control systems", Diabetes Research and Clinical Practice, 74, pp. S187-S190, 2006.

Chant, C., D. Wilson and J. Friedrich, "Validation of an Insulin Infusion Nomogram for Intensive Glucose in Critically Ill Patients", Pharmacotherapy, 25(3), pp. 352-359, 2005.

Chbat, N.W. and T.K. Roy, "Glycemic Control in Critically Ill Patients – Effect of Delay in Insulin Administration", Proc. of the 2005 IEEE, Engineering in Medicine and Biology 27th Annual Conference, Shanghai, China, September 1-4, 2005.

Chee, F. and T. Fernando, "Closed-loop Control of Blood Glucose", Springer-Verlag Berlin and Heidelberg GmbH & Co. KG, Berlin, Germany, 2007.

Chee, F., T.L. Fernando, A.V. Savkin and V. van Heeden, "Expert PID Control System for Blood Glucose Control in Critically Ill Patients", IEEE Trans. on Infor. Tech. in Biomed, 7(4), pp. 43-53, 2003.

Clemens, A.H., **"**Feedback control dynamics for glucose controlled insulin infusion system", Med. Prog. Technol., 6, pp. 91-98, 1979.

Cobelli, C. and A. Mari, "Validation of Mathematical Models of Complex Endocrine-Metabolic Systems. A Case Study on a Model of Glucose Regulation", Medical & Biological Engineering & Computing, 21, pp. 390-399, 1983.

Cobelli, C. and A. Ruggeri, "Evaluation of portal/peripheral route and of algorithms for insulin delivery in the closed-loop control of glucose in diabetes – a modeling study", IEEE Trans. Biomed. Eng., BME-30, pp. 90-103, 1983.

Cobelli, C., G. Federspil, G. Pacini, A. Salvan and C. Scandellari, "An integrated mathematical model of the dynamics of blood glucose and its hormonal control", Mathematical Biosciences, 58, pp. 27-60, 1982.

DCCT - The Diabetes Control and Complications Trial Research Group, "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin- dependent diabetes mellitus", N. Engl. J. Med., 329, pp. 977-986, 1993.

Diabetes., UK, http://www.diabetes.co.uk/insulin/Insulin-pumps.html, Nov 2010.

Doran, C.V., G. Chase, G.M. Shaw, K.T. Moorhead and N.H. Hudson, "Derivative weighted active insulin control algorithms and intensive care unit trials", Control Eng. Practice, 13, pp. 1129-1137, 2005.

Dua, P. and E.N. Pistikopoulos, "Model-Based Control of Blood Glucose for Type 1 Diabetes", Multi-Parametric Model-Based Control, Weinheim: Wiley-VCH, 2007.

Dua, P., V. Sakizlis, V. Dua, F.J. Doyle III and E.N. Pistikopoulos, "Model Based Control for Insulin Delivery for Type 1 Diabetics via parametric Programming", European Symp. On Computer-Aided Process Eng., 14, pp. 1045-1050, 2004.

Eddy D.M. and L. Schlessinger, "Archimedes: A trial-validated model of diabetes"**,** Diabetes Care, 26(11), pp. 3093-3101, 2003a.

Eddy D.M. and L. Schlessinger, "Validation of the Archimedes diabetes model"**,** Diabetes Care, 26(11), pp. 3102-3110, 2003b.

Eren-Oruklu, M., A. Cinar, L. Quinn and D. Smith, "Adaptive control strategy for regulation of blood glucose levels in patients with type 1 diabetes', Journal of Process Control, 19, pp. 1333–1346, 2009.

Esoterix, "Endocrinology expected values and S.I unit conversion tables", http://www.esoterix.com/files/expected_values.pdf, April 2010.

Fabietti, P.G., V. Canonico, M.O. Federici, M.M. Benedetti and E. Sarti, "Control Oriented Model of Insulin and Glucose Dynamics in Type 1 Diabetics", Med. Biol. Eng. Comput., 44, pp. 69-78, 2006.

