Blood Glucose Regulation in Type II Diabetic Patients

by

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Abstract

Type II diabetes is the most pervasive diabetic disorder, characterized by insulin resistance, β-cell failure in secreting insulin and impaired regulatory effects of the liver on glucose concentration. Although in the initial steps of the disease, it can be controlled by lifestyle management, but most of the patients eventually require oral diabetic drugs and insulin therapy. The target for the blood glucose regulation is a certain range rather than a single value and even in this range, it is more desirable to keep the blood glucose close to the lower bound.

Due to ethical issues and physiological restrictions, the number of experiments that can be performed on a real subject is limited. Mathematical modeling of glucose metabolism in the diabetic patient is a safe alternative to provide sufficient and reliable information on the medical status of the patient. In this thesis, dynamic model of type II diabetes has been expanded by incorporation of the pharmacokinetic-pharmacodynamic model of different types of insulin and oral drug to study the impact of several treatment regimens. The most efficient treatment has been then selected amongst all possible multiple daily injection regimens according to the patient’s individualized response.

In this thesis, the feedback control strategy is applied in this thesis to determine the proper insulin dosage continuously infused through insulin pump to regulate the blood glucose level. The logarithm of blood glucose concentration has been used as the controlled variable to reduce the nonlinearity of the glucose-insulin interactions. Also, the proportional-integral controller has been modified by scheduling gains calculated by a fuzzy inference system.
Model predictive control strategy has been proposed in this research for the time that sufficient measurements of the blood glucose are available. Multiple linear models have been considered to address the nonlinearity of glucose homeostasis. On the other hand, the optimization objective function has been adjusted to better fulfill the objectives of the blood glucose regulation by considering asymmetric cost function and soft constraints. The optimization problem has been solved by the application of multi-parametric quadratic programming approach which reduces the on-line optimization problem to off-line function evaluation.
Preface

This thesis entitled "Blood Glucose Regulation in Type II Diabetic Patients" consists of seven chapters. It presents my research during Ph.D. studies, under the supervision of Professor K. E. Kwok and Professor R. B. Gopaluni at Chemical and Biological Engineering Department of the University of British Columbia.

Preliminary results of Chapter 3 and Chapter 4 of the thesis have been published in the literature. A version of Chapter 4 considering the blood glucose regulation in severe type II diabetic patients has been prepared for submission. The materials presented in Chapter 5 for insulin therapy are combined with the metformin therapy as presented in Chapter 3 and being prepared in the manuscript format for publication. Contributions and collaborations to the published, submitted and prepared papers for publication are explained in the following:

1. A version of Chapter 3 entitled “Evaluation of Treatment Regimens for Blood Glucose Regulation in Type II Diabetes Using Pharmacokinetic-Pharmacodynamic Modeling” has been published in the proceeding of Chinese Control Conference (CCC), 2015. This manuscript has been prepared with close collaboration of Professor Kwok and Professor Gopaluni. Ms. Barazandegan helped with preparing type II diabetes model for simulation. I incorporated the pharmacokinetic-pharmacodynamic model of different insulin types and metformin to evaluate different treatment regimens.

2. A version of Chapter 4 has been published:

F. Ekram, L. Sun, O. Vahidi, E. Kwok, and R. B. Gopaluni, “A feedback glu-

This paper has been published with close collaboration of Professor Kwok and Professor Gopaluni. They also have helped in the preparation of the first drafts and revision of the final drafts. Dr. Sun and Dr. Vahidi helped with preparing the first draft of paper using conventional PI controller. I later modified the draft by introducing the fuzzy inference system to improve the performance of conventional PI and prepared the final manuscript for the journal.

3. A version of Chapter 4, entitled “Modified Fuzzy Gain Scheduling Controller for Maintaining the Blood Glucose Level in Type II Diabetic Patients” has been prepared for submission.

This manuscript has been prepared with close collaboration of Professor Kwok and Professor Gopaluni. Ms. Barazandegan helped with preparing type II diabetes model for simulation and writing the mathematical model section. I reduced the nonlinearity of glucose-insulin interactions in the model by using the logarithm of the blood glucose measurement to calculate the feedback error and then developed and applied the gain scheduling strategy for blood glucose regulation. I prepared the final manuscript for submitting to the journal.

4. A version of Chapter 5 combined with PK-PD model of metformin from Chapter 3, entitled “Combination treatment for different stages of type II diabetes using metformin therapy and insulin pump”, is being prepared for submitting to a journal.

This manuscript has been prepared with close collaboration of Professor Kwok and Professor Gopaluni. Ms. Barazandegan helped with preparing type II diabetes model for simulation. I incorporated the PK-PD model of
metformin into type II diabetes model and developed and applied the predictive control strategy for calculating the proper amount of insulin to regulate the blood glucose concentration. I am preparing the final manuscript for the journal submission.
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Nomenclature

The following nomenclature is adopted throughout the mathematical model description in chapter 2:

Model variables in the glucose sub-model

\[ G \] Glucose concentration (mg/dl)
\[ M \] Multiplier of metabolic rates (dimensionless)
\[ Q \] Vascular blood flow rate (dl/min)
\[ r \] Metabolic production or consumption rate (mg/min)
\[ T \] Transcapillary diffusion time constant (min)
\[ t \] time (min)
\[ V \] Volume (dl)

Model variables in the insulin sub-model

\[ I \] Insulin concentration (mU/l)
\[ M \] Multiplier of metabolic rates (dimensionless)
\[ m \] Labile insulin mass (U)
$P$  Potentiator (dimensionless)

$Q$  Vascular blood flow rate (dl/min)

$R$  Inhibitor (dimensionless)

$r$  Metabolic production or consumption rate (mU/min)

$S$  Insulin secretion rate (U/min)

$T$  Transcapillary diffusion time constant (min)

$t$  time (min)

$V$  Volume (dl)

$X$  Glucose-enhanced excitation factor (dimensionless)

$Y$  Intermediate variable (dimensionless)

Model variables in the glucagon sub-model

$\Gamma$  Normalized glucagon concentration (dimensionless)

$M$  Multiplier of metabolic rates (dimensionless)

$r$  Metabolic production or consumption rate (dl/min)

$t$  time (min)

$V$  Volume (dl)

First superscript

$\Gamma$  Glucagon

$B$  Basal condition
\( G \)  Glucose  \\
\( I \)  Insulin

Second superscript

\( \infty \)  Final steady state value

Metabolic rate subscripts

\( BGU \)  Brain glucose uptake  \\
\( GGU \)  Gut glucose uptake  \\
\( HGP \)  Hepatic glucose production  \\
\( HGU \)  Hepatic glucose uptake  \\
\( KGE \)  Kidney glucose excretion  \\
\( KIC \)  Kidney insulin clearance  \\
\( LIC \)  Liver insulin clearance  \\
\( MTC \)  Metabolic glucagon clearance  \\
\( PGC \)  Plasma glucagon clearance  \\
\( PGR \)  Pancreatic glucagon release  \\
\( PGU \)  Peripheral glucose uptake  \\
\( PIC \)  Peripheral insulin clearance  \\
\( PIR \)  Pancreatic insulin release  \\
\( RBGU \)  Red blood cell glucose uptake
First subscripts

\( \infty \) Final steady state value

\( A \) Hepatic artery

\( B \) Brain

\( G \) Gut

\( L \) Liver

\( P \) Periphery

\( S \) Stomach

Second subscripts (if required)

\( C \) Capillary space

\( F \) Interstitial fluid space

\( l \) Liquid

\( s \) Solid
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To my beloved parents
for their pure love and support
for understanding the things I said
and the things I didn’t say

To my adorable sister
for giving me joy in my heart

To my dear friends
for being there for me
through the good times and the bad
Chapter 1

Introduction

1.1 Background

Diabetes mellitus is a metabolic disorder in which the blood glucose levels are not regulated because of the impaired insulin secretion, action or both. The prevalence of diabetes in the world is growing at an unprecedented rate and rapidly becoming a health concern. The International Diabetes Federation states that "diabetes currently affects more than 300 million people in the world, representing 6% of the world's adult population" and "every ten seconds, two people are diagnosed with diabetes somewhere in this world" [11].

The two main types of diabetes mellitus are type I and type II. Type I diabetes mellitus is the result of the abrupt pancreatic beta cell destruction due to an auto-immune process while type II diabetes mellitus is a progressive disease characterized by not only the failure of beta cell in secretion of adequate insulin but also insulin resistance in muscles and adipose tissues [12]. A comparison of type I and type II diabetes is presented in table 1.1 [1].

Diabetes mellitus increases the risk of many serious health problems and can result in a variety of complications. Diabetes is the leading cause of blindness (retinopathy), kidney failure (nephropathy) and nerve damage (neuropathy). Diabetic patients are much more likely to have a stroke, heart disease, or a heart
Table 1.1: Comparison of type I and II diabetes [1]

<table>
<thead>
<tr>
<th>feature</th>
<th>Type I diabetes</th>
<th>Type II diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Mostly in children</td>
<td>Mostly in adults</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Thin or normal</td>
<td>Often obese</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Usually present</td>
<td>Absent</td>
</tr>
<tr>
<td>Endogenous insulin</td>
<td>Low or absent</td>
<td>Normal, decreased or increased</td>
</tr>
<tr>
<td>prevalence</td>
<td>~ 10% of diabetic population</td>
<td>~ 90% of diabetic population</td>
</tr>
</tbody>
</table>

1.1.1 Glucose Metabolism

The body cells obtain their required energy from different fuel sources including carbohydrates, fats and proteins. Amongst them, the main source of energy for the body is carbohydrates. Carbohydrates digest in the gastrointestinal tract and produce a simple sugar called glucose. It is absorbed by the body cells and is used as the primary energy source. The body keeps the blood glucose concentration in a certain range during the fasting state by producing glucose endogenously through two main pathways:

1. Gluconeogenesis: Gluconeogenesis is a metabolic pathway that generates glucose from non-carbohydrate carbon substrates such as lactate, glycerol, and glucogenic amino acids. It occurs in the liver and kidney.

2. Glycogenolysis: Glycogenolysis is a metabolic pathway which results in the generation of glucose from the breakdown of glycogen. It occurs in the liver and muscles.

Liver and kidney release the produced endogenous glucose into the bloodstream while the produced glucose in muscle cells is consumed by themselves. Approximately 85% of endogenous glucose production which is released into the
blood stream is derived from the liver, and the remaining 15% is produced by the kidney [14].

A healthy (non-diabetic) body controls the blood glucose level within a certain range, despite disturbances such as exercise or intake of a meal containing carbohydrates, by precise responses of several organs to any changes in circulating glucose levels [15]. This glucose regulatory control is carried out through feedback systems reacting mainly on glucose, insulin and glucagon concentrations. Insulin and glucagon are two hormones which play an important role in glucose homeostasis in the body and are secreted by the beta and alpha cells, respectively, contained in the islets of Langerhans scattered in the pancreas. The effect of these hormones on glucose metabolism is opposite from one to another (see figure 1.1).

Insulin contributes in lowering the blood sugar level by stimulating some body cells to absorb glucose, suppressing endogenous glucose production and inhibiting glucagon secretion.

Glucagon, on the other hand, contributes to increase the blood sugar level by stimulating the liver to produce more glucose and inhibiting insulin secretion.

When the blood sugar level is high, pancreas secreted more insulin. Secreted insulin has negative paracrine action on the alpha cells causing inhibition of glucagon secretion. Increased concentration of insulin and decreased the concentration of glucagon lead to higher absorption of the blood glucose by body cells and lower endogenous glucose production which in turn decrease the level of blood glucose concentration. Conversely, when the blood glucose concentration is low, the pancreas secretes more glucagon which inhibits secretion of insulin leading to increased endogenous glucose production and lowered absorption of glucose by the body cells which in turn reduces the blood glucose concentration.

Insulin contributes to augment the glucose uptake in the peripheral tissues and the liver through affecting the activity of different enzymes:

1. Insulin enhances the hepatic and peripheral glucose uptake by stimulating the activity of hexokinase, an enzyme responsible for glucose phosphorylation which leads to trapping of glucose inside the cell.
2. Insulin increases the peripheral glucose uptake by regulating the activity of pyruvate dehydrogenase, a key enzyme in the glycolysis pathway.

3. Insulin enhances peripheral and hepatic glucose absorption by stimulating the glycogen synthesis (glycogenesis pathway). Insulin contributes in glycogenesis by activating a group of enzymes directing the glucose through glycogen synthesis (e.g. glycogen synthase) and by inhibiting enzymes contributing the reverse reactions (e.g. glucose-6-phosphatase) [16].

Figure 1.1: Glucose homeostasis control mechanism in the body
1.1.2 Abnormalities of Type II Diabetes Mellitus

Type II diabetes is characterized by multiple abnormalities in some of the body organs such as the liver, the pancreas, muscles and adipose tissues. These abnormalities are classified as follows:

1. Insulin resistance in peripheral tissues: peripheral tissues (i.e. muscle and adipose tissue cells) are dependent on insulin to absorb blood glucose. Studies have shown that in type II diabetic patients, low glucose uptake rates by muscle cells and adipose tissue cells are caused by peripheral insulin resistance and relative insulin deficiency [17–25]. Impairment of several factors is known to be associated with insulin residence in peripheral tissues. De-fronzo reviewed these factors in his paper [14]. some of the factors are as follows:

   • The number of insulin receptors
   • The affinity of insulin receptors
   • Insulin intracellular signaling
   • The number of glucose transporters
   • Glucose transporter translocation on the cell membrane
   • Insulin stimulatory effects on glycogenesis
   • Insulin stimulatory effects on glycolysis

2. Reduced hepatic glucose uptake: Some studies have addressed the reduced hepatic glucose uptake as the result of impaired insulin-induced stimulation effects on hepatic glucose uptake [26–31]. It is believed to be due to the impairment of insulin stimulation effect on glucose phosphorylation in the liver [31].

3. Impaired hepatic glucose production: Many studies have confirmed that hepatic glucose production rate is impaired in type II diabetic patients [20–25, 27, 28, 32–35]. Most of these studies have indicated that insulin-induced
suppression of endogenous glucose production is low in diabetic patients. Basu et al. [34, 35] have demonstrated the impaired effect of insulin suppression on both pathways of endogenous glucose production (i.e. gluconeogenesis and glycogenolysis). However the effects of the glucose suppression on hepatic glucose production rate is still normal in type II diabetic patients [36, 37].

4. Impaired pancreatic insulin secretion: Deficiency in the pancreatic insulin production has the key role in the development of overt diabetes [14], which means that overt diabetes does not develop unless the pancreas fails to produce insulin properly. Pancreatic insulin secretion in response to a glucose stimulus has a biphasic pattern. Type II diabetic patients exhibit two forms of defective pancreatic insulin secretion. One in the early peak of insulin production and the other one is in the overall insulin secretion rate [38–40].

5. Glucose resistance: The glucose-induced stimulation of glucose disposal has been shown to be normal in type II diabetic patients, in an early study done by Alzaid et al. [33]. However, later studies by Del Prato et al. [36] and Nielsen et al. [37] have indicated that high levels of glucose concentration (particularly above 7 mmol/l) impair the glucose stimulation effect on glucose uptake in type II diabetic patients.

1.1.3 Treatments for Type II Diabetes Mellitus

Type II diabetic patients need to get their blood glucose level under control. Blood glucose concentration in type II diabetic patients can be initially controlled by exercise and healthy dieting. Sooner or later patients need diabetes drugs along with diet and lifestyle changes. The short term goal of the treatment is to keep the blood glucose in the normal range and reduce or get rid of the symptoms while the long-term goal is to prevent complications.

There are six groups of oral medicines and 11 different drugs. Each of the six groups of drugs works in a different way to synergize with the disease abnormali-
ties and are summarized in table 2 [2].

Some of the severe type II diabetic patients eventually need insulin therapy along with the oral drugs. The patients under insulin regimen can experience better control of the blood glucose level through the whole day and avoid the symptoms of high blood glucose level. On the other hand, the pressure on the pancreas to produce insulin will be reduced and benefit longer term health.

**Table 1.2:** Oral drugs for diabetes [2]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>This group of drugs, called biguanides, works by keeping the liver from making glucose and allowing more glucose to enter cells.</td>
</tr>
<tr>
<td>Glipizide, Glimepiride &amp; Glyburide</td>
<td>This group of drugs, called sulfonylureas, works by helping the pancreas make more insulin.</td>
</tr>
<tr>
<td>Prandin &amp; Starlix</td>
<td>This group of drugs, called meglitinides, works by helping the pancreas make more insulin.</td>
</tr>
<tr>
<td>Precose &amp; Glyset</td>
<td>This group of drugs, called alpha-glucosidase inhibitors, works by keeping the intestines from absorbing glucose as quickly.</td>
</tr>
<tr>
<td>Januvia</td>
<td>This drug, called a dipeptidyl peptidase 4 inhibitor, works by helping the pancreas release insulin.</td>
</tr>
<tr>
<td>Actos &amp; Avandia</td>
<td>This group of drugs, called thiazolidinediones, works by helping the cells use glucose.</td>
</tr>
</tbody>
</table>

There are different forms of insulin to treat diabetes. They are classified based on the following three characteristics:

- **Onset:** the length of time before insulin reaches the bloodstream and begins lowering blood glucose.

- **Peak time:** the time during which insulin is at maximum strength in terms of lowering the blood glucose.

- **Duration:** how long insulin continues to lower blood glucose.

Table 1.3 lists the types of injectable insulin with details about onset, peak time, duration and the role in the blood sugar management [3].
### Table 1.3: Insulin types [3]

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>10-15 min</td>
<td>60-90 min</td>
<td>4-5 hours</td>
</tr>
<tr>
<td>Fast-acting</td>
<td>30-60 min</td>
<td>2-4 hours</td>
<td>5-8 hours</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>1-3 hours</td>
<td>5-8 hours</td>
<td>Up to 18 hours</td>
</tr>
<tr>
<td>Long-acting</td>
<td>3-4 hours</td>
<td>8-15 hours</td>
<td>22-26 hours</td>
</tr>
</tbody>
</table>

Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with longer-acting insulin. Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes. Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin. Long-acting insulin covers insulin needs for about one full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.

Deciding what type of insulin might be best for a patient will depend on many factors, such as the body’s individualized response to insulin and the lifestyle choices. Multiple daily injection (MDI) therapy and continuous subcutaneous insulin infusion (CSII) with external insulin pumps are the available techniques for insulin delivery to the body. Two studies shows that CSII was as safe and effective as MDI therapy for the treatment of type 2 diabetic patients [41, 42].

### 1.2 Objectives

#### 1.2.1 Clinical Control Objectives

From a clinician’s perspective, the goals of insulin treatment need to be individualized for different groups of the population such as the elderly, children, or even pregnant patients who have diabetes mellitus. It is important to control glucose levels within certain targets to avoid long-term complications. Inadequate short-term control could also cause fatigue, polyuria, polydipsia, blurred vision glucose or infection as well. Unlike in traditional control, optimal control of glu-
cose, however, does not imply minimizing glucose variance around a single target value. Instead, a human body is able to function well as long as the blood glucose is within a certain range. In fact, in the general population, a healthy person may have a fasting blood glucose between 3.5 to 5.7 mmol/L and a random non-fasting blood glucose up to 11.0 mmol/L. A diagnosis of diabetes mellitus can be made and confirmed by a fasting glucose of more than 7.0 mmol/L or random glucose of more than 11.0 mmol/L. For most patients, the most desirable target glucose range is between 4.0 to 6.0 mmol/L during a fasting state, and 5.0 to 10.0 mmol/L during the postprandial phase. The rationale for selecting a higher cut-off of 4.0 mmol/L is to allow for a safety margin to avoid severe hypoglycemia below 3.0 mmol/L which can cause fatigue, tremor, lightheadedness, sweating, or, in extreme cases, death. When a patient has hyperglycemia, symptoms of fatigue, polyuria, polydipsia or infection such as non-healing wounds will become more progressively obvious as the blood glucose increases more than 11 mmol/L. Patients having severe hyperglycemia, such as more than 20 mmol/L, could experience extreme fatigue, loss of consciousness or even coma.

Figure 1.2 provides a graphical impression of the glucose control objectives. It shows the red zones corresponding to severe hypoglycemia and severe hyperglycemia which should be avoided completely. A small margin of tolerance between 3 to 4 mmol/L for hypoglycemia and a large margin of tolerance between 11 and 14 mmol/L for hyperglycemia are shown in yellow. The middle green zone is divided into three sub-zones. The postprandial state consists of a 4-hour period that immediately commences as a meal is ingested. The postabsorptive state is defined as a 6-hour period and follows the postprandial state. The fasting state starts at the end of the postabsorptive state [43]. The graduating shade in the normoglycemic zone indicates that blood glucose should always trend towards the lower range in favor of avoiding low-term complications of diabetes mellitus due to persistently high blood glucose. Therefore, from a control perspective, the homeostasis of glucose in a healthy person is a very well regulated non-linear system which intelligently maintains glucose in a safe and healthy range. For diabetic
patients, linear controllers for glucose regulation will not be suitable or sufficient for achieving such a control objective [44, 45]. Instead, the controller should be designed to return the blood glucose from the hypoglycemia and hyperglycemic zones back to the normoglycemic zone quickly but act aggressively to avoid getting into the severe hypoglycemia and severe hyperglycemic zones. When the blood glucose is within the normoglycemic zone, the controller should gradually bring the blood glucose to the lower limit of the normoglycemic zone.

1.2.2 Thesis Objectives

Tight glycemic control is essential in order to reduce the risks of long-term diabetic complications for both type I and type II diabetes patients [45]. Inadequate short-term control could also cause fatigue, polyuria, polydipsia, blurred vision.

Figure 1.2: Glycemic control zones
or infection as well. Type I diabetic patients should be under intensive insulin therapy because of the lack of insulin production in the pancreas. Although diet and exercise have a role to play in type 1 diabetes management, they cannot reverse the disease or eliminate the need for insulin. However, in initial steps of type II diabetes mellitus, pancreas is still working so that treatment typically includes lifestyle management such as diet modification and control, regular and appropriate exercise and home blood glucose testing but most of the patients with severe type II diabetes mellitus eventually require oral anti-diabetic agent, insulin treatment or combination of them to provide adequate glycemic control.

The application of dynamic modeling and advanced control techniques has increased in every aspect of our lives. The contribution of control engineers in solving the challenging problems in the area of biomedical processes can have significant medical impacts [46, 47].

Mathematical modeling of glucose metabolism in the diabetic patient is helpful and safe in providing reliable information without causing serious and irreversible harm to the subject. Having sufficient amount of data facilitates the development and evaluation of different treatments and control strategies. Automatic control systems can substitute manual control to provide better regulation of the blood glucose, lessen the care tension on the patients and improve the quality of the control.

Most of the studies in the field of modeling and control of diabetes have addressed type I. However; type II diabetes is the most pervasive type which affects 90% of the diabetes population around the world [48]. Therefore, developing control systems can be very helpful to understand the pathophysiology of the disease and find the most efficient therapy to treat properly.

Contrary to type I, in which the only problem is the dysfunction of the pancreas, type II diabetic patients deal with the malfunction of different organs. The desired controller for type I diabetic patients should be designed to mimic the behaviour of real pancreas, while in type II the homeostasis of blood glucose is much more complicated than type I patients as discussed in [1.2.1], so that the control ob-
jective is challenging and not as straight forward as for type I because unlike type I diabetes, multiple abnormalities in different organs as described in section 1.1.2 lead to the deterioration of glucose homeostasis in type II diabetic patients [14].

The objective of this research is to regulate the blood glucose for type II diabetes mellitus by:

- improving the dynamic model of type II diabetes mellitus
- developing efficient control strategies

1.2.3 Thesis Outline

Chapter 2 describes the mathematical modelling previously developed based on Sorensen model [4] for type II diabetes by Vahidi [5, 9]. This model simulated a type II diabetic patient using compartmental modeling approach. In this approach, different organs or parts of the body are represented by a number of compartments. The model equations are derived from the mass balance equations over each compartment. The model comprises three main sub-models which represent the variation of blood glucose, insulin and glucagon concentrations in different parts of the body. Increasing the number of compartments benefits analysis of glucose regulation techniques by providing a better representation of the glucose and insulin concentrations in different organs.

Chapter 3 addresses the problem of evaluating different treatment regimens for patients prescribed with oral agents and/or under multiple daily injections (MDI) therapy. Type II diabetic patients use different types of oral drug and insulin to get their blood glucose level under control as listed in 1.1.3. Deciding on the efficient regimen including drug and insulin therapy is a try and error procedure requiring the performance of several tests on the patients and varies for each individual patient. Since the number of experiments that can be performed on a human body is restricted, the available physiological model, described in Chapter 2, is expanded by incorporation of pharmacokinetic-pharmacodynamic models for four popular
types of insulin and metformin which is a very common diabetic drug. Such expansion represents the effects of drug and insulin administration on the patient. The model is suitable to assess the efficiency of several treatment regimens for blood glucose regulation including mixtures of short-acting and intermediate or long-acting insulin and oral administration of metformin.

Chapter 4 presents the application of feedback control strategy to determine the proper insulin dosage delivered with an insulin pump in continuous subcutaneous insulin infusion (CSII) therapy. Regarding the non-linear homeostasis of blood glucose, conventional PI controller is modified by considering scheduling gains generated by a fuzzy inference system. It is shown that the application of logarithm of blood glucose concentration as the controlled variable can also reduce the nonlinearity of the glucose-insulin interactions and improve the performance of the designed controller. In reality, the patients not only rely on an automatic control device but also act as a feedforward controller and inject extra doses of insulin before each meal. The results of such action are also taken into consideration in this chapter.

Chapter 5 demonstrates the procedure of designing a controller based on predictive control strategy for blood glucose regulation. Multiple linear models are considered to address the nonlinearity of glucose homeostasis and represent the glucose metabolism for different levels of blood glucose. The optimization problem is modified to develop a controller which closely mimics the glucose regulatory system of the body. The asymmetric objective function is considered while the soft constraints allow partial violation of minimum and maximum values of the boundaries. A state estimator is designed to calculate the states associated with the current measurement of the blood glucose concentration. Multi-parametric quadratic programming approach is applied to solve the optimization problem which reduces the on-line optimization problem to off-line function evaluation. It provides a look-up table with all optimal solutions which gives a good insight of patient's status.

Chapter 6 provides the comparison for the performance of the designed con-
trollers in response to variations in the metabolic rates. The metabolic rates are not only different between patients but may also vary within a patient during the disease progress. Since the glucose regulatory system mainly deteriorates as the result of the malfunction of liver, peripheral tissues and pancreas, the performance of the designed controllers is investigated as the metabolic rates decrease in these organs.

Finally, Chapter 7 summarizes and concludes the thesis.
Chapter 2

Mathematical Modeling of Type II Diabetes Mellitus

2.1 Introduction

There are several studies on mathematical modeling of glucose regulation in healthy human subjects starting with simple linear models by Bolie [49] and Ackerman [50]. Makroglo et al. [51], Mari [52] and Cedersund et al. [53] reviewed the various modeling approaches have considered in proposed models. Amongst all those approaches for modeling the glucose regulation in a human body, the compartmental modeling approach is one of the most popular approaches. In this approach, different organs or parts of the body are represented by a number of compartments. The model equations are derived from the mass balance equations over each compartment.

The minimal compartmental model proposed by Bergman et al. [54] was one of the pioneers of this modeling approach which consists of three compartments. The mass balance equations form the non-linear differential equations representing glucose and insulin concentrations in the body. This model has been used widely in many diabetic studies for blood glucose regulations. Increasing the number of compartments benefits analysis of glucose regulation techniques by
providing a better representation of the glucose and insulin concentrations in different organs while at the same time increases the complexity of the model. More complicated compartmental models were proposed by Cobelli [55], Sorensen [4] and Hovorka [56].

Dynamic modeling of glucose metabolism in healthy human body can be modified and adjusted for the patients to be used in studying the physiological behaviour of type I and type II diabetic patients. Type I diabetic patients have no insulin production, therefore the model is easily adjusted for type I diabetes mellitus without changing the structure. The model is ready to be used after setting the insulin production rate term of the healthy subject's model to zero.

A similar approach can be used to develop a model for type II diabetes, however type II diabetes modeling is not as simple as type I diabetes modeling. Type II diabetes is associated with multiple abnormalities in different body organs which leads to the deterioration of glucose homeostasis in type II diabetes. These abnormalities target the glucose metabolic rates in the related organs and the secretion rates of glucose regulatory hormones such as pancreatic insulin secretion rate. Therefore, the same model structure can be used but with the updated parameters. Some studies developed the model for type II diabetes by this approach [5, 9, 57].

In this chapter the equations of Sorensen model is represented along with the parameters updated for type II diabetic patient by Vahidi [4, 9]. The description of the model variables, presented in the equations of this chapter, can be found in nomenclature.

2.2 The Sorensen Model

Sorensen developed his compartmental model of glucose-insulin interactions in a healthy body by modifying the model previously suggested by Guyton et al. [58]. This model considers the regulatory effects of insulin and glucagon hormones on glucose metabolism. The organs associated in diabetes research including the liver, pancreas, muscles and adipose tissues are represented by individual compartments which make the model suitable to address the abnormalities of type II
diabetes as well. The Sorensen model comprises three main sub-models representing variations of blood glucose, insulin and glucagon concentrations in the different part of the body. The number of compartments is different in each sub-model and determined by the significance of the organ's job in maintaining the respective solute concentrations.

**Figure 2.1:** Simplified blood circulatory system[9]

In Sorensen model, the hormonal effects of epinephrine, cortisol, and growth hormone are assumed to be negligible. Physiology of changes in amino acid and free fatty acid substrate levels are not considered, and the physiologic parameters such as blood flow rates and capillary space volumes are selected to represent a typical 70 Kg adult male. Figure 2.1 shows the simplified blood circulatory system
including the major organs which contribute significantly in glucose production and consumption. Oxygen-rich blood is pumped from the heart left ventricle and is delivered to all body organs through the arteries. Deoxygenated blood is drained out of the body organs and delivered to the heart right atrium through the veins.

**Figure 2.2:** General representation of a compartment[9]

In compartmental modeling approach, a compartment represents an organ or a specific part of the human body. Each compartment is generally divided into three well-mixed spaces (sub-compartments) representing the capillary blood space, the interstitial fluid space and the intracellular space. A graphical representation of a typical compartment of the Sorensen model is shown in figure 2.2. The arterial blood inflow feeds in the capillary space and the venous blood outflow drains it. The blood components may diffuse through capillary walls into the interstitial fluid and from interstitial fluid to the intracellular space and vice versa.

Not all these three zones are considered for modeling different parts of the body. If the capillary wall is impermeable to a solute and no extravascular exchange occurs and, therefore, only the capillary blood space is considered, and the two other spaces are omitted (figure 2.3 a). In the case of high permeability of the capillary wall for a solute which leads to a fast equilibrium of the capillary blood and the interstitial fluid spaces, two spaces are considered as one combined
Figure 2.3: Simplified configurations of physiological compartments[9]

sub-compartment with uniform solute concentration (Figure 2.3b). Likewise, the permeability of the cell membrane may be high enough for a solute which causes
fast equilibrium of the interstitial fluid and intracellular fluid spaces. Two spaces are combined in this case and considered as one sub-compartment with uniform solute concentration (Figure 2.3 c). If the permeability of both capillary wall and cell membrane is high enough to a solute which leads to a fast equilibrium of all three spaces, therefore, all three spaces are combined and considered as one space with uniform solute concentration (Figure 2.3 d). Finally, if the rate of solute transport across the cell membrane is not restricted by the concentration of the solute in the intracellular fluid space, the intracellular space is omitted (Figure 2.3 e). So that at most two of these sub-compartments are physiologically required to model a solute transfer from the capillary blood space to the intracellular space for each compartment.

### 2.2.1 Glucose Sub-model

A schematic representation of the glucose sub-model is depicted in figure 2.4.

In this sub-model, the body is divided into six compartments: brain; liver; heart and lungs; periphery (muscles and adipose tissues); gastrointestinal (GI) tract (the stomach and intestinal system); and kidney. The arrows in figure 2.4 represent the blood flow direction. Mass balance equation over each sub-compartment results in eight ordinary differential equations constituting the glucose sub-model:

\[
V_{BC}^G \frac{dG_{BC}}{dt} = Q_B^G (G_H - G_{BC}) - \frac{V_{BF}^G}{T_B^G} (G_{BC} - G_{BF}), \quad (2.1)
\]

\[
V_{BF}^G \frac{dG_{BF}}{dt} = \frac{V_{BF}^G}{T_B^G} (G_{BC} - G_{BF}) - r_{BGU}, \quad (2.2)
\]

\[
V_{H}^G \frac{dG_{H}}{dt} = Q_B^G G_{BC} + Q_L^G G_L + Q_K^G G_K + Q_P^G G_P + Q_H^G G_H - r_{BCU}, \quad (2.3)
\]

\[
V_{G}^G \frac{dG_{G}}{dt} = Q_A^G G_H + Q_G^G G_G - Q_L^G G_L + r_{HGP} - r_{HGU}, \quad (2.4)
\]

\[
V_{L}^G \frac{dG_{L}}{dt} = Q_A^G G_H + Q_G^G G_G - Q_L^G G_L + r_{HGP} - r_{HGU}, \quad (2.5)
\]
\[ \frac{dG}{dt} = Q_K^G(G_H - G_K) - r_{KGE}, \]  

\[ \frac{dG_{PC}}{dt} = Q_P^G(G_H - G_{PC}) - \frac{V_{PF}^G}{T_P^G}(G_{PC} - G_{PF}), \]  

\[ \frac{dG_{PF}}{dt} = \frac{V_{PF}^G}{T_P^G}(G_{PC} - G_{PF}) - r_{PGU}, \]

where \( G \) is the glucose concentration (mg/dl), \( Q \) is the vascular blood flow rate (dl/min), \( V \) is the volume (dl), \( T \) is the transcapillary diffusion time constant (min),
$r$ is the metabolic production or consumption rate (mg/min) and $t$ is time (min). The subscripts of these variables refer to the body organs. Subscript $B$ is the brain, subscript $BC$ is the brain capillary space and subscript $BF$ is the brain interstitial fluid space. Subscript $A$ is the hepatic artery, subscript $G$ is gut, subscript $L$ is liver and subscript $G$ is GI tract (stomach and intestines). Subscript $P$ is periphery, subscript $PC$ is the periphery capillary space and subscript $PF$ is the periphery interstitial fluid space.

The general form of the metabolic production and consumption rates in each organ is as follows:

$$r = M^I(t)M^G(t)M^\Gamma(t)r^B,$$  \hspace{0.5cm} (2.9)

where $M^I$, $M^G$ and $M^\Gamma$ are the independent multiplicative effect of insulin, glucose and glucagon on the metabolic rate, respectively. $r^B$ is the basal metabolic rate and the multipliers have the following general form:

$$M^C = a + b \tanh(c \frac{C}{C^B} - d),$$  \hspace{0.5cm} (2.10)

where $a$, $b$, $c$ and $d$ are the parameters of the model. $C$ is the substance concentration and $C^B$ is the basal concentration of the substance.

The following equations are used to calculate the glucose metabolic rates:

$$r_{BGU} = 70$$  \hspace{0.5cm} (2.11)

$$r_{RBGU} = 10$$  \hspace{0.5cm} (2.12)

$$r_{GGU} = 20$$  \hspace{0.5cm} (2.13)

$$r_{PGU} = M_{PGU}^I M_{PGU}^G r_{PGU}^B,$$  \hspace{0.5cm} (2.14)
\[ r_{PGU}^B = 35 \]  

(2.15)

\[ M_{PGU}^I = 7.03 + 6.52 \tanh(0.338) \left( \frac{I_{PF}}{I_{PF}^B} - 5.82 \right) \]  

(2.16)

\[ M_{PGU}^G = \frac{G_{PF}}{G_{PF}^B} \]  

(2.17)

\[ r_{HGP} = M_{HGP}^I M_{HGP}^G M_{HGP}^\Gamma r_{HGP}^B, \]  

(2.18)

\[ r_{HGP}^B = 35 \]  

(2.19)

\[ \frac{d}{dt} M_{HGP}^I = 0.04 (M_{HGP}^{I_0} - M_{HGP}^I) \]  

(2.20)

\[ M_{HGP}^{I_0} = 1.21 - 1.14 \tanh[1.66 \left( \frac{I_L}{I_L^B} - 0.89 \right)] \]  

(2.21)

\[ M_{HGP}^G = 1.42 - 1.14 \tanh[0.62 \left( \frac{G_L}{G_L^B} - 0.497 \right)] \]  

(2.22)

\[ M_{HGP}^\Gamma = 2.7 \tanh[0.39 \left( \frac{\Gamma}{\Gamma^B} \right) - f] \]  

(2.23)

\[ \frac{d}{dt} f = 0.0154 \left[ \left( \frac{2.7 \tanh[0.39 \left( \frac{\Gamma}{\Gamma^B} \right) - 1]}{2} \right) - f \right] \]  

(2.24)

\[ r_{HGU} = M_{HGU}^I M_{HGU}^G M_{HGU}^\Gamma r_{HGU}^B, \]  

(2.25)

\[ r_{HGU}^B = 20 \]  

(2.26)
\[
\frac{d}{dt} M_{HGU}^I = 0.04(M_{HGU}^{I\infty} - M_{HGU}^I) \tag{2.27}
\]
\[
M_{HGU}^{I\infty} = 2.0 \tanh[0.55(I_B)I_L] \tag{2.28}
\]
\[
M_{HGU}^G = 5.66 + 5.66 \tanh[2.44(G_L)G_B - 1.48)] \tag{2.29}
\]
\[
KGE = 71 + 71 \tanh[0.11(G_K - 460)] \quad 0 \leq G_K < 460
\]
\[
r_{KGE} = 71 + 71 \tanh[0.11(G_K - 460)] \quad G_K \geq 460 \tag{2.30}
\]

where \( r_{BGU} \) is brain glucose uptake rate, \( r_{GGU} \) is gut glucose uptake rate, \( r_{HGP} \) is hepatic glucose production rate, \( r_{HGU} \) is hepatic glucose uptake rate, \( r_{KGE} \) is kidney glucose excretion rate, \( r_{PGU} \) is peripheral glucose uptake rate and \( r_{RBGU} \) is red blood cell glucose uptake rate. \( G, I \) and \( \Gamma \) are the concentration of glucose, insulin and glucagon, respectively. Superscript \( B \) refers to the basal condition and \( \infty \) refer to final steady state value.

As equation 2.17 shows, the form of glucose multiplier of peripheral glucose uptake rate is different from other multipliers. It is a linear function of the peripheral glucose concentration and has the following general form:

\[
M_{PGU}^G = a\left(\frac{G_{PF}}{G_B}\right) + b \tag{2.31}
\]

where \( a \) and \( b \) are the parameters of glucose multiplier of peripheral glucose uptake rate.

### 2.2.2 Insulin Sub-model

Insulin sub-model comprises of seven compartments: brain; liver; heart and lungs; periphery (muscles and adipose tissues); gastrointestinal (GI) tract (the
stomach and intestinal system); kidney; and pancreas. A schematic representation of the insulin sub-model is depicted in figure 2.5.

**Figure 2.5:** Schematic diagram of insulin sub-model[9]

The sub-model equations include mass balance equation over each sub-compartment except for the pancreas compartment. A separate model is considered for the pancreas to capture the complex mechanism of pancreatic insulin production which cannot be described by simple mass balance equations. Mass balance equations over each sub-compartment results in the following equations:

The mass balance equation over the compartments in the insulin sub-model
results in following equations:

\[
V_B^I \frac{dI_B}{dt} = Q_B^I (I_H - I_B),
\]

(2.32)

\[
V_H^I \frac{dI_H}{dt} = Q_B^I I_B + Q_L^I I_L + Q_K^I I_K + Q_P^I I_P - Q_H^I I_H,
\]

(2.33)

\[
V_G^I \frac{dI_G}{dt} = Q_G^I (I_H - I_G),
\]

(2.34)

\[
V_L^I \frac{dI_L}{dt} = Q_A^I I_H + Q_G^I I_G - Q_L^I I_L + r_{PIR} - r_{LIC},
\]

(2.35)

\[
V_K^I \frac{dI_K}{dt} = Q_K^I (I_H - I_K) - r_{KIC},
\]

(2.36)

\[
V_{PC}^I \frac{dI_{PC}}{dt} = Q_P^I (I_H - I_{PC}) - \frac{V_{PE}^I}{T_P^I} (I_{PC} - I_{PF}),
\]

(2.37)

\[
V_{PF}^I \frac{dI_{PF}}{dt} = \frac{V_{PE}^I}{T_P^I} (I_{PC} - I_{PF}) - r_{PIC},
\]

(2.38)

where \( I \) is the insulin concentration (mU/l), \( Q \) is the vascular blood flow rate (dl/min), \( V \) is the volume (dl), \( T \) is the transcapillary diffusion time constant (min), \( r \) is the metabolic production or consumption rate (mg/min) and \( t \) is time (min). The subscripts of the variables refer to the body organs. subscript \( B \) is the brain, subscript \( A \) is the hepatic artery, subscript \( G \) is gut, subscript \( L \) is liver and subscript \( G \) is GI tract (stomach and intestines). Subscript \( P \) is periphery, subscript \( PC \) is the periphery capillary space and subscript \( PF \) is the periphery interstitial fluid space.

The following equations are used to calculate the insulin consumption rates:

\[
r_{LIC} = 0.4 \left[ Q_A^I I_H + Q_G^I I_G + r_{PIR} \right]
\]

(2.39)

\[
r_{KIC} = 0.3 Q_K^I I_K
\]

(2.40)
\[ r_{PIC} = \frac{I_{PF}}{\left( \frac{1 - 0.15Q}{0.15Q} - \frac{20}{V_{PF}} \right)} \]  

(2.41)

where \( R \) is the inhibitor (dimensionless) and \( r \) is the metabolic production or consumption rate (mU/min). \( r_{KIC} \) is kidney insulin clearance rate, \( r_{LIC} \) is liver insulin clearance rate, \( r_{PIC} \) is peripheral insulin clearance rate and \( r_{PIR} \) is pancreatic insulin release rate.

As mentioned before, the simulation of the pancreatic insulin release has been done through a separate model. The changes in blood glucose concentration mainly stimulates the pancreatic insulin release. A healthy pancreas has a biphasic insulin release pattern in response to a glucose concentration step change. A sharp release of insulin for about 5-10 min constitutes the first phase, followed by a gradual increase of insulin release rate, constituting the second phase \[59]\.