Fischer, M.E. and K.L. Teo, "Optimal insulin infusion resulting from a mathematical model of blood glucose dynamics", IEEE Trans. Biomed. Eng., 36(4), pp. 479-485, 1989.

Fischer, U., E. Jutzi, E-J Freyse and E. Salzsieder, "Derivation and experimental proof of a new algorithm for the artificial β-cell based on the individual analysis of the physiological insulin- glucose relationship", Endokrinologie, 71, pp. 65-75, 1978.

Fischer, U., E. Salzsieder, E.J. Freyse and G. Albrecht, "Experimental validation of a glucose-insulin control model to simulate patterns in glucose turnover", Computer Methods And Programs In Biomedicine, 32, pp. 249-258, 1990.

Fischer, U., W. Schenk, E. Salzsieder, G. Albrecht, P. Abel and E-J Freyse, "Does physiological blood glucose control require an adaptive strategy?", IEEE Trans. Biomed. Eng., BME-34, pp. 575-582, 1987.

Fisher, M.E., "A semiclosed-loop Algorithm for the Control of Blood Glucose Levels in Diabetics", IEEE Trans. Biomed. Eng., 38(1), pp. 57-61, 1991.

Furler, S.M., E.W. Kraegen, R.H. Smallwood and D.J. Chisolm, "Blood glucose control by intermittent loop closure in the basal mode: Computer simulation studies with a diabetic model", Diabetes Care, 8, pp. 553-561, 1985.

Gattu, G. and E. Zafiriou, "Nonlinear quadratic dynamic matrix control with state estimation", Ind. Eng. Chem. Res., 31, pp. 1096-1104, 1992.

Goldberg, P.A., M.D. Siegel, R.S. Sherwin, J.I. Halickman, M.Lee, V.A. Bailey, S.L. Lee, J.D. Dziura and S.E. Inzucchi, "Implementation of a safe and Effective Insulin Infusion Protocol in a Medical Intensive care Unit", Diabetes Care, 27(2), pp. 461-467, Feb 2004.

Gopaluni, R.B., H. Raghavan and S.L. Shah, "System Identification from Multi-rate Data", Presented at the International Symposium on Advanced Control of Chemical Processes (ADCHEM), Hong Kong, June 2003.

Guyton, J.R., R.O. Foster, J.S. Soeldner, M.H. Tan, C.B. Kahn, L. Koncz and R.E. Gleason, "A Model of Glucose-Insulin Homeostasis in Man that Incorporates the Heterogeneous Fast Pool Theory of Pancreatic Insulin Release", Diabetes, 27, pp. 1027-1042, 1978.

Heller, A. and B. Feldman, "Electrochemical glucose sensors and their application in diabetes management", Chem. Rev., 108(7), pp. 2482-2505, 2008.

Hovorka, R., "Continuous glucose monitoring and closed-loop systems", Diabetic Medicine, 23, pp. 1-12, 2005.

Hovorka, R., F. Shojaee-Moradie, P.V. Carroll, L.J. Chassin, I.J. Gowrie, N.C. Jackson, R.S. Tudor, A.M. Umpleby and R.H. Jones, "Partitioning glucose distribution/ transport, disposal, and endogenous production during IVGTT", AJP – Endo., 282, pp. 992-1007, 2002.

Hovorka, R., M. E. Wilinska, L. J. Chassin and D. B. Dunger, "Roadmap to the artificial pancreas", Diabetes Res. Clin. Pract., 74, pp. S178–S182, 2006.

Hovorka, R., V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M.O. Federici, T.R. Pieber, H.C. Schaller, L. Schaupp, T. Vering and M.E. Wilinska, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes", Physiol. Meas., 25, pp. 905-920, 2004.

Khargonekar, P.P., K. Poolla and A. Tannenbaum, "Robust Control of Linear Time-Invariant Plants using Periodic Compensation", IEEE Trans. on Automatic Control, AC-30(11), pp. 1088-1096, 1985.

Kienitz, K.H. and T. Yoneyama, "A Robust Controller for Insulin Pumps Based on H-Infinity Theory", IEEE Trans. Biomed. Eng., 40(11), pp. 1133-1137, 1993.

Kraegen E.W., L.V. Campbell, Y.O. Chia, H. Meler and L. Lazarus, "Control of blood glucose in diabetics using an artificial pancreas", Aust. N. Z. J. Med., 7, pp. 280-286, 1977.

Lam, Z.-H., K.-S. Hwang, J.-Y. Lee, J.G. Chase and G.C. Wake, "Active insulin infusion using optimal and derivative-weighted control", Med. Eng. & Physics, 24, pp. 663-672, 2002.

Lakshminarayanan, S., "A Data Selection and Regression Method for Identifying Multirate Systems", Internal Report, Mitsubishi Chemical Corp., Kurashiki, Japan, 2000.

Lehmann, E.D. and T. Deutsch, "A Physiological Model of Glucose-Insulin Interaction in Type 1 Diabetes Mellitus", Journal of Biomedical Engineering, 14, pp. 235-242, 1992.

Li, D., "System Identification and Control of Multirate Systems". Ph.D. Thesis, University of Alberta, 2001.

Li, D., S.L. Shah and T. Chen, "Identification of Fast-rate Models from Multirate Data", Int. J. Control, 74(7), pp. 680-689, 2001.

Lim, C.C. and K.L. Teo, "Optimal insulin infusion control via a mathematical blood glucoregulatory model with fuzzy parameters", Cybernet. Syst., 22, pp. 1-16, 1991.

Lynch, S.M. and B.W. Bequette, "Model Predictive Control of Blood Glucose in Type I Diabetics Using Subcutaneous Glucose Measurements", Proceedings of the American Control Conference, Anchorage, AK May 8-10, pp. 4039-4043, 2002.

Mancia, G., "Blood Pressure and Glucose Control in Patients with Diabetes", American Journal of Hypertension, 20, pp. 3S–8S, 2007.

Marchetti, G., M. Barolo, L. Jovanovic, H. Zisser and D.E. Seborg, "An Improved PID Control Strategy for Type 1 Diabetes", IEEE Trans. Biomed. Eng., 55, pp. 857-865, 2008a.

Marchetti, G., M. Barolo, L. Jovanovic, H. Zisser and D.E. Seborg, "A feedforward-feedback glucose control strategy for type 1 diabetes mellitus", J. Process. Control, 18, pp. 149-162, 2008b.

Marliss E.B., F.T. Murray, E.F. Stokes, B. Zinman, A.F. Nakhooda, A. Denoga, B.S. Leibel and A.M. Albisser, "Normalization of glycemia in diabetics during meals with insulin and glucagon delivery by the artificial pancreas", Diabetes, 26, pp. 663-672, 1977.

May Su Tun, "Identification of Systems from Multirate Data", M. Eng. Thesis, Dept. of Chemical & Biomolecular Engineering, National University of Singapore, 2005.

May Su Tun, S. Lakshminarayanan and G. Emoto, "Data Selection and Regression Method and its Application to Softsensing using Multirate Industrial Data", Journal of Chemical Engineering of Japan, 41(5), pp. 374-383, 2008.

Oliver, N.S., C. Toumazou, A.E.G. Cass and D.G. Johnston, "Glucose sensors: a review of current and emerging technologies", Diabet. Med., 26, pp. 197-210, 2009.

Ollerton, R.L., "Application of Optimal Control Theory to Diabetes Mellitus", International Journal of Control, 50, pp. 2503-2522, 1989.