The pancreatic insulin release model used in the Sorensen model has been proposed by Landahl and Grodsky \[60\]. The aim of Landahl and Grodskys model is to mimic the biphasic behaviour of pancreatic insulin secretion in response to a glucose stimulus. The graphical representation of this model is presented in figure \[2.6\].

![Figure 2.6: Schematic diagram of Landahl and Grodskys model[9]](image)

This model has two compartments. A small labile insulin compartment is assumed to exchange insulin with a large storage compartment. Glucose-stimulated
factor, $P$, regulates the rate at which insulin flows into the labile compartment. The rate of insulin secretion, $S$, depends on glucose concentration, the amount of labile insulin, $m$, and the difference between the instantaneous level of glucose-enhanced excitation factor, $X$, and its inhibitor, $R$. This functionality provides a mathematical description of the pancreas biphasic response to a glucose stimulus. The first phase insulin release is caused by an instantaneous increase in the glucose-enhanced excitation factor ($X$) followed by a rapid increase in its inhibitor ($R$). The second phase release results from the direct dependence of the insulin secretion rate ($S$) on the glucose stimulus and the gradual increase in the level of the labile compartment filling factor ($P$).

The model equations include mass balance equations over compartments and correlations between variables. The mass balance equation over each compartment results in:

$$\frac{dm}{dt} = K'm_S Km + \gamma P - S,$$  \hspace{1cm} (2.42)

$$\frac{dm_S}{dt} = Km - K'm_S - \gamma P,$$  \hspace{1cm} (2.43)

It is assumed that the capacity of the storage compartment is large enough and remains at steady state. For a glucose concentration of zero, $P$ is set to zero. Therefore, the steady state mass balance equation around the storage compartment is:

$$K'm_S = Km_0,$$  \hspace{1cm} (2.44)

where $m_0$ is the labile insulin quantity at a glucose concentration of zero. The rest of the equations for the pancreas model are:

$$\frac{dP}{dt} = \alpha (P_\infty - P),$$  \hspace{1cm} (2.45)

$$\frac{dR}{dt} = \beta (X - R),$$  \hspace{1cm} (2.46)
\[ S = [N_1 Y + N_2 (X - R) + \xi_1 \psi]m \quad x > R, \]  
\[ S = [N_1 Y + \xi_1 \psi]m \quad x \leq R, \]  
\[ P_\infty = Y = X^{1.11} + \xi_2 \psi, \]  
\[ X = \frac{G_{3.27}^3}{132^{3.27} + 5.93G_{1H}^{0.02}} \]  

\( P_\infty \) and \( Y \) reflect the glucose-induced stimulation effects on the liable compartment filling factor and the insulin secretion rate, respectively.

### 2.2.3 Glucagon Sub-model

The glucagon sub-model has one mass balance equation over the whole body as follows:

\[ V^T \frac{d\Gamma}{dt} = r_{P_{TR}} - r_{P_{TC}}, \]  

where \( \Gamma \) is the normalized glucagon concentration (dimensionless), \( V \) is volume (dl), \( t \) is time (min), \( r_{P_{TC}} \) is plasma glucagon clearance rate and \( r_{P_{TR}} \) is pancreatic glucagon release rate.

The metabolic rates for the glucagon sub-model are summarized below:

\[ r_{P_{TC}} = 9.1 \Gamma \]  

\[ r_{P_{TR}} = M^G_{P_{TR}} M^I_{P_{TR}} r^B_{P_{TR}} \]  

\[ M^G_{P_{TR}} = 1.31 - 0.61 \tanh [1.06 \left( \frac{G_H}{G_B} - 0.47 \right)] \]  

\[ M^I_{P_{TR}} = 2.93 - 2.09 \tanh [4.18 \left( \frac{I_H}{I_B} - 0.62 \right)] \]  

\[ r^B_{P_{TR}} = 9.1 \]
where $M$ is the multiplier of metabolic rates (dimensionless) and $r$ is the metabolic production or consumption rate (dl/min).

### 2.3 Type II Diabetes Model

The same structure as presented in Sorensen model can be applied to develop a model for type II diabetes. The parameters of the healthy human body model should be modified for type II diabetic patients to incorporate the abnormalities associated with the patients.

As mentioned in section 1.1.2, several organ malfunctions cause the deterioration of the blood glucose homeostasis and leads to high or low level of blood glucose in type II diabetic patients. These abnormalities are summarized in the following:

- Insulin resistance in peripheral tissues
- Impaired insulin mediated effects on hepatic glucose uptake
- Impaired insulin suppression effects on endogenous glucose production
- Impaired pancreatic insulin secretion both in first phase of release and in overall secretion rate
- Glucose resistance in the liver and peripheral tissues

The parameters of the Sorensen model are a lot but some of these parameters such as capillary space volumes and blood flow rates, are physiological factors that are predetermined by the physical characteristics of the body. The model parameters are listed in table 2.1. The values of these parameters are the same for a healthy person and a diabetic patient and do not need to be updated to describe their impact on abnormalities of diabetic subjects. The remaining parameters are in equations representing metabolic rates of glucose, insulin and glucagon besides the parameters of the pancreas model.
Considering the abnormalities of type II diabetic patients, parameters which are proper candidates for parameter estimation are within the insulin secretion rate and glucose metabolic rates. Considering the functional deficiencies of the liver, peripheral tissues and pancreas and their impact on glucose regulatory system, some related parameters of the Sorensen model are chosen for estimation. These parameters can be estimated using the available clinical data for type II diabetic patients through a non-linear optimization problem.

Vahidi et al. [5, 9] picked nineteen parameters and estimated them. Table 2.1: The model parameters [4]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{BC}^G$</td>
<td>3.5 dl</td>
</tr>
<tr>
<td>$Q_B^G$</td>
<td>5.9 dl/min</td>
</tr>
<tr>
<td>$T_B^G$</td>
<td>2.1 min</td>
</tr>
<tr>
<td>$V_{BF}^G$</td>
<td>4.5 dl</td>
</tr>
<tr>
<td>$Q_H^G$</td>
<td>43.7 dl/min</td>
</tr>
<tr>
<td>$T_P^G$</td>
<td>5.0 min</td>
</tr>
<tr>
<td>$V_H^G$</td>
<td>3.5 dl</td>
</tr>
<tr>
<td>$Q_A^G$</td>
<td>2.5 dl/min</td>
</tr>
<tr>
<td>$T_P^I$</td>
<td>20 min</td>
</tr>
<tr>
<td>$V_L^G$</td>
<td>25.1 dl</td>
</tr>
<tr>
<td>$Q_L^G$</td>
<td>12.6 dl/min</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.0482 min$^{-1}$</td>
</tr>
<tr>
<td>$V_{BF}^G$</td>
<td>11.2 dl</td>
</tr>
<tr>
<td>$Q_G^G$</td>
<td>10.1 dl/min</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.931 min$^{-1}$</td>
</tr>
<tr>
<td>$V_K^G$</td>
<td>6.6 dl</td>
</tr>
<tr>
<td>$Q_K^G$</td>
<td>10.1 dl/min</td>
</tr>
<tr>
<td>$K$</td>
<td>0.00794 min$^{-1}$</td>
</tr>
<tr>
<td>$V_{PC}^G$</td>
<td>10.4 dl</td>
</tr>
<tr>
<td>$Q_P^G$</td>
<td>12.6 dl/min</td>
</tr>
<tr>
<td>$N_1$</td>
<td>0.00747 min$^{-1}$</td>
</tr>
<tr>
<td>$V_{PF}^G$</td>
<td>67.4 dl</td>
</tr>
<tr>
<td>$Q_B^I$</td>
<td>0.45 l/min</td>
</tr>
<tr>
<td>$N_2$</td>
<td>0.0958 min$^{-1}$</td>
</tr>
<tr>
<td>$V_B^I$</td>
<td>0.26 l</td>
</tr>
<tr>
<td>$Q_H^I$</td>
<td>3.12 l/min</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.0958 U/min</td>
</tr>
<tr>
<td>$V_H^I$</td>
<td>0.99 l</td>
</tr>
<tr>
<td>$Q_A^I$</td>
<td>0.18 l/min</td>
</tr>
<tr>
<td>$m_0$</td>
<td>6.33 U</td>
</tr>
<tr>
<td>$V_G^I$</td>
<td>0.94 l</td>
</tr>
<tr>
<td>$Q_K^I$</td>
<td>0.72 l/min</td>
</tr>
<tr>
<td>$V_I^I$</td>
<td>1.14 l</td>
</tr>
<tr>
<td>$Q_P^I$</td>
<td>1.05 l/min</td>
</tr>
<tr>
<td>$V_K^I$</td>
<td>0.51 l</td>
</tr>
<tr>
<td>$Q_G^I$</td>
<td>0.72 l/min</td>
</tr>
<tr>
<td>$V_{PF}^I$</td>
<td>6.74 l</td>
</tr>
<tr>
<td>$V^\Gamma$</td>
<td>6.74 l</td>
</tr>
</tbody>
</table>
Table 2.2: Abnormalities associated with type II diabetes and their corresponding equations

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Corresponding Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance in peripheral tissues</td>
<td>Insulin multiplier in peripheral glucose uptake rate</td>
</tr>
<tr>
<td>Insulin-induced stimulation of hepatic glucose uptake</td>
<td>Insulin multiplier in hepatic glucose uptake rate</td>
</tr>
<tr>
<td>Insulin-induced stimulation of hepatic glucose production</td>
<td>Insulin multiplier in hepatic glucose production rate</td>
</tr>
<tr>
<td>Glucose-induced stimulation of hepatic glucose uptake</td>
<td>glucose multiplier in hepatic glucose uptake rate</td>
</tr>
<tr>
<td>Glucose-induced stimulation of peripheral glucose uptake</td>
<td>glucose multiplier in peripheral glucose uptake rate</td>
</tr>
<tr>
<td>Pancreatic insulin secretion rate both in early peak and overall rate</td>
<td>$N_1$ and $N_2$ in the pancreas model</td>
</tr>
</tbody>
</table>

Table 2.2 summarizes the abnormalities associated with type II diabetes and their corresponding model equations whose parameters are selected for estimation. As shown in equation 2.10, multipliers which represent multiplicative effects of glucose, insulin and glucagon on glucose metabolic rates have four parameters. Out of nineteen selected parameters, twelve of them are chosen from the insulin multiplier parameters in peripheral glucose uptake rate, hepatic glucose uptake rate and hepatic glucose production rate; and five others are selected from the glucose multiplier parameters in hepatic glucose uptake rate and peripheral glucose uptake rate. From the pancreas model, only two parameters $N_1$ and $N_2$ which represent the early peak of pancreatic insulin release and overall pancreatic insulin secretion rate, respectively, are sufficient to be chosen for the parameter estimation. The results of the parameter estimation are presented in table 2.3. For the insulin sub-model, the estimation results are $N_1 = 0.00595$ and $N_2 = 0.0467$.

Having reliable information from the patient status is helpful to provides in-
Table 2.3: Parameter estimation results for the glucose sub-model [5]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M^{I}_{PGU}$</td>
<td>2.551</td>
<td>1.66</td>
<td>0.69</td>
<td>3.454</td>
</tr>
<tr>
<td>$M^{I}_{HGP}$</td>
<td>1.173</td>
<td>1.073</td>
<td>0.993</td>
<td>1.164</td>
</tr>
<tr>
<td>$M^{I}_{HGU}$</td>
<td>0.662</td>
<td>0.731</td>
<td>0.985</td>
<td>0.493</td>
</tr>
<tr>
<td>$M^{G}_{HGU}$</td>
<td>1.855</td>
<td>1.85</td>
<td>2.047</td>
<td>1.244</td>
</tr>
<tr>
<td>$M^{G}_{PGU}$</td>
<td>0.897</td>
<td>0.103</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

sights for the clinicians to find an effective treatment for each individual. Human experimentation is a way of obtaining useful and reliable information about the medical status of a patient; however, due to ethical issues, physiological restrictions and high expenses of human experimentation, it is limitedly performed mostly for research studies. Mathematical modeling is a popular alternative in obtaining useful information about the glucose metabolism and understanding the medical condition of the diabetic patients. The model is also used to evaluate the different control strategies for administering the proper amount of insulin to the patient body. Furthermore, the type II diabetes model is used to develop pharmacokinetic-pharmacodynamic models for various medicines which allow studying the effectiveness of oral medicines on regulating the blood sugar.
Chapter 3

Evaluation of Treatment Regimens for Blood Glucose Regulation in Type II Diabetes Using Pharmacokinetic-Pharmacodynamic Modelling

3.1 Introduction

Blood glucose concentration in type II diabetic patients can be initially controlled by exercise and healthy dieting [61–64]; however, as the disease progresses, medication and insulin therapy are needed.

The treatment strategies suggested by the clinicians are vary from different types of oral agents to various insulin therapy regimens. The treatment should be individualized for each patient so that the regular measurement of the blood glucose concentration is needed to get the update information about the subject’s response to each treatment.
Several studies compared the effects of different insulin regimens on various groups of type II diabetic patients by conducting experiments and monitoring the blood glucose concentration during a period of time. Wolfsdorf et.al. showed the effects of insulin regimen with human ultralente before supper and NPH before breakfast in children and adolescents [65]. Yki-Jarvinen et.al. reported the results of 153 type II diabetic patients treated by five different insulin regimens [66]. Wolffenbuttel et.al. also studied 95 elderly patients with type II diabetes who were poorly controlled, despite diet and maximal doses of oral agents. They compared three insulin administration regimens during a 6-month period [67]. However, such studies need regularly performed monitoring of the blood glucose either at home or in the hospital. Also, due to ethical standards and risks posed to the human body, the number and variety of experiments that can be performed on a patient is limited.

Development of dynamic models, representing a patient in a simulation environment, is useful to collect sufficient data. In this chapter we modified the model presented in Chapter 2 to assess the performance of different control strategies using different insulin types, oral agents or the combination of them and choose the right one for an individual patient.

Different types of oral drugs were summarized in table 1.2. Amongst them metformin is the first-line drug of choice for the treatment of type II diabetes. It increases the rate of intestinal glucose consumption, allows more glucose to enter cells and keeps the liver from making glucose due to decreased hepatic gluconeogenesis and increased glycogenesis and lipogenesis [68]. Some studies described the pharmacokinetic-pharmacodynamic(PK-PD) model of metformin [7, 69, 70]. Pharmacokinetics is defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. Pharmacodynamics refers to the relationship between drug concentration at the site of action and the effects. In this chapter PK-PD model of metformin is incorporated into type II diabetes model to analyze the glucose-lowering effect of this oral agent on the patients.

Oral agents are helpful in initial steps of diabetes, but most of the patients
with type II diabetes finally need insulin therapy to better regulate their blood glucose level. Insulin can be delivered by multiple daily injections or infused continuously through the insulin pump. Multiple dose injection (MDI) therapy, also known as multiple daily injections, involves several injections a day, gives the diabetic patient more control over their life and their diabetes by using different combinations of insulin [71].

There are some studies presented the pharmacokinetic-pharmacodynamic (PK-PD) model of different insulin types for simulation purposes. Berger and Rodbard developed a computer program for the simulation of plasma insulin and glucose dynamics after subcutaneous injection of insulin. This program is based on a physiologic model of minimal complexity, which describes the pharmacokinetics of absorption and clearance of subcutaneous insulin and the dynamics of glucose utilization as dependent on both prevailing glucose and insulin levels [6, 72]. Wu et.al. reported a two-compartment model that includes glucose and insulin dynamics and its evaluation using patient data [73]. Therefore, the dynamics of plasma insulin after the injections of various combinations of short, intermediate and long-acting insulins can be simulated by using PK-PD model. Such model is used, in this chapter to address the problem of finding the most efficient regimen for multiple daily injections (MDI) therapy during Chapter 4 and 5 deals with developing control strategies for continuous subcutaneous insulin infusion (CSII) therapy using the insulin pump.

The following section represents the modification of the mathematical modeling for type II diabetes mellitus by incorporating PK-PD models of metformin and four popular types of insulin (regular, NPH, lente and ultralente) to simulate the patient response to the meal ingestion with different treatment regimens. The results are presented and discussed in section 3.3 for different therapies, amongst them the most efficient one can be applied to the patient.
3.2 Expansion of Type II Diabetes Mellitus Mathematical Model

Pharmacokinetic-Pharmacodynamic (PK-PD) modeling of metformin and different insulin types can be incorporated into the physiological model of type II diabetes to better understand the underlying kinetic phenomena involved with these treatments. The model should also be updated by adding the meal sub-model to describe the digestion of the carbohydrate content of the meal. The mathematical models are presented in the following subsections.

3.2.1 Pharmacokinetic-Pharmacodynamic Modeling of Subcutaneous Injected Insulin

The PK-PD model of subcutaneously injected insulin consists of two compartments, describing the dynamics in subcutaneous injection site and the plasma insulin compartment [6,72].

The following two equations define the dependency of insulin absorption on insulin types and dose.

\[ A\% (t) = 100 - \frac{100.t^s}{(T_{50\%}) + t^s} \]  \hspace{1cm} (3.1)

\[ T_{50\%} (D) = a.D + b \]  \hspace{1cm} (3.2)

where \( A\% \) is percent of injected insulin remaining at the absorption site, \( t \) is time after injection, \( s \) characterizes time course of absorption, and \( T_{50\%} \) is time interval to permit 50% of injected dose to be absorbed. \( a \) and \( b \) are parameters to characterize dependency of \( T_{50\%} \) on dose and \( D \) is insulin dose \((U)\). \( a, b \) and \( s \) have been estimated for four popular types of insulin (regular, NPH, lente and ultralente) and reported in [6] as depicted in table 3.1.
Table 3.1: parameter values of insulin PK-PD model [6]

<table>
<thead>
<tr>
<th>insulin type</th>
<th>$s$</th>
<th>$a(\text{hr}/U)$</th>
<th>$b(\text{hr})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>regular</td>
<td>2.0</td>
<td>0.05</td>
<td>1.7</td>
</tr>
<tr>
<td>NPH</td>
<td>2.0</td>
<td>0.18</td>
<td>4.9</td>
</tr>
<tr>
<td>lente</td>
<td>2.4</td>
<td>0.15</td>
<td>6.2</td>
</tr>
<tr>
<td>ultralente</td>
<td>2.5</td>
<td>0</td>
<td>13</td>
</tr>
</tbody>
</table>

The rate of change of plasma insulin is calculated by adding a first-order plasma elimination rate to the first derivative of equation (3.1):

\[
\frac{dA}{dt} = s.t^s.(T_{50\%})^s.D \frac{t.\|T_{50\%}\|^s + t^s\|^2}{t^s + t^s\|^2} - k_e.A
\]  

(3.3)

where $A$ is plasma insulin and $k_e$ is first-order elimination constant. Dividing plasma insulin by distribution volume for insulin yields plasma concentration at time $t$ after injection:

\[
I(t) = \frac{A(t)}{V_t}
\]  

(3.4)

where $I$ is plasma insulin concentration and $V_t$, is distribution volume for insulin which is assumed to be 12 L as reported in [6] for a patient with 70 kg of body weight.

Type II diabetes model, presented in Chapter 2, is modified by considering plasma insulin concentration as an input to the heart compartment of insulin sub-model (equation 2.33).
3.2.2 Pharmacokinetic-Pharmacodynamic Modeling of Metformin

Due to the multifactorial mechanism of action of metformin, a multi-compartment PK-PD model of metformin for the treatment of type II diabetes mellitus is used as described in [7, 69, 70]. This model constitutes three compartments including the GI tract (gut), liver and periphery. GI lumen and GI wall are considered as sub-compartments of the gut compartment, because the accumulation of metformin in the GI wall is not only through the GI lumen, but also via arterial blood supply to the intestine.

The following mass balance equations, with first-order kinetic, are used to describe the transfer of metformin between different compartments.

\[
\begin{align*}
\dot{X}_1 &= -X_1 (k_{go} + k_{gg}) + X_0 \\
\dot{X}_2 &= X_1 k_{gg} + X_4 k_{pg} - X_2 k_{gl} \\
\dot{X}_3 &= X_2 k_{gl} + X_4 k_{pl} - X_3 k_{lp} \\
\dot{X}_4 &= X_3 k_{lp} - X_4 (k_{pl} + k_{pg} + k_{po})
\end{align*}
\] (3.5-3.8)

where \(X_1, X_2, X_3, \) and \(X_4\) are the mass of metformin in the GI lumen, GI wall, liver, and periphery compartments, respectively. \(X_0\) is the flow rate of metformin as a result of a single oral ingestion. The rate constants are: \(k_{go}\), drug elimination via the fecal route; \(k_{gg}\), drug transfer from the GI lumen to the GI wall compartment; \(k_{gl}\), drug transfer from the GI wall to the liver compartment; \(k_{lp}\) and \(k_{pl}\), drug transfer from the liver to the periphery compartment and vice versa; \(k_{pg}\), drug transfer from the periphery to the GI wall compartment; and \(k_{po}\), drug elimination via the urination route.

In this modelling approach, metformin is distributed to the GI lumen, liver, and periphery compartment following oral administration. For the oral administration, the pharmacokinetics of metformin from mouth to the GI lumen is described by the following equation:
\[ X_O = Ae^{-\alpha t} + Be^{-\beta t} \]  

(3.9)

where \( \alpha \) and \( \beta \) are rate constants; \( A \) and \( B \) represent the contribution of the corresponding exponentials. These parameters were estimated by optimization using experimental data points in [7] and reported in table 3.2.