Ooyama, S., K. Onodera, Y. Hashimoto, H. Fujii and S. Lakshminarayanan, "Identification of Multi-rate Process Systems", Presented at the 49th Canadian Chemical Engineering Conference, Saskatoon, Canada, October 1999.

Parker, R.S., Personal correspondence, 2002.

Parker, R.S., "Model-Based Analysis and Control for Biosystems", Ph.D. Thesis, Dept. of Chemical Engineering, University of Delaware, 1999.

Parker, R.S., F.J. Doyle III and N.A Peppas, "The Intravenous Route to Blood Glucose Control", IEEE Engineering in Medicine and Biology, 20, pp. 65-73, 2001.

Parker, R.S., F.J. Doyle III and N.A Peppas, "Uncertainty and Robustness in Diabetic Patient Blood Glucose Control", AIChE Meeting, Miami, 1998.

Parker, R.S., F.J. Doyle III, J.H.Ward and N.A. Peppas, "Robust H_∞ Glucose control in Diabetes Using a Physiological Model", AIChE J., 46, pp. 2537-2549, 2000.

Parker, R.S., F.J. Doyle III and N.A. Peppas, "A Model-Based Algorithm for Blood Glucose Control in Type I Diabetic Patients", IEEE Trans. Biomed. Eng., 46(2), pp. 148-157, Feb 1999.

Parrish D.K. and D.B. Ridgely, "Control of an artificial human pancreas using the SDRE Method", In Proc. American Control Conf. Albuquerque, NM, pp. 1059-1060, 1997.

Pfeiffer E.F., Ch. Thum and A.H. Clemens, "The artificial beta cell - A continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system)", Horm. Metab. Res., 487, pp. 339-342, 1974.

Plank, J., J. Blaha, J. Cordingley, M.E. Wilinska, L.J. Chassin, C. Morgan, S. Squire and M. Haluzik, "Multicentric, Randomized, Controlled Trial to Evaluate Blood Glucose Control by the Model Predictive Control Algorithm Versus Routine Glucose Management Protocols in Intensive care Unit Patients", Diabetes Care, 29(2), pp. 271-276, Feb 2006.

Pørksen, N., "The *in vivo* regulation of pulsatile insulin secretion", Diabetologia, 45, pp. 3-20, 2002.

Puckett, W.R., "Dynamic Modeling of Diabetes Mellitus", Ph.D. Dissertation, Department of Chemical Engineering, University of Wisconsin-Madison, 1992.

Puckett, W.R. and E.N. Lightfoot, "A Model for Multiple Subcutaneous Insulin Injections Developed from Individual Diabetic Patient Data", American Journal of Physiology, 269 (Endocrinology metabolism 32), pp. E1115-E1124, 1995.

Quon, M. J., C. Cochran, S.I. Taylor and R.C. Eastman, "Non-insulin-mediated glucose disappearance in subjects with IDDM. Discordance between experimental results and minimal model analysis", Diabetes, 43, pp. 890-896, 1994.

Ramprasad, Y., G.P Rangaiah and S. Lakshminarayanan, "Enhanced IMC for Glucose Control in Type I Diabetic patients", IFAC 7th DYCOPS meeting, Boston, July 2004a.

Ramprasad, Y., G.P. Rangaiah and S. Lakshminarayanan, "Robust PID Controller for Blood Glucose Regulation in Type 1 Diabetics", Industrial and Engineering Chemistry Research, 43(26), 8257-8268, 2004b.

Roy, A. and R.S. Parker, "Dynamic Modeling and Model-Based Control of Exercise Disturbances in Type 1 Diabetic Patients", Paper presented at the 2006 AIChE annual meeting, San Francisco, 2006.

Ruiz-Velazquez, E., R. Femat and D. U. Campos-Delgado, "Blood glucose control for type I diabetes mellitus: A robust tracking H_∞ problem", Control Engineering Practice, 12, pp. 1179-1195, 2004.

Shen, J. C., "New tuning method for PID controller", ISA Transactions, 41, pp. 473-484, 2002.