**Table 3.2:** parameter values of metformin PK-PD model [7]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A ) (mg/min)</td>
<td>( 2.7 \times 10^4 )</td>
</tr>
<tr>
<td>( B ) (mg/min)</td>
<td>( 2.7 \times 10^4 )</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.06</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.1</td>
</tr>
<tr>
<td>( k_{go}(min^{-1}) )</td>
<td>( 1.88 \times 10^{-3} )</td>
</tr>
<tr>
<td>( k_{gg}(min^{-1}) )</td>
<td>( 1.85 \times 10^{-3} )</td>
</tr>
<tr>
<td>( k_{gl}(min^{-1}) )</td>
<td>0.46</td>
</tr>
<tr>
<td>( k_{lp}(min^{-1}) )</td>
<td>0.91</td>
</tr>
<tr>
<td>( k_{pi}(min^{-1}) )</td>
<td>( 1.01 \times 10^{-2} )</td>
</tr>
<tr>
<td>( k_{pg}(min^{-1}) )</td>
<td>4.13</td>
</tr>
<tr>
<td>( k_{po}(min^{-1}) )</td>
<td>0.51</td>
</tr>
</tbody>
</table>

The transient changes of metformin amounts at different biophases can be obtained as indicated in equations 3.5-8. The glucose-lowering effect of metformin mainly involves the stimulation of glucose consumption in the GI tract and periphery (\( E_{GI} \) and \( E_P \)) and the inhibition of glucose production in the liver (\( E_L \)), of which the metabolic rate of the gut glucose consumption (\( r_{PK-PD}^{GGU} \)) is only attributed to the GI wall. These three coefficients \( E_{GI} \), \( E_L \), and \( E_P \) are modified the metabolic rates of the corresponding compartments in the physiological model described in Chapter 2 to present the behaviour of a type II diabetic patient with the treatment of metformin.

As metformin is known to increase glucose consumption by the gut, the rate of gut glucose consumption (\( r_{PK-PD}^{GGU} \)) in the type II diabetic model is modified as shown in equation 3.10.

\[ r_{PK-PD}^{GGU} = (1 + E_{GI})r_{GGU} \]  

(3.10)
where \( r_{GGU} \) is the rate of the gut glucose consumption with no metformin effect (equation 2.13), and \( E_{GI} \) is a weight coefficient that represents the increment of the rate \( r_{GGU} \) following the administration of metformin. Similarly, metformin is known to lower hepatic glucose production, whose rate \( \left( r_{HGP}^{PK-PD} \right) \) is modified as shown in equation 3.11,

\[
r_{HGP}^{PK-PD} = (1 - E_L) r_{HGP} \quad (3.11)
\]

where \( r_{HGP} \) is the rate of the hepatic glucose production without the effect of metformin for type II diabetic patients (equation 2.18), and \( E_L \) is a weight coefficient that indicates the inhibition of glucose production in the liver (L). Also, the rate of the periphery glucose uptake \( \left( r_{PGU}^{PK-PD} \right) \) is modified to the following equation:

\[
r_{PGU}^{PK-PD} = (1 + E_P) r_{PGU} \quad (3.12)
\]

where \( r_{PGU} \) is the rate of the periphery glucose uptake without the treatment of metformin (equation 2.14), and \( E_P \) is a weight coefficient that indicates the stimulation of glucose consumption in the periphery (P) with the metformin effect.

According to the literature published by Stepensky et al. [8], the corresponding weight coefficients in three compartments (\( E_{GI} \), \( E_L \), and \( E_P \)) are calculated as follows:

\[
E_{GI} = \frac{\nu_{GI,max} \times (X_2)^{n_{GI}}}{(\phi_{GI,50})^{n_{GI}} + (X_2)^{n_{GI}}} \quad (3.13)
\]

\[
E_L = \frac{\nu_{L,max} \times (X_3)^{n_L}}{(\phi_{L,50})^{n_L} + (X_3)^{n_L}} \quad (3.14)
\]
\[ E_P = \frac{v_{P,\text{max}} \times (X_4)^{n_P}}{(\phi_{P,50})^{n_P} + (X_4)^{n_P}} \]  

(3.15)

where \( v \) is the parameter representing the maximum effect of metformin in each compartment (\( v_{GI,\text{max}}, v_{L,\text{max}} \) and \( v_{P,\text{max}} \)); \( \phi_{GI,50}, \phi_{L,50} \) and \( \phi_{P,50} \) are the mass of metformin at the biophase that produces 50\% of its maximal effect; and \( n_{GI}, n_L, \) and \( n_P \) are the shape factors. The model parameters can be found in [70] as summarized in table 3.3.

**Table 3.3:** Parameter values of metformin PK-PD model [8]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Shape Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_{GI,\text{max}} )</td>
<td>0.486</td>
<td>( \mu g )</td>
<td>2</td>
</tr>
<tr>
<td>( v_{L,\text{max}} )</td>
<td>0.378</td>
<td>( \mu g )</td>
<td>5</td>
</tr>
<tr>
<td>( v_{P,\text{max}} )</td>
<td>0.148</td>
<td>( \mu g )</td>
<td>5</td>
</tr>
<tr>
<td>( \phi_{GI,50} )</td>
<td>431</td>
<td>( \mu g )</td>
<td></td>
</tr>
<tr>
<td>( \phi_{L,50} )</td>
<td>521</td>
<td>( \mu g )</td>
<td></td>
</tr>
<tr>
<td>( \phi_{P,50} )</td>
<td>1024</td>
<td>( \mu g )</td>
<td></td>
</tr>
</tbody>
</table>

### 3.2.3 Mathematical Representation of the Glucose Absorption Model

For clinical evaluation, the oral glucose tolerance test (OGTT) is usually used to assess the patient's insulin reserve and response to a glucose load. The test uses a standard dose of glucose orally administered to determine the body's ability to regulate the blood sugar. A standard amount of oral glucose was administered to evaluate the efficiencies of the treatments. The mathematical representation of the glucose absorption model has been described in [74]. Lehmann and Deutsch presented the rate of gastric emptying of the ingested glucose as a function of time with a trapezoidal form. The duration of the period \( (T_{\text{maxge}}) \) for which gastric emptying is constant and maximal \( (V_{\text{maxge}}) \) is a function of the carbohydrate content of the meal ingested.

\[ T_{\text{maxge}} = \left[ Ch - \frac{1}{2} V_{\text{maxge}} (T_{\text{ascge}} + T_{\text{desge}}) \right] / V_{\text{maxge}} \]  

(3.16)
where $V_{\text{max ge}}$ is the maximal rate of gastric emptying and $T_{\text{asc ge}}$ and $T_{\text{des ge}}$ are the respective lengths of the ascending and descending branches of the gastric emptying curve. The default values for $T_{\text{asc ge}}$ and $T_{\text{des ge}}$ are 30 min (0.5 h) and the maximal rate of gastric emptying is 120 mmol/h. Linear interpolation can be applied to obtain the rate of gastric emptying for meals containing $Ch$ millimoles of carbohydrate as follows:

$$G_{\text{empt}} = \frac{V_{\text{max ge}}}{T_{\text{asc ge}}}t; \quad t < T_{\text{asc ge}}$$
$$G_{\text{empt}} = V_{\text{max ge}}; \quad T_{\text{asc ge}} < t \leq T_{\text{asc ge}} + T_{\text{max ge}}$$
$$G_{\text{empt}} = V_{\text{max ge}} - \frac{V_{\text{max ge}}}{T_{\text{des ge}}}(t - T_{\text{asc ge}} - T_{\text{max ge}}); \quad T_{\text{asc ge}} + T_{\text{max ge}} \leq t < T_{\text{max ge}} + T_{\text{asc ge}} + T_{\text{des ge}}$$
$$G_{\text{empt}} = 0; \quad \text{elsewhere}$$

$t$ is the elapsed time from the start of the meal.

Figure 3.1 indicates the connection of the glucose absorption model and also PK-PD models of insulin injection and metformin with the Sorensen model. The PK-PD model of metformin is placed into three compartments of glucose sub-model as shown with the arrows. It updates the metabolic rates in gut, liver and periphery compartments as explained in equations 3.10 to 3.12.

As the arrow shows, the glucose absorption model is placed into the gut compartment of the glucose sub-model and is responsible for the calculation of the glucose appearance rate into the blood stream following an oral glucose intake. The calculated value of the glucose appearance rate is added as a source of glucose into the equation 2.4 which represents the mass balance over the gut compartment of the glucose sub-model.

Finally, the PK-PD model of insulin injection is placed into the heart compartment of insulin sub-model. The model calculates the plasma insulin concentration which is entered into the blood stream after the injection as the heart circulates the blood. Therefore, the plasma insulin concentration is added to equation 2.33 as the source of insulin.
3.3 Simulation Results and Discussion

The modified model, proposed in the previous section, can be applied to simulate the response of the patient to the various amount of glucose intake at different times during the day while different combinations of insulin types and dosages are injected as daily multiple injection regimen. The simulations can also show the effect of metformin on the glucose concentration for type II diabetic patients. Therefore, the most efficient regimen can be chosen to be applied on the patient.

The simulation is considered for the whole day, starting from 6 am. It is assumed that the patient eats 275 g of carbohydrate during the day, 75 g of glucose for breakfast at 8 AM, 100 g of glucose for lunch at 1 PM and 100 g of glucose for dinner at 8 PM. Without the administration of oral agents and insulin injections, the blood glucose goes higher than 11 mmol/L as shown in figure 3.2.
Figure 3.2: The simulated patient response to the meal disturbance during the day without drug and insulin therapy

3.3.1 Simulation Results for Different Insulin Injection Regimens

Regular insulin is a short-acting insulin. It has an onset of action 15 to 60 min after injection, a peak effect 2 to 4 h after injection, and a duration of action of ranging from 5 to 8 h. Neutral protamine Hagedorn insulin (NPH) is an intermediate-acting insulin. NPH has an onset of action 2 h after injection, a peak effect 6 to 10 h after injection, and a duration of action ranging from 13 to 20 h. Lente is also an intermediate-acting insulin with an onset of action 2.5 h after injection, a peak effect 6 to 16 h after injection, and a duration of action up to 24 h. Ultralente is very stable crystalline insulin considered as long-acting insulin that has its peak
activity 8 to 18 h after injection and a duration of action of 30 h. [71].

The plasma insulin profile for each of the four types of insulin is shown in figure 3.3 using the pharmacokinetic-pharmacodynamic model presented in section 3.2.1. The simulation results are consistent with the known characteristics of the insulin types regarding the onset of action, peak time and the duration of action. A

**Figure 3.3:** plasma insulin profile for regular, NPH, lente and ultralente insulin

mixture of intermediate or long-acting insulins in addition to short-acting insulin are used to both keep the basal insulin level of the body in the normal range and also regulate the blood glucose after food intake. The following results discuss the effects of changes in insulin dose, type and injection time on the blood glucose concentration.


**Insulin dose**

The blood glucose profile is affected by changing injected insulin dose. To better illustrate the effects of different insulin amounts on the blood glucose regulation, the body responses after systematically changing the insulin dose has been shown in figures 3.4 and 3.6.

---

**Figure 3.4:** The simulated patient blood glucose profile after the subcutaneous insulin injection according to regimen 1 (black solid line), regimen 2 (blue dashed line) and regimen 3 (red dotted line) to study the effects of changes in regular insulin dose.

The black solid line in figure 3.4 demonstrates the result of the injection of 5 units of regular insulin at each meal time and 5 units of NPH insulin in the morning and evening (regimen 1) which is considered as the observed profile. For understanding the effects of changes in regular insulin, the NPH insulin dose is...
kept the same as regimen 1 while the regular insulin dose is changing. The blue dashed line shows the result when no regular insulin is injected with the meals (regimen 2). The result of an increase in regular insulin from 5 to 10 units is shown by the red dotted line (regimen 3).

**Figure 3.5:** The simulated patient plasma insulin profile after the subcutaneous insulin injection according to regimen 1 (black solid line), regimen 2 (blue dashed line) and regimen 3 (red dotted line) to show the insulin resistance in body cells.

Without the injection of regular insulin, the blood glucose level goes up to hyperglycemia zone colored in yellow after lunch and dinner. Increasing regular insulin dose causes severe hypoglycemia which is dangerous for the patient especially during the night. However, an increase in regular insulin does has little effect on blood glucose peak after each meal. The reason is that the body cells
become insulin resistant in type II diabetes, so the presence of excess amount of insulin does not help the more absorption of glucose by cells and only increase the plasma insulin level as shown with the red dotted line in figure 3.5.

**Figure 3.6:** The simulated patient blood glucose profile after the subcutaneous insulin injection according to regimen 1 (black solid line), regimen 4 (blue dashed line) and regimen 5 (red dotted line) to study the effects of changes in NPH insulin dose.

The effect of changing in NPH dose is depicted in figure 3.6. The black solid line presents the result for regimen 1. The blue dashed line and the red dotted line shows the results for a decrease in NPH dose from 5 to zero (regimen 4) and an increase from 5 to 10 (regimen 5), respectively while the regular insulin dose does not change. An increase in NPH yields the glucose profile with the severe hypoglycemia after lunch and during night. Again the excess amount of NPH can
not help lowering the blood glucose level because of insulin resistance in body cells.

It can be seen that despite of eliminating intermediate or long-acting insulin in regimen 4, the blood glucose profile still is acceptable and kept in normoglycemia zone. This can be understood from the fact that the pancreas still secretes some insulin in type II diabetes which provides the basal insulin level of the body but is not sufficient for preventing the blood glucose rise after the meals. This can be demonstrated better by monitoring the plasma insulin concentration while no external insulin is injected (see figure 3.7).

**Figure 3.7:** The simulated patient plasma insulin profile produced by pancreas without any external insulin injection
Insulin type

In figure 3.8 different types of intermediate- or long-acting insulin are applied with regular insulin as short-acting insulin. Combination of regular insulin with NPH, lente and ultralente sufficiently prevent hyperglycemia.

Regarding the problem of hypoglycemia, a mixture of regular and ultralente before dinner causes a modest reduction in fasting blood glucose level during the night (red dotted line). Compared with a mixed dose of regular and ultralente, the similar dose of a mixture of regular and NPH (black solid line) or lente (blue dashed line) increases the risk of hypoglycemia while the patient is sleeping. Available clinical data in the literature also shows a modest reduction in fasting blood glucose using ultralente as long-acting insulin which confirms the simulation results [65].

The only precaution that should be taken into the consideration is that the zinc in ultralente retards the onset of action of the regular insulin, and so it should be immediately injected after withdrawal from the vial.

Timing of insulin injection

Choosing the proper time of injection affects the quality of blood glucose regulation. Figure 3.9 shows the effect of the time of injection on the blood glucose profile.

In this figure insulin injection according to regimen 8 is considered as the observed glucose profile (black solid line) and is used to investigate the effects of advancing and delaying all the injections by an hour, applying the identical insulin type and dose to regimen 8, as shown with blue dashed line and red dotted line, respectively.

Having the morning injection followed by an hour delay to commence the breakfast decrease the fasting blood glucose level and causes severe hypoglycemia. This also occurs when the injection happens an hour before the dinner. However, for type II diabetic patient whose pancreas still is capable of secreting insulin an hour delay in insulin injection is not that much a problem and body can main-
Figure 3.8: The simulated patient response to the subcutaneous insulin injection to study the effects of NPH according to regimen 6 (black solid line), lente according to regimen 7 (blue dashed line) and ultralente according to regimen 8 (red dotted line)

Table 3.4 summarizes all the discussed regimens. The comparison of the proposed regimens helps to propose an efficient regimen for a patient to prevent hypoglycemia and hyperglycemia while bringing back the blood glucose to the lower...
Figure 3.9: The simulated patient response to the subcutaneous insulin injection to study the effect of changes in the timing of the injection. Glucose profile for regimen 8 (black solid line) applied at the meal time is compared with the glucose profile of advancing (blue dashed line) and delaying (red dotted line) all the injections by an hour.

Table 3.5 provides better comparison between the regimens by considering the following factors for each glucose profile:

- minimum concentration of blood glucose before lunch ($BG_{min}^B$)
- minimum concentration of blood glucose before dinner ($BG_{min}^L$)
- minimum concentration of blood glucose during the night ($BG_{min}^D$)
- maximum concentration of blood glucose after breakfast ($BG_{max}^B$)
Table 3.4: Insulin injection regimen

<table>
<thead>
<tr>
<th>regimen#</th>
<th>insulin type</th>
<th>breakfast at 8 am 75 g of glucose</th>
<th>lunch at 1 pm 100 g of glucose</th>
<th>dinner at 8 pm 100 g of glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>regular NPH</td>
<td>5 units</td>
<td>5 units</td>
<td>5 units</td>
</tr>
<tr>
<td>(2)</td>
<td>regular NPH</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(3)</td>
<td>regular NPH</td>
<td>10 units</td>
<td>10 units</td>
<td>10 units</td>
</tr>
<tr>
<td>(4)</td>
<td>regular NPH</td>
<td>5 units</td>
<td>5 units</td>
<td>5 units</td>
</tr>
<tr>
<td>(5)</td>
<td>regular NPH</td>
<td>5 units</td>
<td>5 units</td>
<td>5 units</td>
</tr>
<tr>
<td>(6)</td>
<td>regular NPH</td>
<td>3 units</td>
<td>3 units</td>
<td>3 units</td>
</tr>
<tr>
<td>(7)</td>
<td>regular lente</td>
<td>3 units</td>
<td>3 units</td>
<td>3 units</td>
</tr>
<tr>
<td>(8)</td>
<td>regular ultralente</td>
<td>3 units</td>
<td>3 units</td>
<td>3 units</td>
</tr>
<tr>
<td>(9)</td>
<td>regular ultralente</td>
<td>3 units</td>
<td>5 units</td>
<td>3 units</td>
</tr>
</tbody>
</table>

- maximum concentration of blood glucose after lunch ($BG_{max}^{L}$)
- maximum concentration of blood glucose after dinner ($BG_{max}^{D}$)
- time in minutes needed to bring back the blood glucose level under 7 mmol/L after breakfast ($t^B$)
- time in minutes needed to bring back the blood glucose level under 7 mmol/L after lunch ($t^L$)
- time in minutes needed to bring back the blood glucose level under 7 mmol/L
after dinner ($t^D$)

Table 3.5: Comparison of different regimens

<table>
<thead>
<tr>
<th>regimen#</th>
<th>$BG^B_{\text{min}}$</th>
<th>$BG^L_{\text{min}}$</th>
<th>$BG^D_{\text{min}}$</th>
<th>$BG^B_{\text{max}}$</th>
<th>$BG^L_{\text{max}}$</th>
<th>$BG^D_{\text{max}}$</th>
<th>$t^B$</th>
<th>$t^L$</th>
<th>$t^D$</th>
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<td>318</td>
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<tr>
<td>(2)</td>
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<td>8.01</td>
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<td>317</td>
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<td>8.07</td>
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<td>322</td>
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<td>317</td>
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<td>270</td>
<td>320</td>
<td>318</td>
</tr>
<tr>
<td>(7)</td>
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<td>3.75</td>
<td>2.37</td>
<td>8.12</td>
<td>10.87</td>
<td>10.75</td>
<td>271</td>
<td>320</td>
<td>316</td>
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<tr>
<td>(8)</td>
<td>5.28</td>
<td>4.35</td>
<td>3.82</td>
<td>8.23</td>
<td>11.05</td>
<td>10.81</td>
<td>277</td>
<td>322</td>
<td>320</td>
</tr>
<tr>
<td>(8)</td>
<td>4.63</td>
<td>2.74</td>
<td>4</td>
<td>8.4</td>
<td>11.10</td>
<td>10.76</td>
<td>280</td>
<td>324</td>
<td>320</td>
</tr>
<tr>
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<td>4.03</td>
<td>3.54</td>
<td>8.37</td>
<td>11.13</td>
<td>11</td>
<td>275</td>
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<tr>
<td>(9)</td>
<td>5.34</td>
<td>4.15</td>
<td>4.29</td>
<td>8.25</td>
<td>10.96</td>
<td>10.82</td>
<td>304</td>
<td>336</td>
<td>337</td>
</tr>
</tbody>
</table>

An efficient regimen can keep the minimum concentration of the blood glucose in the normal glycemic zone without traversing to hypoglycemia and severe hypoglycemia. Moreover, the maximum blood glucose concentration should not go to hyperglycemia and severe hyperglycemia zones. The yellow color in Table 3.5 shows the occurrence of hypoglycemia or hyperglycemia and the red color is used to demonstrate the severe hypoglycemia state.

Table 3.5 shows that regimens 1 and 7 cause hypoglycemia before having dinner and severe hypoglycemia during the night. Regimens 3 and 5 result in severe hypoglycemia both before dinner and during the night. Severe hypoglycemia also occurs in regimen 6 during the night and in regimen 8 before dinner when the injection is advanced by an hour. Hypoglycemia and hyperglycemia are happened
in regimen 8 both when insulin is injected at the meal time and delayed by an hour. Regimen 2 prevents hypoglycemia but causes hyperglycemia after lunch and dinner.

Regimen 9 as described in table 3.4 includes the injections of 3 units of regular insulin in addition to 5 units of ultralente in the morning and evening and 5 units of regular insulin with lunch. This regimen assures a reliable regulation of blood glucose depicted in figure 3.10. The superiority of this regimen over regimen 4 is that it is performing better in keeping blood glucose concentration closer to the lower bound of the green zone which is more desirable (see table 3.5).

Figure 3.10: The simulated patient response to the subcutaneous insulin injection corresponding to regimen 9 which proposes an efficient blood glucose regulation.
3.3.2 Simulation Results for Administration of Metformin

The glucose lowering effects of metformin are defined through the weight coefficients which are used to modify the metabolic rates in liver, GI lumen and periphery compartments. $E_L$, $E_{GI}$ and $E_P$ are calculated according to equations 3.13 to 3.15 and depicted in figure 3.11.

![Figure 3.11: Glucose lowering effect of metformin in liver, GI tract and periphery ($E_L$, $E_{GI}$ and $E_P$)](image)

Figure 3.12 shows and compares the effect of administration of 500 and 1000 mg of metformin twice during the day, once in the morning with the breakfast at 8 am and the second time in the evening with dinner at 8 pm. Metformin itself cannot prevent hyperglycemia and severe hyperglycemia. The higher amount of metformin causes more decrease in blood glucose level after each meal, but the
Figure 3.12: The simulated patient response to the administration of 500 mg metformin (black solid line) and 1000 mg metformin (blue dashed line) two times a day at 8 am and 8 pm.

Maximum dosage for metformin should not exceed 2500 mg per day. High doses of metformin may cause lactic acidosis which is the elevation of lactic acid that can cause a serious electrolyte imbalance.

Since the mono-therapy with metformin can not assure the satisfactory glycemic control and the patient still experience hyperglycemia, the insulin therapy alone or in combination with metformin can be considered as the treatment. Metformin's multiple effects not only benefit individuals with glycemic control but also help with cardiovascular problems, endocrine problems, retinopathies, nephropathies, cancer or decreased immunity, infections and weight gain. Therefore most pa-
Figure 3.13: The simulated patient response to the administration of 500 mg (black solid line) and 1000 mg (blue dotted line) metformin at 8 am and 8 pm along with the insulin injection according to regimen 9.

Patients continue the administration of metformin along with insulin therapy.

Figure 3.13 presents the blood glucose concentration as the result of the insulin injection according to regimen 9 and the administration of different dosages of metformin in the morning and the evening. The results show the satisfactory regulation of the blood glucose concentration in the region corresponding to normoglycemia without passing through hypoglycemia and hyperglycemia zones except for a negligible undershoot to hypoglycemia zone for the administration of 1000 mg of metformin.

Using the diabetic model presented in Chapter 2, the concentration of the glucose in other organs can be investigated besides the plasma glucose level. Figures
Figure 3.14: The blood glucose concentration in gut without administration of metformin (black solid line) and with administration of 1000 mg metformin at 8 am and 8 pm (blue dotted line)

Figure 3.14-3.16 illustrates the effect of 1000 mg metformin on the blood glucose concentration of gut, liver and periphery (blue dotted line) and compares it with the blood glucose profile without administration of metformin (black solid line).

The glucose profile in the gut (figure 3.14) assures the effect of metformin in decreasing gastrointestinal absorption of glucose. Figure 3.15 shows a decrease in blood glucose concentration administering metformin which is the result of the reduced liver’s production of glucose. Metformin also improves insulin sensitivity and increase the absorption of glucose in peripheral tissues which causes lower blood glucose level as shown in figure 3.16.
Figure 3.15: The blood glucose concentration in liver without administration of metformin (black solid line) and with administration of 1000 mg metformin at 8 am and 8 pm (blue dotted line)

3.4 Conclusion

The incorporation of the pharmacokinetic-pharmacodynamic model for oral agents and different insulin types into the available physiological model for type II diabetes mellitus makes it possible to compare various regimens and choose the most efficient one for each individual patient.

The simulation results confirm that mono-therapy with metformin does not assure the satisfactory glycemic regulation in type II diabetic patients and they eventually need insulin therapy.

In multiple daily injection therapy a mixture of short-acting insulin along with
Figure 3.16: The blood glucose concentration in periphery without administration of metformin (black solid line) and with administration of 1000 mg metformin at 8 am and 8 pm (blue dotted line)

intermediate or long-acting insulin are used to regulate the blood glucose. The proper selection of the insulin type, dose and injection time affects the quality of the blood glucose control. The efficient injection regimen is the one which is able to prevent hypoglycemia and hyperglycemia while bringing the blood glucose under 7 mmol/L in a timely manner during the postprandial state and gradually decrease it to around 4 mmol/L during the fasting state.

Amongst the investigated regimens the one containing mixture of 3:5 units regular and ultralente insulin in the morning and evening and 5 units of regular insulin for the lunch shows the best performance. Combinations of orally administered agents with insulin aid in achieving glycemic goals by taking advantage
of differing mechanisms of action such as the reduced glucose production rate in liver and increase the glucose uptake rate in peripheral tissues and gut.
Chapter 4

Development of a Controller for Blood Glucose Regulation in Type II Diabetes Using Proportional-Integral (PI) Control Strategy

4.1 Introduction

Continuous subcutaneous insulin infusion (CSII) with external pumps is an alternative to multiple daily injections (MDI) therapy and can be beneficial for type II diabetic patients who require intensive insulin therapy.

For type II diabetic patients being treated with CSII, a blood glucose automatic control system can be very useful and effective. The control objective is not as straightforward as that for type I since type II involves not only the pancreatic insulin secretion dysfunction but also malfunction of different organs such as insulin resistance in muscles and adipose tissues and impaired hepatic regulatory
effects [17]. During the past few decades, a variety of glucose control strategies for type I diabetic patients has been reported [75].

The proportional-integral-derivative (PID) control algorithm is known to be applicable to a wide variety of dynamic systems, and many past studies focused on conventional or modified linear PID controllers [76]. PID controllers are suitable to control the blood glucose concentration when the detailed knowledge of the patient's internal metabolic behavior is not available. The output data describing the patient's response to the specific input is the basis for control design [75].

Studies showed that the $\beta$ cells which are responsible for insulin secretion include a 3-phase response very similar to the characteristics of a PID. The three components of the $\beta$ cell model are proportional to glucose, the rate of the changes in glucose concentration and a slow increment corresponds to an integrator [77]. Steil et al. demonstrated a discrete PID control strategy is desirable for glucose control because of its ability to mimic the first- and second-phase responses that the pancreatic $\beta$ cells behave in the secretion of insulin [77, 78].

Bellazi et al. derived a proportional-derivative controller with a pole assignment strategy and tested in patients [79]. Chee et al. proposed a PID control system based on a sliding-scale approach and successfully tested it in patients in an intensive care unit [80].

Gantt et al. developed an asymmetric PI control algorithm to act properly during hypoglycemia and hyperglycemia states. The glucose measurement has been compared to the normal value, and the proportional gain of the controller has been adapted based on the output error. The negative values of the error, corresponding to hypoglycemia state treated more aggressively. The evaluation of the controller based on the modified minimal model showed that the asymmetric PI controller performed better compared to a normal PI, but still could not completely prevent the hypoglycemia state [81].

A switching PID control algorithm with a time-varying setpoint was proposed by Marchetti et al. A decision-making system was designed to determine the proper switching time for the controller which depends on direct blood glucose
measurement. Extended Hovorka model was used as an artificial patient to test the performance of the controller. The results showed improvements in the controlled blood glucose concentration profile compared with a manual insulin therapy [82].

Control scheme based on fuzzy logic control theory have also shown promising results in blood glucose control for type I diabetes and mimic the performance of the real pancreas [83–85].

However, to the best of our knowledge, none of these studies have been applied to the regulation of blood glucose in type II diabetes mellitus regarding insulin therapy. Although type I and type II diabetic patients share similar features such as symptoms and long-term complications, the homeostasis of blood glucose in type II diabetic patients is much more complicated than type I patients.

The target of blood glucose control is not a simple set point, but rather a range with different lower and upper bounds asymmetrically. Regarding the non-linear homeostasis of blood glucose, linear control strategies like PI controllers can still be considered but should be modified to deal with such nonlinearity. In this chapter, the nonlinearity between insulin and glucose as the input and output of the control loop is reduced by using the logarithm of blood glucose concentration as the controlled variable. On the other hand, a gain scheduling (GS) control scheme is developed to address the existing nonlinearity and improve the controller performance to achieve a desirable response.

Designing a sufficient GS controller depends on two factors. The proper selection of scheduling variables that capture the nonlinearities of the process and determination of the scheduling function by means of which the gains are changed as a function of the scheduling variable. Fuzzy logic has capabilities which can be used to implement effective scheduling gains [86].

Fuzzy Logic is also a tool for describing and analyzing unconventional constraints on a process. Fuzzy control systems can be an alternative to simple linear PI control or complicated model-based control, especially when applied to biomedical systems. Our literature survey found that a two-loop advisory control scheme for type I diabetic patients was developed by using fuzzy systems [87].
The application of fuzzy logic was proposed to act as an artificial pancreas [88]. A fuzzy-based closed-loop control algorithm was also proposed for type I patients [89].

In the current chapter, type II diabetic model presented in Chapter 2 is used as a base for the closed-loop simulations. In the following section, it is shown that the nonlinearity of the glucose-insulin interactions can be reduced by the application of logarithm of blood glucose concentration. Also, a conventional PI controller is modified to a gain scheduling (GS) PI controller by penalizing the feedback error using a fuzzy inference system (FIS) based on clinician knowledge and recommendations. Finally, the simulation results of a PI controller and the fuzzy-based GS PI controller is presented.

4.2 Feedback Control Strategy

Once the response of the body to insulin treatment is known, a clinician can determine the dosing for each individual patient considering the caloric intake and exercise level. Many intrinsic and extrinsic factors can affect the blood glucose which can vary from day to day. Intrinsic factors may be related to the metabolic rate of the day, stress, anxiety, or even having a simple respiratory tract infection. Exercise and diet are common extrinsic factors which alter the consumption of glucose and production of insulin. Therefore, monitoring of blood glucose for diabetic patients should be done more frequently if not continually. The current technological advance in diabetic care has made feedback blood glucose control possible. Portable continuous infusion pumps for insulin have been commonly used by type I patients. Continuous blood glucose sensors are available. However, their usage is less popular because the sensors can only last a few days long and may not be accurate. Therefore, patients usually act as both the feedback and feedforward controllers rather than relying on an automatic control device. This means that patients always dial-up the infusion rate for a short period before a meal to avoid hyperglycemia, and make frequent feedback adjustments if the glucose is not within the desired range.
The following sections suggest the possible modifications to develop a feedback control strategy which sufficiently regulate the blood glucose. The controller should be able to address the nonlinearity of the glucose-insulin interactions. Therefore, the application of logarithm of blood glucose and scheduling gains for a conventional PI controller are discussed.

4.2.1 Reducing Nonlinearity of Glucose-Insulin Interaction

The homeostasis of blood glucose in type II is complicated, and the patients deal with the malfunction of different organs which eventually leads to the deterioration of glucose homeostasis [14].

The model derived for type II diabetes mellitus should be able to represent the interactions between different organs and determine the concentrations of glucose and insulin along with the hormonal effects of glucagon. Model equations include mass balance equations over each sub-compartment and results in a set of nonlinear ordinary differential equations. The rate of mass accumulation is the net additive result of contributions by convection, diffusion, and any metabolic sources or sinks which add or remove mass from the sub-compartments. Since insulin is produced in the pancreas in a complex mechanism which cannot be described by simple mass balance equations, a separate model is considered for insulin production in the pancreas.

The controlled output of this system is the blood glucose concentration, which is regulated by the insulin infusion rate as the manipulated variable. According to the nonlinear factors appearing in the model equations, the relationship between the rate of changes in the blood glucose concentration and the infusion rate of insulin is highly nonlinear. Fig. 4.1 shows a typical such nonlinear relationship. Each point on this figure represents the gain of the system for specific amount of step change in the rate of insulin infusion as shown on the horizontal axis.

Cesar Palerm and Lane Desborough in a poster prepared for Medtronic Diabetes R&D session mentioned that using logarithm of the blood glucose concentration decrease the nonlinearity and make the data analysis simpler. In this
research, the same strategy is considered as a possible method to decrease the
nonlinearity of the response for type II diabetes. Figure 4.2 demonstrates the pro-
file of the logarithm of the absolute value of the gain for different amounts of step
change in the insulin infusion rate. The red lines represent the best linear regres-
sion model fit to the data in each figure. $R^2$ value for the suggested linear function
which relates the gain to the step changes in insulin infusion rate is 0.89, while
this value for the logarithm of the gains as a linear function of the insulin infusion
rate is 0.98. The comparison of these two values confirms that the logarithm of
the blood glucose can be employed to reduce the system nonlinearity.

Figure 4.3 presents the block diagram of the feedback control loop using PI
controller. The logarithm of the measured blood glucose is used as the feedback
Figure 4.2: Variation of the logarithm of the gain for different step changes (the black points connected with the blue line) and the regression line (dashed red line)

Figure 4.3: Block diagram of the feedback control strategy using logarithm of the blood glucose as the controlled variable
signal and compared to the logarithm of the setpoint to calculate the error. The controller calculates the insulin infusion rate based on the amount of error.

4.2.2 Gain Scheduling Control Strategy Based on Fuzzy Logic

As described in the previous section, the clinical objective of blood glucose control is not a single target (or a set point in standard control parlance). Due to the nonlinear homeostasis of blood glucose and asymmetric dynamics of hyperglycemic and hypoglycemic states a linear controller will not provide satisfactory performance. The large number of highly variable intrinsic and extrinsic factors within each patient makes it complicated and unappealing to use adaptive model-based predictive control - to both clinicians and patients alike. The gain scheduling (GS) control strategy is proved to be helpful in many areas dealing with nonlinear dynamics including biological systems [90].

The gain scheduling strategy enhances the performance of conventional PI controllers by facilitating the variations of controller parameters based on the changes of the plant operating conditions. An appropriate variable, known as scheduling variable should be chosen to detect the changes in operating conditions. Therefore, the gain values can be calculated through the implementation of a scheduling function by means of which the gains are changed as a function of the scheduling variable. The important consideration in the gain scheduling problem is the design of the switching logic to obtain a smooth plant response all over the operation range.

Fuzzy logic can be useful in the design procedure of scheduling function of GS controller as shown in previous studies [86]. In 1965, the concept of fuzzy sets was proposed by Zadeh [91]. A fuzzy set is a set without a clearly defined boundary, characterized by membership function which assigns a degree of membership to each element. Fuzzy systems can handle linguistic variables whose values are words. Contrary to variables in mathematics which usually take numerical values, linguistic variables can be defined in fuzzy logic to describe certain facts and express the underlying rules of a system. A membership function is assigned
to each linguistic variable. Although linguistic variables are less precise, they make it easier to incorporate common sense and expert knowledge into the set of rules to be used in fuzzy inference mechanism and deal with different types of uncertainties involving in most design problems [92].

Fuzzy inference systems consist of three main parts, a fuzzifier, an inference engine and a defuzzifier. In the fuzzification step, crisp input data are fuzzified using membership functions which represent linguistic variables. The inference engine is built by a set of fuzzy rules based on expert knowledge. By means of linguistic variables, common sense and knowledge from the clinicians can be easily incorporated into set of rules and used in fuzzy inference system. During the inferring step, those rules whose antecedents are satisfied will determine the fuzzy output. Finally, a numerical value of the fuzzy output is determined in the defuzzification step using the pre-defined membership functions of the outputs.

Fuzzy logic in combination with gain scheduling control strategy can be a useful tool to achieve the clinical control objective. The principle idea is to select the measured blood glucose concentration as the scheduling variable and apply fuzzy logic to determine the importance of the error and scheduling gains. Figure 4.4 is a simple block diagram to illustrate the control strategy. In this figure, the glucose measurement is being used as a feedback signal for the feedback controller and an input for the fuzzy logic inference system. A weighting factor is generated from the inference system and multiplied to the error between the glucose set point and measurement.

For the regulation of blood glucose in diabetic patients, the division of different blood glucose regions does not need to be as precise as the ones shown in figure 1.2. Therefore, in our approach, the linguistic variables are applied to different regions for the blood glucose level. A membership function is also assigned to each of these linguistic variables. Figure 4.5 shows the fuzzification design.

The Mamdani’s fuzzy inference method is the most commonly seen fuzzy methodology and is used in the current design. The input to this system is blood glucose level (G), and the output is the weighting factor to penalize the error ac-
Figure 4.4: Block diagram of the feedback control strategy using fuzzy inference system to define weighting factors

Figure 4.5: Fuzzy membership functions[10]
cording to the lower panel of figure 4.5. The proper fuzzy sets for inputs and outputs were defined by the clinical control objectives and experience explained in section 1.2.1. The set of allowable values of the blood glucose concentration is partitioned into four fuzzy sets corresponding to hypoglycemia (Hypo), normoglycemia (NG), postprandial (PP) and hyperglycemia (Hyper) states. When the risk of hypoglycemia or hyperglycemia is high, the penalizing weighting factor should be increased. On the other hand, in regions near normal glucose levels, only moderate control action may be sufficient. Accordingly, four fuzzy sets were created to generate an output as one of the four choices: small (S), normal (N), large (L), and extra large (XL).

Based on the definition of the input and output fuzzy sets, four IF-THEN rules were defined as follows:

- IF input is Hypo then output is XL.
- IF input is NG then output is S.
- IF input is PP then output is N.
- IF input is Hyper then output is L.

The output is calculated by the centroid defuzzification method. This method is also known as the center of gravity or center of area defuzzification and was developed by Sugeno [93]. It returns the center of the area under the curve.

The selection of the tuning parameters of the PI controller can be achieved by an off-line assessment using different performance indices. In this work, the IAE performance tuning method is used to obtain the controller tuning parameters [94] as follows:

\[
IAE = \int_{0}^{\infty} |e(t)| dt
\]
4.3 Simulation Results and Discussion

For a 70 kg diabetic adult patient, the usual daily caloric intake varies depending on the activity level. Clinically, a healthy person should be able to process 100 g of glucose without exceeding 11.1 mmol/L 4 to 5 hours after the intake. The closed-loop simulation assumes that the patient's initial blood glucose is around 7.0 mmol/L.

![Figure 4.6: Patient response to 100 g of meal disturbance at 100 min in absence of insulin infusion](image)

To provide a baseline for comparison, figure 4.6 shows the simulated response of a diabetic patient with no insulin infusion. The meal disturbance of 100 g glucose was introduced at time 100 min. Because the model represents a type II patient, the body is still able to produce insulin despite the reduced insulin production, increased insulin resistance, and impaired glucose regulation in the body tissue. Therefore, the small meal disturbance of 100 g glucose causes the simulated blood glucose to increase up to 17 mmol/L before returning to the normoglycemic range. It takes almost 6 hours after the intake to have the blood glucose back around 7 mmol/L.

As described in the previous section a PI controller is modified by reducing the nonlinearity between insulin, as the manipulated variable, and glucose, as the controlled variable, through using logarithm (log) of blood glucose. Also, a fuzzy inference system is designed as discussed in section 4.2.2 to produce variable
Figure 4.7: Response of the conventional PI controller with a 100 g meal disturbance at 100 min

gains for the PI controller. Figures 4.7 to 4.11 show the simulation results for conventional PI controller and the modified controllers.

Figure 4.7 presents the result of the application of conventional PI controller. Based on the IAE performance function, the tuning parameters of the controller were determined to be $K_P = 12.7$ and $K_I = 0.05$. The disturbance of 100 g glucose is introduced at 100 min to the simulated patient using conventional PI controller. PI controller performance is acceptable in preventing hyperglycemia, but it can not avoid hypoglycemia and the blood glucose traversed into the red zone of severe hypoglycemia. It demonstrates that a linear PI controller is not suitable for the non-linear blood glucose system. The bottom part of figure 4.7 shows the rate of
A conventional PI controller with the same tuning parameters is applied to the simulated patient using the logarithm of the blood glucose as the controlled variable. The result is demonstrated in figure 4.8. The conventional PI is capable of preventing hypoglycemia as the result of the reduced nonlinearity as discussed in section 4.2.1. However, the patient is exposed to high blood glucose for two hours as the glucose profile passes through the yellow zone of hyperglycemia before returning to normoglycemic zone. It is desired that the controller returns
Figure 4.9: Response of the fuzzy-based PI controller with a 100 g meal disturbance at 100 min

Figure 4.10: Block diagram of the feedback control strategy using fuzzy inference system to define weighting factors when logarithm of blood glucose is considered as the controlled variable
**Figure 4.11:** Response of the fuzzy-based PI controller with a 100 g meal disturbance at 100 min with nonlinearity reduction in the patient model using log of blood glucose

**Figure 4.12:** Weight factor from the fuzzy inference system
the blood glucose to the lower bound of the normoglycemic (dark green) zone which is not achieved by this controller design. Comparing to the previous design, less amount of insulin is delivered to the patient (bottom part of figure 4.8).

**Figure 4.13:** Block diagram of the feedback and feedforward control strategy

In figure 4.9, the fuzzy-based PI controller can keep the blood glucose within the normoglycemic zone most of the time with small undershoots to the hypoglycemic zone. This clearly shows the nonlinear nature of the fuzzy-logic-based controller which is able to handle the asymmetric control objective of blood glucose regulation. The controller can return the blood glucose from the postprandial state to the fasting state of the normoglycemic zone within 5 hours and maintain it within the safe zone most of the time.

The fuzzy gain scheduling PI controller can be considered using the logarithm of the measured blood glucose as the controlled variable to reduce the nonlinearity of the glucose-insulin interactions. The block diagram of such control strategy is presented in figure 4.10.