Sorensen, J. T., "A Physiologic Model of Glucose Metabolism in Man and its use to Design and Assess Improved Insulin Therapies for Diabetes", Ph.D. Thesis, Dept. of Chemical Engineering, MIT, USA, 1985.

Studer, C., W. Sankou, A. Penfornis, S. Pili-Floury, M. Puyraveau, A. Cordier, J.-P. Etievent and E. Samain, "Efficacy and safety of an insulin infusion protocol during and after cardiac surgery", Diabetes & Metabolism, 36, pp. 71-78, 2010.

Sun, J., A.W. Olbrot and M.P. Polis, "Robust Stabilization and Robust Performance Using Model Reference Control and Modeling Error Compensation", IEEE Transactions on Automatic Control, 39(3), pp. 630-635, 1994.

Swan, G. W., "An optimal control model of diabetes mellitus", Bull. Math. Bio., 44, pp. 793-808, 1982.

The MathWorks Inc., The control system toolbox, MATLAB, version 6.5, 1998.

The MathWorks Inc., The control system toolbox, MATLAB, version 7.6, 2008.

The MathWorks, Inc., The optimization toolbox, MATLAB, version 7.6, 2008a.

The MathWorks, Inc., System Identification Toolbox, MATLAB, version 7.6, 2008b.

Tu, J.F. and J.L. Stein, "Model error compensation for observer design", Int. J. Control, 69(2), pp. 329-345, 1998.

Van den Berghe, G., "Insulin Therapy for the Critically Ill patient", Clinical Cornerstone, Complications of Diabetes, 5(2), pp. 56-63, 2003.

Van den Berghe, G., A. Wilmer, G. Hermans, W. Meersseman, P.J. Wouters, I. Milants, E.V. Wijngaerden, H. Bobbaers and R. Bouillon, "Intensive Insulin Therapy in the Medical ICU", The New England Journal of Medicine, 354(5), pp. 449-461, 2006.

Van den Berghe, G., P.J. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlassclaers, P. Ferdinande, P. Lauwers and R. Bouillon, "Intensive Insulin Therapy in Critically Ill Patients", The New England Journal of Medicine, 345(19), pp. 1359-1367, 2001.

Verhaegen, M. and X. Yu, "A class of subspace model identification algorithms to identify periodically and arbitrarily time-varying systems", Automatica, 32, pp. 201-216, 1995.

Wang, J., T. Chen and B. Huang, "Multirate sampled-data systems: computing fast-rate models", Journal of Process Control, 14, pp. 79-88, 2004.

Wikipedia, the free encyclopedia, "Diabetes mellitus type 1", http://en.wikipedia.org/wiki/Diabetes_mellitus_type_1, November 2009a.

Wikipedia, the free encyclopedia, "Homeostasis", http://en.wikipedia.org/wiki/Homeostasis, November 2009b.

Wilinska, M.E. and R. Hovorka, "Simulation models for *in silico* testing of closed-loop glucose controllers in type 1 diabetes", Drug Discov. Today: Dis. Model., 5(4), pp. 289-298 (DOI:10.1016/j.ddmod.2009.07.005), 2009.

Wilinska, M.E., L.J. Chassin, H.C. Schaller, L. Schaupp, T.R. Pieber and R. Hovorka, "Insulin Kinetics in Type-1 Diabetes: Continuous and Bolus Delivery of Rapid Acting Insulin", IEEE Trans. Biomed. Eng., 52(1), pp. 3-12, 2005.

Young, L.L. and M.A. Koda-Kimble. "Applied Therapeutics: The clinical use of drugs", Chapter 48. Applied Therapeutics, Inc., Vancouver WA, 7th ed., 2000.