The performance of the fuzzy-based PI controller with using the logarithm of the blood glucose, presented in figure 4.11 shows even more improvement in blood glucose regulation. The controller returns the blood glucose to the lower bound of the normoglycemic zone after almost 5 hours without exceeding 11.1 mmol/L and prevents hypoglycemia state while keeping the blood glucose level close to the lower bound of the normoglycemic zone.
The weighting factors which are calculated by fuzzy inference system (FIS) is presented in figure 4.12. According to the importance of avoiding the danger of hypoglycemia state, the designed FIS assigns higher weights to the low blood glucose level rather than high blood glucose level as shown in figure 4.12. It helps the controller to act more aggressively to prevent the complications caused by low blood glucose concentration. As long as the blood glucose is in the normoglycemic zone, the weighting factors are small for the gradual return of the blood glucose to the lower bound of this zone.

In reality, patients always act as the feedforward controller which means that patients always provide themselves with some additional insulin before consum-
Figure 4.15: Response of the conventional PI controller with a 100 g meal disturbance at 100 min and 10 mU/min insulin injection at 100 for 3 hours with non-linearity reduction in the patient model using log of blood glucose.

Figure 4.13 demonstrates the block diagram of combined feedback and feedforward control strategy.

In the next set of simulations, an additional 10 mU/min of insulin is added to the body for 3 hours when the 100 g of glucose is introduced at 100 min. Figures 4.14 and 4.15 respectively present the responses of the conventional PI controller without and with nonlinearity reduction. The performances of the fuzzy-based PI controller are also depicted in figures 4.16 and 4.17 without and with using logarithm of blood glucose, respectively. In all figures, the glucose concentrations had an initial drop at the time of the additional insulin injection because insulin...
enters the body through the interstitial tissue much faster than glucose absorption through the digestive tract. Conventional PI and fuzzy-based PI controllers are already infused high amounts of insulin to the body and the additional insulin injection has a negligible effect on the quality of control. In the case of using the logarithm of blood glucose, receiving the additional insulin injection reduces the amount of hyperglycemia using conventional PI controller while the fuzzy-based PI controller remains acceptable for handling this meal disturbance.

**Figure 4.16:** Response of the fuzzy-based PI controller with a 100 g meal disturbance at 100 min and 10 \( mU/min \) insulin injection at 100 for 3 hours
Figure 4.17: Response of the fuzzy-based PI controller with a 100 g meal disturbance at 100 min and 10 mU/min insulin injection at 100 for 3 hours after non-linearity reduction in the patient model using log of blood glucose.

4.4 Conclusions

In this chapter, a conventional PI controller was modified to address the nonlinear homeostasis of the blood glucose regulation problem. Table 4.1 presents some of the characteristics of the designed controllers. The first three rows of table 4.1 summarizes the features applied in each of the designed controllers. Some of the controllers use the logarithm of the blood glucose to partially reduce the nonlinearity. Some others modify the feedback error by scheduling gains calculated by a fuzzy inference system. Some of the simulations considered the injection of the
additional insulin.

The next four rows show the performance of the designed controllers in preventing severe hyperglycemia, hyperglycemia, hypoglycemia and severe hypoglycemia. It can be seen that all the controllers can handle severe hyperglycemia, but controllers NO.1, NO.3, NO.5 and NO.7 do not avoid severe hypoglycemia (marked in red) and can not be sufficient for the blood glucose regulation. Amongst the rest, controllers NO.2, NO.4 and NO.6 cause hyperglycemia (marked in yellow) but the amount of overshoot to the hyperglycemia zone is negligible for controllers NO.4 and NO.6. Therefore, these two controllers along with controller NO.8 can be considered as the potential candidates for the blood glucose regulation.

All of the controllers are able to bring back the blood glucose concentration under 7 mmol/L in about 5 hours. It is desired that the controller gradually brings back the blood glucose to the lower bound of normoglycemia zone around 4 mmol/L. Amongst controllers NO.4, NO.6 and NO.8, the blood glucose concentration at the settling time for controller NO.6 is around 5.5 mmol/L which is still high for the fasting state. Therefore, controllers NO.4 and NO.8 are better candidates since they can keep the blood glucose level in the normal range with the infusion of less amount of insulin in total which can be seen in the last row of table 4.1.

The comparison of the designed controllers demonstrates the superiority of a gain-scheduling PI controller based on fuzzy logic using the logarithm of the blood glucose over other controllers for the control of blood glucose for type II diabetic patients.
Table 4.1: Comparison of the designed controllers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NO.1</th>
<th>NO.2</th>
<th>NO.3</th>
<th>NO.4</th>
<th>NO.5</th>
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<td>Is the log of blood glucose applied to reduce the nonlinearity?</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
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<td>Is scheduling gains considered using FIS?</td>
<td>NO</td>
<td>NO</td>
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<td>NO</td>
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<td>Is the additional insulin injected with the meal disturbance?</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<td>Does the controller cause severe hyperglycemia?</td>
<td>NO</td>
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<td>Does the controller cause hyperglycemia?</td>
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<td>Does the controller cause hypoglycemia?</td>
<td>YES</td>
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<td>Does the controller cause severe hypoglycemia?</td>
<td>YES</td>
<td>NO</td>
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<td>How long does it take to bring the blood glucose under 7 mmol/L? (hours)</td>
<td>5</td>
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<td>what is the blood glucose concentration at settling time? (mmol/L)</td>
<td>2</td>
<td>5.5</td>
<td>3.5</td>
<td>4</td>
<td>2</td>
<td>5.5</td>
<td>3.5</td>
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<tr>
<td>what is the total amount of infused insulin? (Units)</td>
<td>48.6</td>
<td>3.9</td>
<td>43.1</td>
<td>7.3</td>
<td>48.7</td>
<td>5.1</td>
<td>42.8</td>
<td>7.5</td>
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Chapter 5

Development of a Controller for Blood Glucose Regulation in Type II Diabetes Using Predictive Control Strategy

5.1 Introduction

It can be argued that after PID controller, model predictive controller (MPC) is the most influential developed algorithms in control [47]. The concept of predictive control can be applied to control a wide variety of processes [95] and has made huge inroads into various application areas including biomedical engineering since it is very intuitive and easy to be understood for those with a limited knowledge of control.

The term Model Predictive Control (MPC) designates a range of control strategies which make explicit use of the process model to predict the future behaviour of the system. The control signal is obtained by solving an optimization such that the future output of the process converges towards the reference trajectory. The ability of MPC to impose constraints on both manipulated and controlled vari-
ables, alongside the possibility of adjusting the optimization objective function according to the problem requirements, introduces it as an alternative to enhance the performance of blood sugar control systems for diabetic patients. MPC has the capability of anticipating the impact of the meal disturbance and adapting the proper amount of insulin injection in time. The clinical acceptable insulin injection amount per day is limited; on the other hand insulin pump mechanism restrains the insulin infusion rate. Both constraints can be considered by defining the boundaries for the insulin injection rate in the model predictive control design. Furthermore, blood glucose concentration can be bounded with the lower and upper level of the normoglycemia zone.

There are many studies in the literature considering the model predictive control strategy to improve the blood glucose regulation in type I diabetic patients to pursue the aim of developing artificial pancreas [75]. However, to the best of our knowledge none of these studies consider the problem of maintaining the blood glucose in normal range for type II diabetic patients. Some of the studies considered the problem for type I are listed below.

Parker et al. [96, 97] represented a linear MPC algorithm using a self-developed linear step-response model as the internal model. The evaluation of the controller has been done by the application of the extended version of the Sorensen [4, 74] patient model for type I. The behaviour of the controller was investigated in response to 50 g oral glucose tolerance tests.

Lynch et al. [98, 99] applied the 5-th order linearized minimal model to design a linear MPC. A first order meal disturbance model from either Lehmann et al. [74] or Fisher [100] and a first order model for glucose transport from plasma to interstitium was added to the internal model of the controller. The controller showed satisfactory results in presence of 50 g glucose meal disturbance and measurement and disturbance noise while Sorensen model [4] for type I diabetic patient was used as artificial patient.

An advisory mode linear MPC algorithm has been proposed by Gillis et al. [101] including the linearized minimal model modified by sub models of Hovorka
et al. [56] to determine the subcutaneous insulin infusion rate in type I diabetic patients based on subcutaneous glucose measurements in presence of 50 g glucose meal ingestion. Lack of the information for individual subject and the model mismatch problem was compensated by adding an unknown disturbance term. A discrete linear MPC was presented by Magni et al. [102, 103] in which they avoided the state estimation by using Dalla Man et al. model [57, 104] with input-output representation of insulin rate and blood glucose concentration. Evaluation of the controller performance was done by using the whole glucose insulin model of Dalla Man et al. [57, 104]. The comparison of the proposed controller with a common PID control method showed better regulation of the blood glucose, closer to the setpoint, and prevention of hypoglycemia state in presence of the discrete linear MPC.

Dua et al. [105] selected Bergman model [54] to develop the model predictive controller. They suggested parametric programming approach to reduce the repetitively solved on-line optimization problem to a simple function calculation which explicitly defines the relationship between the current blood glucose concentration and the optimal insulin injection rate.

Non-linear Model predictive controller has been proposed in some studies for the blood glucose control in type I diabetes mellitus. One of the studies considering the design of a continuous nonlinear MPC was done by Magni et al. [103] including the entire nonlinear glucose-insulin model of Dalla Man et al. [57, 104]. Nonlinear MPC in comparison with linear MPC using the same model showed improvement by reducing post-prandial hyperglycemia.

Another nonlinear MPC was proposed by Hovorka et al. [56]. It is a self-adapting nonlinear MPC algorithm based on their 8th order nonlinear glucose-insulin model. Since the insulin sensitivity of glucose consuming cells changes according to the day time, physical activity, patient age and health status, some parameters were defined to describe the insulin sensitivity which were re-estimated at each control step depending on the current blood glucose measurement.

However, better performance of nonlinear MPC will achieve in the expense
of the increased computational efforts in comparison with linear MPC. Decisions should be made whether such improvement is worthwhile.

The mathematical model representing the glucose-insulin interactions is a non-linear model and has a slow dynamic for performing on-line optimization. Therefore, in this chapter model predictive controller is developed using multiple linearized models presented in section 5.3. The optimization problem of designing model predictive controller was solved using the multi parametric quadratic programming approach explained in the following section. The formulation of the state estimator is presented in section 5.4. Section 5.5 represents the simulation results.

5.2 Predictive Control Strategy

The model predictive control (MPC) strategy makes explicit use of the process model to predict the future behavior of the system. The various MPC algorithms use different types of models to represent the process and use a customized objective function that is to be minimized. The control signal is obtained by solving an optimization problem such that the future output of the process converges towards a reference trajectory. It is also known as receding horizon control because at each instant an open-loop optimal control problem is solved over a finite horizon. Only the first control signal of the sequence is applied to the system. At the next time step, the horizon is moved toward the future and a new optimal control problem is solved based on the new measurements over a shifted prediction horizon [106,107].

5.2.1 Linear Model Predictive Control (LMPC)

The formulation of the optimization problem for designing the model predictive controller was presented in [108]. Consider the general mathematical description
of a discrete-time, linear time invariant state-space system:

\[ x_{t+1} = Ax_t + Bu_t \]
\[ y_t = Cx_t \]  \hspace{1cm} (5.1)

subject to the following constraints:

\[ y_{min} \leq y_t \leq y_{max}, \]
\[ u_{min} \leq u_t \leq u_{max}, \]

where \( x_t \in \mathbb{R}^n \), \( u_t \in \mathbb{R}^m \), and \( y_t \in \mathbb{R}^p \) are the state, input, and output vectors, respectively, subscripts \( min \) and \( max \) denote lower and upper bounds, respectively, and the matrix pair \((A, B)\) is stabilizable. The linear MPC problem for regulating system (5.1) to the origin is presented as the following quadratic programming problem:

\[
\min_U J(U, x_t) = x_t^{\prime+N_y}Px_{t+N_y} + \sum_{k=0}^{N_y-1} x_{t+k}^{\prime}Qx_{t+k} + u_{t+k}^{\prime}Ru_{t+k} \]
\hspace{1cm} (5.2)

subject to:

\[ y_{min} \leq y_t \leq y_{max}, \quad k = 1, \ldots, N_c \]
\[ u_{min} \leq u_t \leq u_{max}, \quad k = 1, \ldots, N_c \]
\[ x_{t+1} = x_t, \]
\[ x_{t+k+1} = Ax_{t+k} + Bu_{t+k}, \quad k \geq 0 \]
\[ y_{t+k+1} = Cx_{t+k}, \quad k \geq 0 \]
\[ u_{t+k+1} = Kx_{t+k}, \quad N_u \leq k \leq N_y \]

where \( U \equiv \{u_t, \ldots, u_{t+N_u-1}\} \), \( Q = Q' \geq 0 \), \( R = R' > 0 \), \( P \geq 0 \) and \( N_u, N_y, N_c \) are the input, output, and constraint horizons, respectively, such that \( N_y \geq N_u \), \( N_c \leq N_y - 1 \), and \( K \) is a stabilizing state feedback gain. The optimization problem
in [5.2] is solved repetitively at each time $t$ for the current state $x_t$ and the vector of predicted state variables, $x_{t+1|t}, \ldots, x_{t+k|t}$ at time $t+1, \ldots, t+k$, respectively, and corresponding optimal control actions are obtained:

$$U^* = \{u^*_t, \ldots, u^*_{t+k+1}\},$$  \hspace{1cm} (5.3)

The input that is applied to the system is the first control action:

$$u_t = u^*_t,$$  \hspace{1cm} (5.4)

and the procedure is repeated at time $t+1$, based on the new state $x_{t+1}$.

The state feedback gain, $K$, and the terminal cost function matrix, $P$, usually are used to guarantee stability for the MPC. $K$ and $P$ can be chosen as the solutions of the unconstrained, infinite-horizon linear quadratic regulation (LQR) problem, i.e., when: $N_c = N_u = N_y = \infty$

$$K = -(R + B'PB)^{-1}B'PA,$$
$$P = (A + BK)'P(A + BK) + K'RK + Q,$$  \hspace{1cm} (5.5)

The following relation is derived from equation (5.1),

$$x_{t+k|t} = A^k x_t + \sum_{j=0}^{k-1} A^j Bu_{t+k-1-j-t},$$  \hspace{1cm} (5.6)

Substituting equation (5.6) in equation (5.2) results in the following quadratic programming (QP) problem:

$$J^*(x_t) = \min_U \left\{ \frac{1}{2} U'HU + x'_t FU + \frac{1}{2} x'_t Yx(t) \right\},$$  \hspace{1cm} (5.7)

subject to:

$$GU \leq W + Ex_t$$

where $U \equiv \{u_t, \ldots, u_{t+N_u-1}\} \in \mathbb{R}^n$, $s \equiv mN_u$ is the vector of optimization vari-
ables, and $H, F, Y, G, W, E$ are obtained from $Q, R$ and the system matrices. The term involving $Y$ in equation (5.7) is usually dropped, since it does not affect the optimal solution.

MPC is applied by repetitively solving the QP problem in (5.7) at each time $t \geq 0$ for the current value of the states. Due to this formulation, the solution $U^*$ of the QP is a function $U^*(x_t)$ of the state $x_t$. The control action is given by:

$$u_t = \begin{bmatrix} I & 0 & \cdots & 0 \end{bmatrix} U^*(x_t)$$ (5.8)

The problem in equation 5.2 obviously describes the constrained linear quadratic regulation problem, while equation 5.7 is the formulation of the MPC as a QP optimization problem [106–111].

The optimization problem can be modified to better address the control objectives for regulating the blood glucose level. It is desired to keep the blood glucose concentration within the certain range. The fact is that the boundaries of such range can be slightly violated while being still acceptable. On the other hand violation of the lower bound is more crucial because of the higher dangers of hypoglycemia state for the patient. The following modifications help to improve the controller design.

**Soft constraints**

As discussed the constraints on the output are soft which means that they are preferred but not required to be satisfied and can be partially violated. The constraints can be modified as:

$$y_{min} - \nu_l \leq y_t \leq y_{max} + \nu_u$$ (5.9)

which means that the output is still acceptable to some degree if it violates the minimum and the maximum values less than $\nu_l$ and $\nu_u$, respectively. $\nu_l$ and $\nu_u$ are chosen by the designer to fulfill the requirements of the patient.

The inequality constraints could be expressed in normalized form so they are
fully satisfied if they are negative:

\[ y_n = \begin{cases} 
1 - \frac{y}{y_{min}} & \text{for lower bound} \\
\frac{y}{y_{max}} - 1 & \text{for upper bound}
\end{cases} \quad (5.10) \]

where \( y_n \) is the normalized inequality constraint for the output \( y \). \( y_{min} \) and \( y_{max} \) are lower and upper bounds of the output, respectively. Therefore, the degree of acceptance is assigned to the output by using a linear membership function as follows:

\[ \mu_{y_n} = \begin{cases} 
1 & y_n \leq 0 \quad \text{fully satisfied} \\
\frac{d - y_n}{d} & 0 < y_n \leq d \\
-1 & y_n \leq d \quad \text{strongly violated}
\end{cases} \quad (5.11) \]

where \( \mu_{y_n} \) is the membership function for each inequality constraint on the output. \( d \) is the acceptable tolerance in normalized form. \( \mu_{y_n} \) is used to update the constraint matrices represented in equation (5.7). The constraints can be divided into two parts: \( GU \leq W_1 \) for the input and \(-Ex_t \leq W_2\) for the output, in which \( W = W_1 + W_2 \). \( E \) and \( W_2 \) are updated by multiplication of \( \mu_{y_n} \) to partially allow the violations in the lower and upper bounds of the output.

**Asymmetric control objective**

The membership function, as defined in equation (5.11), is used to update the constraint on the upper and lower bounds of the output to prevent hyperglycemia and hypoglycemia. Although both hyperglycemia and hypoglycemia states should be avoided to handle diabetes complications, hypoglycemia is much more dangerous since patients can have a seizure or go into the coma due to low blood glucose.

In order to address the asymmetric nature of the control objective, the membership function, \( \mu_{y_n} \) is considered to be \(-10\) instead of \(-1\) for the time that the lower bound is strongly violated. This makes the controller act more aggressively in preventing hypoglycemia.
Despite the fact that efficient QP solvers are available to solve equation (5.7), computing the input online may require significant computational effort. In the next section, the parametric optimization approach is discussed to reduce the computational effort and also represents a lookup-table to find the proper insulin infusion rates as a function of the states.

5.2.2 Multi-Parametric Quadratic Programming Approach

As discussed before, in model predictive control strategy the control signal is calculated by solving an optimization problem. The optimizer should be run at regular time intervals, which requires large on-line computational efforts. Thus, it is fair to state that an efficient implementation of on-line optimization tools relies on a quick and repetitive on-line computation of optimal control actions.

Parametric programming approach can be considered to avoid this repetitive solution. The optimization problems with a quadratic performance criterion and linear constraints are formulated as multi-parametric quadratic programs (mp-QP) to design model predictive controller. The input and state variables are treated as optimization variables and parameters, respectively, and the control variables are obtained as an explicit function of the state variables. Therefore, the on-line optimization is solved off-line and breaks down into simple function evaluations, at regular time intervals, for the given state of the system to compute the corresponding control actions. This results in a very small computational effort in comparison with a repetitively solving of an optimization problem.

It can be shown that the control law is piece-wise linear and continuous. Thus, the on-line control computation reduces to the simple evaluation of an explicitly defined piecewise linear function of the states [108, 112–114]. The following linear transformation is considered to transform the QP problem (5.7) into a multi parametric programming problem:

\[ z \equiv U + H^{-1}F'x_t \]  

(5.12)
The quadratic programming (QP) problem described in (5.7) is then formulated to the following multi parametric quadratic programming (mp-QP) problem:

\[ V_z(x_t) = \min_{z} \frac{1}{2} z'Hz \]  

subject to

\[ Gz \leq W + Sx_t \]

where \( S = E + GH^{-1}F' \), \( z \) is the vector of optimization variables and \( x_t \) is the vector of parameters.

The main advantage of writing equation (5.2) in the form given in equation (5.13) is that \( z \) and \( U \) can be obtained as an affine function of \( x \) for the complete feasible space of the states.

The following theorem has to be established to proceed with a method to solve equation (5.13). The proofs of this theorem can be found in [112].

**Theorem 1.** Let \( x_0 \in \mathbb{R} \) be a vector of parameters and \((z_0, \lambda_0)\) be a KKT pair for problem (5.13), where \( \lambda_0 = \lambda_0(x_0) \) is a vector of non-negative Lagrange multipliers, \( \lambda \) and \( z_0 = z(x_0) \) is feasible in equation 5.13. Also assume that the (i) linear independence constraint satisfaction and (ii) strict complementary slackness conditions hold. Then, there exists in the neighbourhood of \( x_0 \) a unique, once continuously differentiable function \([z(x), \lambda(x)]\) where \( z(x) \) is a unique isolated minimizer for equation 5.13, and

\[ \left( \begin{array}{c} \frac{dz(x_0)}{dx} \\ \frac{d\lambda(x_0)}{dx} \end{array} \right) = -(M_0)^{-1}N_0 \]  

where

\[ M_0 = \begin{pmatrix} H & G^T_1 & \cdots & G^T_q \\ -\lambda_1 G_1 & -V_1 & \cdots & \\ \vdots & \vdots & \ddots & \\ -\lambda_p G_q & & & -V_q \end{pmatrix} \]
where $G_i$ denotes the $i$th row of $G$, $S_i$ denotes the $i$th row of $S$, $V_i = G_iz_0 - W_i - S_ix_0$, $W_i$ denotes the $i$th row of $W$, and $Y$ is a null matrix of dimension $(s \times n)$.