Zheng, Y., H.T.C. Kreuwel, D.L. Young, L.K.M. Shoda, S. Ramanujan, K.G. Gadkar, M.A. Atkinson and C.C. Whiting. "The virtual nod mouse - applying predictive biosimulation to research in type 1 diabetes", How do we best employ animal models for Type 1 diabetes and multiple sclerosis?, 1103, pp. 45-62, 2007.

Appendix A

Yale Insulin Infusion Protocol & Lam et al.'s Meal Model

A.1 Yale Insulin Infusion Protocol

The following Yale Insulin Infusion Protocol (YIIP) is taken from Goldberg et al. (2004).

This insulin infusion protocol is intended for use in hyperglycemic adult patients in an ICU setting, but is not specifically tailored for those individuals with diabetic emergencies, such as diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar states (HHS).

When these diagnoses are being considered, or if BG>=500 mg/dL, an MD should be consulted for specific orders. Also, please notify an MD if the response to the insulin infusion is unusual or unexpected, of if any situation arises that is not adequately addressed by these guidelines.

Initiating an Insulin Infusion

1) Insulin Infusion: Mix 1U Regular Human Insulin per 1cc 0.9%NaCl. Administer via infusion pump (in increments of 0.5U/hr).
2) Priming: Flush 50cc of insulin through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing).
3) Target Blood Glucose (BG) Levels: 100-139mg/dL
4) Bolus & Initial Infusion Rate: Divide initial BG level by 100, then round to nearest 0.5U for bolus AND initial infusion rate.
5) Examples:
   a. Initial BG = 325mg/dL: 325 ÷ 100 = 3.25, round to 3.5: IV bolus 3.5U + start infusion @ 3.5U/hr.
   b. Initial BG = 174mg/dL: 174 ÷ 100 = 1.74, round to 1.5: IV bolus 1.5U + start infusion @ 1.5U/hr.

Blood Glucose (BG) Monitoring

1) Check BG hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (i.e., fingersticks) may be inaccurate and obtaining the blood sample from an indwelling vascular catheter is acceptable.

2) Then check BG 2 hourly; once stable for 12-24 hours, BG checks can then be spaced 4 hourly IF:
   a. no significant change in clinical condition AND
   b. no significant change in nutritional intake.

3) If any of the following occur, consider the temporary resumption of hourly BG monitoring, until BG is stable again (2-3 consecutive BG values within target range):
   a. any change in insulin infusion rate (i.e., BG out of target range)
   b. significant changes in clinical condition
   c. initiation or cessation of pressor or steroid therapy
   d. initiation or cessation of renal replacement therapy (hemodialysis, CVVH, etc.)
   e. initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feedings, etc.)

Changing the Insulin Infusion Rate

If BG < 50 mg/dL

D/C^ Insulin Infusion: Give 1 amp (25 g) D50 IV; recheck BG at every 15 min. (When BG >= 100 mg/dL, wait 1 hour, then restart insulin infusion at 50% of original rate)

If BG 50-74 mg/dL

D/C^ Insulin Infusion: If symptomatic (or unable to assess), give 1 amp (25 g) D50 IV: recheck BG at every 15min.

If asymptomatic, give ½ Amp (12.5 g) D50 IV or 8 ounces juice; recheck BG at every 15-30 min.

(When BG >= 100 mg/dL, wait 1 hour, then restart insulin infusion at 75% of original rate)

If BG >= 75 mg/dL

Step 1: Determine the <u>CURRENT BG LEVEL</u> – identifies a <u>COLUMN</u> in the table below.

Step 2: Determine the <u>RATE OF CHANGE</u> from the prior BG level – identifies a <u>CELL</u> in the table – Then move right for INSTRUCTIONS:

[Note: If the last BG was measured 2-4 hours before the current BG, calculate the hourly rate of change. Example: If the BG at 2PM was 150 mg/dL and the BG at 4PM (now) 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is -30mg/dL ÷ 2 hours = -15 mg/dL/hr.]