The optimization variable $z_x$ can then be obtained as an affine function of the state $x_t$ by exploiting the first-order Karush-Kuhn Tucker (KKT) conditions for equation (5.13).

**Theorem 2.** Let $x$ be a vector of parameters and assume that assumptions (i) and (ii) of Theorem 1 hold. Then, the optimal $z$ and the associated Lagrange multipliers $\lambda$ are affine functions of $x$.

An observation, resulting from Theorems 1 and 2, is given in the next corollary.

**Corollary 1.** From Theorem 1 and 2,

$$\begin{bmatrix} z(x) \\ \lambda(x) \end{bmatrix} = -(M_0)^{-1}N_0(x-x_0) + \begin{bmatrix} z_0 \\ \lambda_0 \end{bmatrix}$$

(5.15)

The results of Theorems 1 and 2 and Corollary 1 are summarized in the following theorem:

**Theorem 3** For the problem in equation (5.13) let $x_0$ be a vector of parameter values and $(z_0, \lambda_0)$ a KKT pair, where $\lambda_0 = \lambda_0(x_0)$ is a vector of non-negative Lagrange multipliers, $\lambda$, and $z_0 = z(x_0)$ is feasible in equation (5.13). Also assume that (i) the linear independence constraint qualification and (ii) the strict complementary slackness conditions hold. Then,

$$\begin{bmatrix} z(x) \\ \lambda(x) \end{bmatrix} = -(M_0)^{-1}N_0(x-x_0) + \begin{bmatrix} z_0 \\ \lambda_0 \end{bmatrix}$$

(5.16)

where

$$M_0 = \begin{pmatrix} H & G_1^T & \cdots & G_q^T \\ -\lambda_1G_1 & -V_1 & \cdots & \\ \vdots & \vdots & \ddots & \\ -\lambda_pG_q & & & -V_q \end{pmatrix}$$

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where \( G_i \) denotes the \( i^{th} \) row of \( G \), \( S_i \) denotes the \( i^{th} \) row of \( S \), \( V_i = G_i z_0 - W_i - S_i x_0 \), \( W_i \) denotes the \( i^{th} \) row of \( W \), and \( Y \) is a null matrix of dimension \((s \times n)\).

The presented theorem shows that the solution \( z(x) \) and \( \lambda(x) \) can be obtained for any parameter vector \( x \) from equation (5.16), given the solution \( z_0 \) and \( \lambda_0 \) for a specific vector of parameters \( x_0 \). Thus, the optimization variable \( z \) and eventually the control sequence \( U \) are linear, affine functions of the state \( x \). Therefore, the sequence of control actions is obtained as an explicit function of the state. It remains now to establish for which values of the parameter (state) \( x \), this solution remains optimal. The set of \( x \) where the solution of equation (5.16) remains optimal is defined as the critical region \((CR^0)\) and can be obtained as follows.

Let the critical region, \( CR^R \) represent the set of inequalities obtained (i) by substituting \( z(x) \) into the inactive constraints in equation 5.13, and (ii) from the positivity of the Lagrange multipliers corresponding to the active constraints, as follows:

\[
CR^R = \{ \tilde{G}z(x) \leq \tilde{W} + \tilde{S}x(t), \tilde{\lambda}(x) \geq 0 \} \tag{5.17}
\]

then \( CR^0 \) is obtained by removing the redundant constraints from \( CR^R \) as follows:

\[
CR^R = \triangle\{CR^R\} \tag{5.18}
\]

where \( \triangle \) is an operator which removes the redundant constraints. Since for a given space of state variables, \( X \), so far we have characterized only a subset of \( X \), i.e., \( CR^0 \subseteq X \), in the next step the rest of the region \( CR^{rest} \), is obtained as follows:

\[
CR^{rest} = X - CR^0 \tag{5.19}
\]

More information on identifying the regions can be found in [115]. The above steps, 5.16-5.19, are repeated and a set of \( z(x), \lambda(x) \) and corresponding \( CR^0 \) is obtained. The solution procedure terminates when no more regions can be obtained, i.e., when \( CR^{rest} = \emptyset \). The regions with the same solution can be unified to give a
The optimal control sequence $U^*(x)$, once $z(x)$ is obtained by equation 5.16, is calculated from equation 5.12.

$$U^*(x) = z(x) - H^{-1}F'x \quad (5.20)$$

Finally, the feedback control law is given by:

$$u_t = \begin{bmatrix} I & 0 & \cdots & 0 \end{bmatrix} U^*(x_t) \quad (5.21)$$

### 5.3 Prediction Model for Type II Diabetes

The number of experiments that can be performed on a human body is restricted due to ethical standards and risks posed to the subject. On the other hand, it is necessary to obtain reliable information from diabetic patients to describe the glucose-insulin interactions. Mathematical modeling can be considered as an alternative approach to provide sufficient information about the medical status of the patient. Dynamic modeling of glucose metabolism is helpful to evaluate control strategies developed for diabetic patients to prevent serious and irreversible harm to the subject. The model derived for type II diabetes mellitus should be able to represent the interactions between different organs and determine the concentrations of glucose and insulin along with the hormonal effects of glucagon.

The homeostasis of blood glucose in type II is complicated and the patients deal with the malfunction of different organs as described in 1.1.2 which eventually leads to the deterioration of glucose homeostasis [14].

To develop a control system based on MPC, a linear model of the patient is needed. Such a model can be built up from a set of experimental data. Because of many limitations in carrying out human experimental studies, the available dynamic model described in Chapter 2 can be used as a simulator of the patient body to collect input-output data and develop prediction model for designing MPC.

According to the nonlinear factors appearing in the model equations, the re-
The relationship between the rate of changes in the blood glucose concentration and the infusion rate of insulin is highly nonlinear. Multiple linear models have been considered to better represent such a nonlinear behavior of glucose-insulin interactions. Each model is a discrete state-space model with two states and was obtained using the MATLAB system identification toolbox. One of these models represents the blood glucose concentration corresponding to severe hypoglycemia, hypoglycemia and fasting states (low blood glucose level), the second one is for postprandial and postabsorptive states of normoglycemia zone (normal blood glucose level) and the third one is for the high blood glucose level in hyperglycemia and severe hyperglycemia states as depicted in figure 1.2. Equation (5.22) shows the model structure and the matrices for each model are presented in table 5.1.

\[
x_{t+1} = Ax_t + Bu_t + Ke(t) \\
y_t = Cx_t + e(t)
\]

(5.22)

**Table 5.1: Prediction models matrices**

<table>
<thead>
<tr>
<th></th>
<th>Severe hypoglycemia, hypoglycemia and fasting states</th>
<th>Normoglycemia state</th>
<th>Severe hyperglycemia and hyperglycemia states</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.792 -0.015</td>
<td>0.849 0.026</td>
<td>0.851 -0.112</td>
</tr>
<tr>
<td></td>
<td>[-0.042 0.794]</td>
<td>[-0.084 0.791]</td>
<td>[-0.149 0.682]</td>
</tr>
<tr>
<td>B</td>
<td>-0.0235 0.0009</td>
<td>-0.0017 0.0003</td>
<td>-0.0061 0.0002</td>
</tr>
<tr>
<td></td>
<td>[-0.0816 0.0014]</td>
<td>[-0.018 0.0002]</td>
<td>[-0.0143 0.0002]</td>
</tr>
<tr>
<td>C</td>
<td>7.234</td>
<td>9.85</td>
<td>18.13</td>
</tr>
<tr>
<td></td>
<td>[-2.205]</td>
<td>[-1.56]</td>
<td>[-7.895]</td>
</tr>
<tr>
<td>K</td>
<td>0.159 0.067</td>
<td>0.113 0.086</td>
<td>0.650 0.289</td>
</tr>
</tbody>
</table>

The inputs of these models (u) are insulin infusion rate (mU/min) and meal glucose disturbance (mg/min), and the output (y) is glucose concentration (mmol/L). x is the vector of two states. The sampling time is 5 minutes which is suitable for
the measurement sensor.

## 5.4 State Estimation

Since the blood glucose concentration is the only measurement that we have, a state estimator should be designed to obtain the current estimation of the states at each sampling time. The prediction model is linear and a steady-state Kalman filter can be designed.

\[
\begin{align*}
  x[t+1] &= Ax[t] + B(u[t] + \omega[t]) \\
  y[t] &= Cx[t]
\end{align*}
\]  

(5.23)

Considering equation (5.23) as the model with gaussian noise \(\omega[t]\) on the input \(u[t]\), the equations of the steady-state Kalman filter are as follows:

**Measurement update:**

\[
\hat{x}[t|t] = \hat{x}[t|t-1] + M(y_u[t] - C\hat{x}[t|t-1])
\]

(5.24)

**Time update:**

\[
\hat{x}[t+1|t] = A\hat{x}[t|t] + Bu[t]
\]

(5.25)

\(y_u\) is the output measurement, \(\hat{x}[t|t-1]\) is the estimation of \(\hat{x}[t]\), given past measurements up to \(y_u[t-1]\) and \(\hat{x}[t|t]\) is the updated estimate based on the last measurement, \(y_u[t]\).

Equation (5.25) predicts the value of the state one step ahead, given the current estimation (\(\hat{x}[t|t]\)). Equation (5.24) then adjusts this prediction based on the new measurement \(y_u[t+1]\). The correction term is a function of the difference between the measured and predicted values of \(y[t+1]\):

\[
y_u[t+1] - C\hat{x}[t+1|t]
\]

(5.26)

The gain \(M\) in equation (5.24) is chosen to minimize the steady-state covariance.
of the estimation error, given the noise covariances as follows:

\[ E(\omega'[t]\omega'[t]^T) = Q \quad E(\nu'[t]\nu'[t]^T) = R \quad E(\omega'[t]\nu'[t]^T) = 0 \]  

Combining equation 5.24 and 5.25 results in the following equation for the Kalman filter (equation 5.28) which gives the optimal estimates of the states and the output.

\[
\hat{x}[t+1|t] = A(I - MC)\hat{x}[t|t-1] + Bu[t] + AM\nu[t] \\
\hat{y}[t|t] = C(I - MC)\hat{x}[t|t-1] + CM\nu[t] 
\]  

(5.28)

More details on state estimation and Kalman filter can be found in [116, 117]

### 5.5 Simulation Results and Discussion

The model predictive controller was designed by using multiple linear prediction models as discussed in section 5.3. The application of the model predictive controller gives the opportunity of imposing constraints on the variables. The first constraint confines the blood glucose concentration to be within the desired range which is below 11 mmol/L after a meal ingestion during the postprandial state, and below 7 mmol/L, as close as possible to 4 mmol/L, during the fasting state. The second constraint keeps the insulin infusion rate between 0 to 100 mU/min which is suitable for an insulin pump. Soft constraints for the blood glucose concentration were introduced as shown in equation 5.9 of section 5.2. The allowable violation degrees, \( \nu_l \) and \( \nu_u \), are 1 for both lower and upper bounds of the constraints on the blood glucose concentration.

The block diagram of the control strategy is demonstrated in figure 5.1.

For the evaluation of the controller performance, the nonlinear model of the patient has been used as the simulated patient to predict the current value of the output (the blood glucose concentration) for the current input (insulin infusion rate).

In order to implement the model predictive controller based on parametric
programming, the states associated with the current measurement of the blood glucose concentration should be calculated through a state estimator. Therefore, the region corresponding to the states is identified to compute the optimal control action.

The proper linearized model is selected based on the estimated states from the models presented in section 5.3 and used to predict the future outputs.

The asymmetric objective function and the soft constraints are introduced to the optimizer block. The optimization problem is solved using the multiparametric quadratic programming approach, which results in partitioning of the space of the feasible states into polyhedral regions. High prediction horizons increased the computational efforts but did not improve the performance that much, so the prediction horizon is set to two. The steps of mp-QP algorithm, explained in [112], are as follows:

- Step 1: for a given space of $x$ solve equation 5.13 by treating $x$ as a free variable and obtain $[x_0]$
• Step 2: in equation 5.13 fix $x = x_0$ and solve equation 5.13 to obtain $[z_0, \lambda_0]$
• Step 3: obtain $[z(x), \lambda(x)]$ from equation 5.16
• Step 4: define $CR^R$ as given in equation 5.17
• Step 5: from $CR^R$ remove redundant inequalities and define the region of optimality $CR^0$ as given in equation 5.18
• Step 6: define the rest of the region, $CR^est$, as given in equation 5.19
• Step 7: if no more regions to explore, go to the next step, otherwise go to step 1
• Step 8: collect all the solutions and unify a convex combination of the regions having the same solution to obtain a compact representation

The control law for each of the partitions of the state-space was obtained by using the above algorithm. The region boundaries and corresponding control law which is an affine function of the states are reported in tables 5.2, 5.3 and 5.4 for the model corresponding to low, normal and high blood glucose levels, respectively.

In order to provide a baseline for the assessment of the designed controller, some standard clinical tests can be performed. Oral glucose tolerance test (OGTT) is a common test in which a standard amount of dissolved glucose in water is given to the patient to see how the body respond to glucose intake in the absence of injected insulin. Figure 5.2 presents the blood glucose concentration for introducing a 100 g glucose disturbance at time 100 minutes to the simulated patients when no control is applied.

The result shows an increase in blood glucose concentration which would cause the patient to experience hyperglycemia and severe hyperglycemia states for three hours before returning to normoglycemia zone. The pancreas of type II diabetic patients can still secrete some but not the adequate amount of insulin, and the patient needs the exogenous insulin injection. The basal blood glucose

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Table 5.2: Parametric solution regions for low blood glucose concentration (< 7 mmol/L)

<table>
<thead>
<tr>
<th>Region#</th>
<th>Region boundary</th>
<th>Insulin Infusion Rate</th>
</tr>
</thead>
</table>
| 1       | \[
\begin{bmatrix}
-11.83 & 13.18 \\
-1 & 0 \\
0 & -1 \\
1 & 0 \\
0 & 1
\end{bmatrix}x \leq
\begin{bmatrix}
0 \\
0 \\
0 \\
1.5 \\
1.5
\end{bmatrix}
\] | \[7.14\] |
| 2       | \[
\begin{bmatrix}
11.83 & -13.18 \\
-1 & 0 \\
0 & 1
\end{bmatrix}x \leq
\begin{bmatrix}
-7.14 \\
0 \\
-6.5 \\
1.5
\end{bmatrix}
\] | \[-7.23 -2.2\] \(x + 4\) |

Table 5.3: Parametric solution regions for normal blood glucose concentration (7 – 11 mmol/L)

<table>
<thead>
<tr>
<th>Region#</th>
<th>Region boundary</th>
<th>Insulin Infusion Rate</th>
</tr>
</thead>
</table>
| 1       | \[
\begin{bmatrix}
-34.63 & 38.47 \\
-1 & 0 \\
0 & -1 \\
1 & 0
\end{bmatrix}x \leq
\begin{bmatrix}
0 \\
0 \\
0 \\
1.5
\end{bmatrix}
\] | \[-7.25\] |
| 2       | \[
\begin{bmatrix}
34.63 & -38.47 \\
-1 & 0 \\
1 & 0 \\
0 & 1
\end{bmatrix}x \leq
\begin{bmatrix}
7.25 \\
0 \\
1.5 \\
1.5
\end{bmatrix}
\] | \[-9.85 -1.56\] \(x + 4\) |

level for the simulated patients is around 7 mmol/L and the available insulin in the body returns the blood glucose concentration to normoglycemia zone 6 hours after the 100 g glucose administration.

The model predictive controller is implemented to calculate the proper insulin
Table 5.4: Parametric solution regions for high blood glucose concentration (> 11 mmol/L)

<table>
<thead>
<tr>
<th>Region#</th>
<th>Region boundary</th>
<th>Insulin Infusion Rate</th>
</tr>
</thead>
</table>
| 1       | \[
\begin{bmatrix}
-34.35 & -58.08 \\
-1 & 0 \\
0 & -1 \\
1 & 0 \\
\end{bmatrix} x \leq \begin{bmatrix} 6.55 \\ 0 \\ 0 \\ 1.5 \end{bmatrix} \\
\begin{bmatrix}
34.35 & 58.08 \\
-1 & 0 \\
39.2 & -17.14 \\
1 & 0 \\
0 & 1 \\
\end{bmatrix} x \leq \begin{bmatrix} -6.55 \\ 0 \\ -4 \\ 1.5 \\ 1.5 \end{bmatrix} \\
\begin{bmatrix}
-39.2 & 17.14 \\
-1 & 0 \\
0 & 1 \\
\end{bmatrix} x \leq \begin{bmatrix} 4 \\ 0 \\ 1.5 \end{bmatrix} \\
\]
| \[
\begin{bmatrix} 18.13 & -7.89 \end{bmatrix} x + 4 \\
\begin{bmatrix} -16.22 & 50.18 \end{bmatrix} x - 2.55 \\
\begin{bmatrix} -21.07 & 9.24 \end{bmatrix} x \\
\]

infusion rate for the insulin pump to regulate the blood glucose concentration. As discussed in section 1.2.1, minimizing glucose variance around a single target value is not the goal if the controller is to mimic the behavior of a healthy body in regulating blood glucose. Therefore, the goal is to keep the blood glucose concentration within a certain range while gradually attempting to bring it closer to the lower bound of the range.

A 100 g glucose bolus was introduced at time 100 minutes as a meal disturbance, and the test result is presented in figure 5.3 using the proposed model predictive control. The upper part of figure 5.3 represents the blood glucose concentration (mmol/L) and the lower part shows the insulin infusion rate (mU/min) calculated by the controller. The controller can avoid hyperglycemia state and bring the blood glucose back below 7 mmol/L after 4 hours, during postprandial state. It gradually decreases the blood glucose near the lower bound of normo-
Figure 5.2: The simulated patient response to 100 gr of glucose ingestion as a meal disturbance with no automatic control

Figure 5.3: The simulated patient response to 100 gr of glucose ingestion using model predictive control strategy
glycemia zone, without entering the hypoglycemia state.

Figure 5.4: Response of the conventional PI controller with a 100 g meal disturbance at 100 min

For comparison, conventional PI controller and fuzzy-based PI controller using the logarithm of blood glucose, as designed in Chapter 4 are considered and the results are demonstrated in figure 5.4 and 5.5 for the administration of a 100 g meal disturbance to the simulated patient at 100 minutes.

The proportional gain is considered to be 12.7, and the integral gain is 0.05. The result shows that a conventional PI controller is capable of handling high blood glucose level but is not sufficient for blood glucose regulation since it cannot prevent hypoglycemia. On the other hand, the amount of injected insulin is much more than the amount suggested by MPC. The injection rate exceeds the
maximum infusion rate of the insulin pump, and the controller output is saturated. The excess insulin does not help the glucose absorption since the body cells are insulin resistant in type II diabetic patients. It would accumulate in the blood and increase the plasma insulin level.

Fuzzy-based PI controller using the logarithm of blood glucose acts properly as shown in figure 5.5. It can handle the postprandial blood glucose increase with a small overshoot to hyperglycemia zone. Its performance is also acceptable in preventing hypoglycemia for the patient.

In the presence of sufficient amount of data, the model predictive control strategy can be considered to design a controller for regulation of blood glucose. How-
ever if collecting data from the patient is impossible, fuzzy-based PI controller using the logarithm of blood glucose is a reliable option for automatic control of the blood glucose.

5.6 Conclusion

In this chapter, model predictive control strategy has been introduced as an alternative for the blood glucose regulation problem. The optimization problem has been modified by consideration of asymmetric objective function and incorporation of soft constraints to develop a controller which closely mimics the glucose regulatory system of a healthy individual. The parametric programming approach which has been applied to solve the optimization problem, not only reduces the computational efforts of solving an on-line optimization problem but also provides a lookup-table with all optimal solutions of the feasible space of states.

The multiple linear models for different blood glucose levels have been considered to capture the nonlinear and complex nature of glucose-insulin interactions. The designed controller is able to handle the meal disturbance in a timely manner. The blood glucose concentration is kept in normoglycemia zone since the application of asymmetric objective function strictly prevents the risk of the severe hypoglycemic state. The controller is also capable of avoiding high level of the blood glucose during the postprandial state. The blood glucose concentration is brought back closer to the lower bound during the postabsorptive state and kept as low as desired during the fasting state.
Chapter 6

Comparison of Controller Performance in response to variations in the metabolic rates

6.1 Introduction

The parameters of the model described in Chapter 2 were estimated for an individual patient. These parameters may vary between patients with different ages, genders, weights and activity levels. They may also change within a patient as the disease is progressing. The malfunctions of liver, peripheral tissues and pancreas result in the deficiency of the glucose regulatory system in type II diabetic patient. Therefore, the metabolic rates of these organs are subject to more variations from one patient to another and also within a patient during the course of the disease. In this chapter, the performance of the proposed control algorithms are presented and compared with each other as the result of the variations in the parameters related to these organs.

The following section investigates the performance of the gain-scheduling PI controller and model predictive controller as designed in Chapter 4 and Chapter 5, respectively. The body response is plotted for the administration of 100 g oral
glucose as the meal disturbance once without automatic control and next with the application of controllers. As the disease becomes more severe, the glucose metabolic rates reduce and worsen the condition of the patient. Therefore, a 50% decrease in glucose uptake and production rates of the liver, peripheral glucose uptake rate and pancreatic insulin secretion rate is considered. Finally, the results are discussed and concluded.

6.2 Controller Performance Investigation

6.2.1 Variation in Liver Metabolic Rates

The liver plays a central role in maintaining the blood glucose level. It balances the uptake and storage of glucose via glycogenesis during postabsorptive state, after ingestion of glucose-containing meals and the release of glucose via glycogenolysis and gluconeogenesis during fasting state, between meals and overnight[118, 119]. The need to store or release glucose is primarily signaled by the hormones insulin and glucagon. The high levels of insulin and suppressed levels of glucagon caused by glucose ingestion inhibits endogenous hepatic glucose production and promote the storage of glucose as glycogen (red path in figure 6.1). When blood glucose is reduced by small increments in circulating insulin, a rebound increase in glucose output from the liver is the initial or principal mechanism counteracting the fall in blood glucose concentration (blue path in figure 6.1).

As the disease become more severe, liver loses its capability to regulate the blood glucose and hepatic glucose uptake, and production rates decrease. The solid black line in figure 6.2 demonstrates the body response to the administration of 100 g glucose at time 100 minutes when both hepatic glucose uptake and production rates are decreased by 50%. The blue dashed line provides a baseline for comparison and shows the blood glucose profile before the rates reduction. The blood glucose goes up to severe hyperglycemia zone. The maximum blood glucose concentration after the meal ingestion increases from 16.2 to 18 mmol/L as the deficiencies of the liver are worsening.
Another test is performed to measure the insulin sensitivity of the body on the simulated patients. In this test, the plasma insulin concentration is increased and clamped at a high level by a continuous infusion rate of insulin. Figure 6.3 shows the blood glucose concentration while a constant rate of insulin at 10 mU/min is being infused. In the case of low blood glucose level, a healthy body converts the glycogen stored in the liver and muscles to glucose during glycogenolysis. The hepatic glucose production rate is impaired in type II diabetic patients, and the endogenous glucose production is lower than the healthy patient. The liver of the patient who is in the initial steps of the disease (blue...
Figure 6.2: The simulated patient response to 100 gr of glucose ingestion as a meal disturbance for 50% decrease in hepatic glucose uptake and production rates (black solid line) and before the rate reduction (blue dashed line)

Figure 6.3: Plasma blood glucose concentration in presence of continuous insulin infusion rate of 10 mU/min for the reduced rates (black solid line) and before the reduction (blue dashed line)

dashed line) is still capable of releasing glucose to prevent hypoglycemia, but as the hepatic glucose production rate is reduced, the blood glucose level decreases to severe hypoglycemia if no glucose ingested (black solid line).

This test shows the importance of the better control to prevent hypoglycemia state since the improper insulin infusion can drastically decrease the blood glucose concentration if the hepatic glucose production rate is low.
The designed controllers are expected to handle the situation by determining the proper insulin injection dose. An increase in plasma insulin concentration stimulates the liver to uptake and store more glucose during hyperglycemia state. A decrease in insulin level gives the signal to the liver for taking care of hypoglycemia state by releasing glucose. Figure 6.4 indicates the performance of fuzzy gain-scheduling controller using the logarithm of the blood glucose as the controlled variable.

The controller keeps the blood glucose in normoglycemia zone for most of the period with an overshoot to hyperglycemia zone and a negligible undershoot to hypoglycemia zone which is still acceptable since it prevents the severe hyper-
glycemia and hypoglycemia states.

As discussed in Chapter 4, two features were considered to enhance conventional PI controller for handling the nonlinear dynamic of glucose homeostasis. Using logarithm of the blood glucose reduces the nonlinearity and makes PI controller an acceptable, yet simple alternative to the nonlinear control strategies. On the other hand, gain scheduling technique helps the controller to be designed for prevention of severe hyperglycemia and hypoglycemia while gradually returning the blood glucose to the lower bound of normoglycemia zone. The scheduling gains are calculated by a fuzzy inference system which has the advantage of interpreting the expert knowledge and clinician’s insight into the set of rules. Through such rules, the weighting factors are defined to modify the gains based on the current blood glucose level. Figure 6.5 represents the weighting factors for the designed controller.

![Weight factor from the fuzzy inference system](image)

**Figure 6.5:** Weight factor from the fuzzy inference system

The performance of the model predictive controller is presented in figure 6.6. Model predictive control acts similar to the fuzzy gain-scheduling controller in handling high blood glucose level. Also, it can completely avoid hypoglycemia state and bring back the blood glucose to the lower bound of normoglycemia zone, 6 hours after the meal disturbance applied.

The model predictive controller, as designed in Chapter 5, takes the asymmetric nature of the glucose regulation problem into consideration. Therefore, it
Figure 6.6: The performance of model predictive controller after 100 gr of glucose ingestion as a meal disturbance for 50% decrease in hepatic glucose uptake and production rates efficiently avoids hypoglycemia state which causes more complications since it may put the patient in the coma. The proposed technique for solving the problem reduce the optimization problem into simple function calculations and provide a look-up table which gives an insight to the proper insulin infusion rate at each state of the patient and makes it easier to be understood by the patients and clinicians.

The total amount of insulin infused into the body in the presence of model predictive controller through insulin pump is less than the infusion amount as the fuzzy gain-scheduling controller is applied. The excess amount of insulin increases the plasma insulin concentration and finally excretes from the body.
6.2.2 Variation in Periphery Metabolic Rate

Insulin resistance is a characteristic feature of type II diabetes and plays an important role in the pathogenesis of the disease even before the failure of $\beta$-cells to produce insulin. The causes of insulin resistance can be placed into three categories: abnormal products secreted by $\beta$-cells, circulating insulin antagonists and the reduced response of peripheral tissues to insulin [120].

As the disease is progressing, the body cells lose their sensitivity to insulin and as the result, the peripheral glucose uptake rate decreases. Figure 6.7 shows the body response to 100 g meal disturbance when the peripheral glucose uptake rate is decreased by 50%. The failure of the peripheral tissues to absorb glucose causes the increase of the blood glucose level to severe hyperglycemia zone up to $19 \text{ mmol/L}$, which is 15% higher than the maximum blood glucose level before the decrease in the peripheral glucose uptake rate.

The insulin acts on cells throughout the body to stimulate uptake and utilization of glucose. The effects of insulin on glucose metabolism vary depending on the target tissue, but mainly insulin facilitates the diffusion of glucose into muscle, adipose and several other tissues. There are some tissues that do not require insulin for efficient uptake of glucose such as brain and the liver.
Figure 6.8: The performance of fuzzy gains-scheduling controller after 100 gr of glucose ingestion as a meal disturbance for 50% decrease in peripheral glucose uptake rate

In peripheral tissues, GLUT4 is the major glucose transporter which is used for uptake of glucose through the action of insulin. Binding of insulin to the receptors on cells leads rapidly to the insertion of the glucose transporters on the plasma membrane, thereby giving the cells the ability to efficiently take up glucose. When blood levels of insulin decrease and insulin receptors are no longer occupied, the glucose transporters are recycled back into the cell cytoplasm.

The study that has been done by Prato et al. shows that hyperinsulinemia, which is the condition of having excess levels of insulin circulating in the blood than expected relative to the level of glucose, can normalize total body glucose uptake [121]. Therefore, the insulin therapy can still benefit type II diabetic pa-
Figure 6.9: The performance of model predictive controller after 100 gr of glucose ingestion as a meal disturbance for 50% decrease in peripheral glucose uptake rate

tients with insulin resistance and increase the glucose uptake in peripheral tissues. Providing more insulin through insulin infusion pump also reduces the burden on the pancreas to secrete more insulin.

Figure 6.8 represents the performance of gain scheduling PI controller base on fuzzy logic. Administration of 100 g glucose 100 minutes after starting the simulation, is following by increasing the insulin infusion rate by the controller. This increase in insulin level avoids the blood glucose to go as high as 19 mmol/L which could happen without control (as seen in figure 6.7). However, the patient still experiences severe hyperglycemia for a short period, but the controller is capable of returning the blood glucose back to normoglycemia zone in 3 hours.
The controller performance is also acceptable in bringing the blood glucose to the lower bound of normoglycemia zone with a negligible undershoot to hypoglycemia zone and preventing the severe hypoglycemia.

The response of the simulated patient with 50% decrease in peripheral glucose uptake rate to 100 g meal disturbance at 100 minutes is shown in figure 6.9 in the presence of model predictive controller. In comparison with the fuzzy-based PI controller, MPC acts better in preventing severe hyperglycemia and hypoglycemia. The overshoot to the severe hyperglycemia is negligible, and the blood glucose is brought back to the lower bound of normoglycemia zone without any undershoot to the hypoglycemia zone.

### 6.2.3 Variation in Pancreatic Insulin Secretion Rate

The insulin secretion rate has been reduced at the time of diagnosis in most of the type II diabetic patients. The secretion of insulin further diminishes during the course of the disease.

Insulin secretory capacity depends on both function and mass of β-cells. Some studies highlighted the pieces of evidence that the reduced insulin secretion results from two dissociable factors, a decrease in the population of the functional insulin-
Figure 6.11: The performance of fuzzy gains-scheduling controller after 100 gr of glucose ingestion as a meal disturbance for 50% decrease in pancreatic insulin secretion rate producing β-cells and the intrinsic secretory defect. Both of these factors play important roles in the development and progression of type II diabetes [122, 123].

Figure 6.10 shows the blood glucose concentration profile for the administration of 100 g oral glucose at 100 minutes to the simulated patient. As the result of the reduced insulin secretion rate the blood glucose level increases and goes higher than 20 mmol/l. The insulin therapy is helpful since it compensate the lack of the endogenous insulin in the body.

The performance of the gain-scheduling PI controller based on fuzzy logic and model predictive controller are presented in figure 6.11 and 6.12, respectively. Both controller responses are satisfactory in preventing the hyperglycemia and hy-
Figure 6.12: The performance of model predictive controller after 100 gr of glucose ingestion as a meal disturbance for 50% decrease in pancreatic insulin secretion rate

Poglycemia states. The controllers apply the proper insulin infusion rate to reduce the blood glucose concentration. It takes almost 5 hours for both controllers to bring the blood glucose concentration under 7 mmol/L and an extra hour for settling down near the lower bound of the normal range which is the desirable level of the blood glucose in the fasting state.

6.3 Discussions

Type II diabetes is a progressive disease and caused by malfunction of different organs. The glucose metabolic rates are varying in a patient during the course of
Table 6.1: Assessment of the blood glucose regulation using the designed controllers for the decreased metabolic rates

<table>
<thead>
<tr>
<th>50% decrease in hepatic glucose uptake and production rates</th>
<th>severe hypoglycemia</th>
<th>hypo-glycemia</th>
<th>normo-glycemia</th>
<th>hyper-glycemia</th>
<th>severe hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without control (Figure 6.2)</td>
<td>0</td>
<td>0</td>
<td>52</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>GS-PI controller (Figure 6.4)</td>
<td>0</td>
<td>6</td>
<td>68</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>MPC (Figure 6.6)</td>
<td>0</td>
<td>0</td>
<td>78</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>50% decrease in peripheral glucose uptake rate</th>
<th>severe hypoglycemia</th>
<th>hypo-glycemia</th>
<th>normo-glycemia</th>
<th>hyper-glycemia</th>
<th>severe hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without control (Figure 6.7)</td>
<td>0</td>
<td>0</td>
<td>44</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>GS-PI controller (Figure 6.8)</td>
<td>0</td>
<td>10</td>
<td>60</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>MPC (Figure 6.9)</td>
<td>0</td>
<td>0</td>
<td>72</td>
<td>22</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>50% decrease in pancreatic insulin secretion rate</th>
<th>severe hypoglycemia</th>
<th>hypo-glycemia</th>
<th>normo-glycemia</th>
<th>hyper-glycemia</th>
<th>severe hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without control (Figure 6.10)</td>
<td>0</td>
<td>0</td>
<td>40</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>GS-PI controller (Figure 6.11)</td>
<td>0</td>
<td>0</td>
<td>94</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>MPC (Figure 6.12)</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The disease, especially within those organs which play important roles in the regulation of the blood glucose. The variation in the hepatic glucose uptake and pro-
duction rate, peripheral glucose uptake rate, and the pancreatic insulin secretion rate were considered, and the performance of the gain-scheduling PI controller based on fuzzy logic and the model predictive controller were presented in section 6.2 for 50% decrease in each of these metabolic rates. Table 6.1 represents the percentage of the simulation time spent in each glycemic zone after the ingestion of 100 g glucose (from 100 minutes to 600 minutes) as the body is trying to regulate the blood glucose level without and with the designed controllers.

As the glucose uptake and production rates decrease in the liver, the patient experiences severe hyperglycemia for 160 minutes (32% of the simulation time) as can be seen in the first section of table 6.1. The designed controllers are successful in calculating the proper insulin infusion rate to prevent severe hyperglycemia (see figures 6.4 and 6.6). In the presence of both controllers, it takes about 2 hours for the blood glucose level to return to normal glycemic zone from the yellow safety margin which is not ideal but still acceptable since the blood glucose is below 14 mmol/L. The model predictive controller is capable of preventing both hypoglycemia and severe hypoglycemia and returning the blood glucose to the lower bound of normoglycemia zone. The performance of the fuzzy-based PI controller is also satisfactory for handling hypoglycemia except for a negligible period (6% of the simulation time i.e. 30 minutes) that the blood glucose goes to the yellow zone of hypoglycemia.

In comparison with the decrease of hepatic glucose uptake and production rate, the reduced peripheral glucose uptake rate causes higher blood glucose concentration (19 mmol/L) which stays a bit longer in severe hyperglycemia zone (36% of the simulation time) before returning to normoglycemia zone as seen in the second section of table 6.1. Although the designed controllers are able to reduce the time spent in the severe hyperglycemia zone from 36% to 18% for GS-PI controller and to 6% for MPC, but cannot avoid it completely. Therefore, the oral agents such as metformin can be helpful for the patients with insulin resistance in their cells to stimulate the peripheral tissues for more absorption of glucose.

Figure 6.13 demonstrates the body response to the treatment including both
metformin administration and insulin infusion using the model predictive controller for the reduced peripheral glucose uptake rate. Metformin increases the glucose uptake in the peripheral tissues and decreases the blood glucose concentration. Therefore the blood glucose level return to normoglycemia zone from hyperglycemia zone after almost 2 hours without exceeding to severe hyperglycemia zone except for a negligible period.

Regarding the problem of low blood glucose level, MPC acts better in avoiding both hypoglycemia and severe hypoglycemia, while fuzzy-based PI controller causes a small undershoot to hypoglycemia zone for 50 minutes (10% of the sim-
ulation time).

Finally, the performance of the designed controllers was assessed for 50% decrease in pancreatic insulin secretion rate as the results have been summarized in the third section of table 6.1. Insulin therapy can keep the blood glucose in normal range since it provides the body with the proper amount of insulin to compensate the lack of pancreatic insulin secretion. It can be seen from table 6.1 that MPC can ideally keep the blood glucose in normal range all the time. Fuzzy-based PI controller also has an acceptable performance with a small overshoot to yellow zone of hyperglycemia for 30 minutes (6% of the simulation time).

6.4 Conclusion

It can be concluded that the problem of regulating the blood glucose in type II diabetic patients is more complicated than type I. The controller which is designed for type I diabetic patients should be able to mimic the performance of pancreas in secreting insulin. However, there are other complications involved with type II diabetes such as the insulin resistance in the body cells and liver failure to fulfill its role in regulating the blood glucose. Providing insulin through the insulin pump or multiple injections provide intensive care for the patient with type II diabetes and prevent further complications. Better control can be achieved with the treatments combining both oral agents and insulin therapy.
Chapter 7

Conclusion and Future Work

7.1 Research Summary and Conclusion

A person who is diagnosed with type II diabetes mellitus in initial steps can manage the disease with modification of diet and improvement of the lifestyle by doing appropriate exercise. They should also regularly monitor their blood glucose level and as the disease becomes serious the patient requires oral anti-diabetic drugs.

Metformin is a very common oral agent for diabetic patients. Chapter 3 represents the pharmacokinetic-pharmacodynamic model of metformin which was incorporated into the available physiological model for type II diabetes mellitus which was described in Chapter 2. The simulation results were shown for different dosages of metformin which demonstrates that in severe type II diabetic patients mono-therapy with metformin does not assure the satisfactory glycemic regulation and the patients eventually need insulin therapy.

Deciding what type of insulin might be best for a patient will depend on many factors, such as the body’s individualized response to insulin and the lifestyle choices such as caloric intake and exercise level. Multiple daily injections (MDI) therapy and continuous subcutaneous insulin infusion (CSII) with external insulin pumps are the available techniques for insulin delivery to the body.

The pharmacokinetic-pharmacodynamic models for four different insulin types
were presented in Chapter 3 including short, intermediate and long-acting insulins. In multiple daily injections therapy, a mixture of short-acting insulin along with intermediate or long-acting insulin are used to regulate the blood glucose. The body response to several regimens were depicted in Chapter 3 for comparison and the most efficient one has been introduced to an individual patient.

The monitoring of blood glucose for diabetic patients should be done more frequently if not continually. The current technological advance in diabetic care has made feedback blood glucose control possible. Portable continuous infusion pumps for insulin have been commonly used by Type I patients and can be used safely by type II patients.

Many past studies proposed conventional or modified PID controllers for regulation of blood glucose in type I diabetic patients but the homeostasis of blood glucose in type II diabetes is an inherently non-linear system. It was shown in Chapter 4 that the application of logarithm of the blood glucose reduces the non-linearity of glucose-insulin interactions. A fuzzy inference system has been designed as explained in Chapter 4 to generate scheduling gains for PI controller so that the controller demonstrates an improved performance by having more aggressive control for larger deviations from the normal range and less aggressive control for smaller deviations from the normal range. It is also able to handle the asymmetric control objective in which more tolerance is allowed for hyperglycemia and less tolerance for hypoglycemia. Simulations results demonstrate the potential benefit of using a gain scheduling PI controller with the logarithm of blood glucose as the controlled variable over a conventional linear PI controller for the control of blood glucose for type II diabetic patients.

One of the most common algorithms, relied on dynamic models of the process, is model predictive control (MPC). During the past few years, MPC has been typically applied in biomedical process control. In case that, enough amount of data is available for a patient, model predictive control strategy was considered in Chapter 5 to design a controller to regulate the blood glucose. The nonlinear and complex nature of glucose homeostasis in type II diabetes made it difficult to
capture glucose-insulin interactions without using multiple linear models for different blood glucose levels. Parametric programming not only reduced the computational efforts of solving an on-line optimization problem but also provided a lookup-table with all optimal solutions of the feasible space of states. The incorporation of soft constraints helped the development of a controller to closely mimic the glucose regulatory system of a healthy individual. The final controller was able to handle the meal disturbance in a timely manner without exceeding the upper range of normoglycemia zone. The blood glucose concentration is brought back closer to the lower bound during the postabsorptive state and kept as low as desired within a fasting state while the application of asymmetric membership functions prevents the risk of the severe hypoglycemic state.

7.2 Research Limitations

Development of models which precisely represent the glucose-insulin dynamics in the body is the key factor in finding the efficient treatments and control strategies for diabetic patients. The parameters of a physiological model should be updated for each individual based on the available measurements. The access to the sufficient data for each individual patient is needed for building a meaningful and successful model of the glucose metabolism. The available data should be of high quality, free of errors, omissions and conflicts, and adequate in quantity. However, the estimation of the parameters is limited as only a few blood glucose and insulin measurements per day are available in a non-clinical setting.

Another limitation of this research is that the expanded mathematical model of type II diabetes is limited to study the effects of the administration of metformin on the patients. Metformin is the most common anti-diabetic drug in the biguanides class which works by keeping the liver from making glucose and allowing more glucose to enter cells. There are also other types of drugs which work differently to reduce the diabetic abnormalities. Some of them like biguanides and thiazolidinediones help the body cell to absorb and use glucose. Some others such as sulfonylureas, meglitinides and dipeptidyl peptidase 4 inhibitor help the pan-
creas to produce and release more insulin. Alpha-glucosidase inhibitors is another group of anti-diabetic medication which keeps the intestines from quickly absorbing glucose. Biguanides also keep the liver from producing glucose.

7.3 Recommendations for Future Work

A potential research area in the study of type II diabetes mellitus is developing the efficient methods of estimating the model parameters of the blood glucose when the glucose and insulin concentrations are only available at irregular intervals. Such studies help to overcome the limitations that are caused by the lack of access to the sufficient data.

I have contributed to a study which applies on-line sequential Monte Carlo (SMC) to estimate the states and parameters of the state-space model for type II diabetic patients under various levels of randomly missing clinical data. The results of this study have been published in [124].

Another research area which can be taken into more consideration is the study of different groups of oral drugs which help diabetic patients to deal with various abnormalities and complications of the disease.

The Pharmacokinetic-Pharmacodynamic (PK-PD) model of metformin, which is the most common oral agent for type II diabetic patients has been incorporated into the patient mathematical model. The similar approach can be applied to develop the PK-PD model of other anti-diabetic agents to investigate the effects of each medicine on the body organs. The PK-PD model should be attached to the patient model followed by the corresponding structural modifications made in the model to represent the effects of the medication on the body organs.

These models provide the opportunity to simulate and study the effects of medications safely on the patients, both separately and in combination with each other without any administration which may be harmful to the patients. Development of PK-PD models for different medicines will increase the chance of prescribing an efficient medication for the patients in a safe and cost-effective way.
Bibliography


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