BG 75-99mg/dL	BG 100-139mg/dL	BG 140-199mg/dL	BG ≥ 200mg/dL	INSTRUCTIONS*
		BG↑ by > 50 mg/dL/hr	BG↑	↑ INFUSION by "2Δ"
	BG↑ by > 25 mg/dL/hr	BG↑ by > 1-50 mg/dL/hr *OR* BG unchanged	BG↑ unchanged *OR* BG↓ by > 1-25 mg/dL/hr	↑ INFUSION by "Δ"
BG↑	BG↑ by > 1-25 mg/dL/hr, BG unchanged, *OR* BG↓ by > 1-25 mg/dL/hr	BG↓ by > 1-50 mg/dL/hr	BG↓ by > 26-75 mg/dL/hr	NO INFUSION CHANGE
BG↑ unchanged *OR* BG↓ by > 1-25mg/dL/hr	BG↓ by > 26-50 mg/dL/hr	BG↓ by > 51-75 mg/dL/hr	BG↓ by > 76-100 mg/dL/hr	↓ INFUSION by "Δ"
BG↓ by > 25 mg/dL/hr See below†	BG↓ by > 50 mg/dL/hr	BG↓ by > 75 mg/dL/hr	BG↓ by > 100 mg/dL/hr	HOLD×30min, then ↓ INFUSION by "2Δ"

† D/C^ INSULIN INFUSION: Check BG at every 30 min, when BG ≥ 100 mg/dL, restart infusion @75% of most recent rate.

^ Discontinue

*<u>CHANGES IN INFUSION RATE</u> ("Δ") are determined by the current rate:

Current Rate (U/hr)	Δ = Rate Change (U/hr)	2Δ = 2× Rate Change (U/hr)
<3.0	0.5	1
3.0 – 6.0	1	2
6.5 – 9.5	1.5	3
10 – 14.5	2	4
15 – 19.5	3	6
20 – 24.5	4	8
≥ 25	≥ 5	10 (consult MD)

A.2 Lam et al.'s Meal Model

The associated meal model for Bergman T1D patient model that is developed by Lam et al. (2002) is described here.

This meal model is designed originally for OGTT and is modelled by the lognormal distribution function as in equation (B.1). The glucose input is modelled to be smooth, continuously differentiable and to ensure zero initial conditions. This function can be easily implemented and is physiologically representative.

$$P(t) \;=\; P_m exp(-a(ln(bt) - c)^2) \hspace{4cm} \text{(B.1)}$$

where,

P_m = the peak value of exogenous glucose absorption rate

a, b and c = constants which determine the slopes and curvature of exogenous glucose absorption rate

The model parameter values can be defined to represent the different absorption rate profiles for different meals.

Appendix B

Publications and Presentation

B.1 Publications

May Su Tun, S. Lakshminarayanan, and G. P. Rangaiah, "Glycemic Control for Type 1 Diabetes using Multirate System Identification and Modeling Error Compensator", Proceedings of 2008 International Symposium on Advanced Control of Industrial Processes (ADCONIP 2008 conference), Jasper, Canada, pp. 249-256, 2008.

May Su Tun, S. Lakshminarayanan, and G. P. Rangaiah, "Classification and Treatment of Type 1 Diabetics", Annals of the Academy of Medicine, Singapore (AAMS), Ann Acad Med Singapore 2010; 39 (Suppl), pp. S96, 2010.

May Su Tun, S. Lakshminarayanan, and G. P. Rangaiah,"Effectiveness of Modified YIIP on Type 1 Diabetic Patients", Manuscript in preparation, 2013.

May Su Tun, S. Lakshminarayanan, and G. P. Rangaiah, "Finding Model from Multirate Data of Type 1 Diabetic Patients and Blood Glucose Control", Manuscript in preparation, 2013.

B.2 Presentation

"Glycemic Control for Type 1 Diabetes using Multirate System Identification and Modeling Error Compensator", ADCONIP 2008 conference, Jasper, Canada, 2008.