Dynamic Modeling of Glucose Metabolism for the Assessment of
Type II Diabetes Mellitus

by

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Abstract

Diabetes mellitus is one of the deadliest diseases affecting millions of people worldwide. Due to ethical issues, physiological restrictions and high expenses of human experimentation, mathematical modeling is a popular alternative approach in obtaining reliable information on a disease in a safe and cost effective way.

In this thesis, I have developed and expanded a compartmental model of blood glucose regulation for type II diabetes mellitus based on a former detailed physiological model for healthy human subjects. The original model considers the interactions of glucose, insulin and glucagon on regulating the blood sugar. I have expanded the model by eliminating the main drawback of the original model which was its limitation on the route of glucose entrance to the body only to the intravenous glucose injection. I have added a model of glucose absorption in the gastrointestinal tract and incorporated the stimulatory hormonal effects of incretins on pancreatic insulin secretion followed by oral glucose intake. The parameters of the expanded model are estimated and the results of the model are validated using available clinical data sets taken from diabetic and healthy subjects. The estimation of model parameters is accomplished through solving nonlinear optimization problems.

To obtain more information about the medical status of the subjects, I have designed some in silico tests based on the existing clinical tests, applied them to the model, and analyzed the model results. To accommodate model uncertainties and measurement noises, noise effects are included into the states and outputs of the model and a filtering method called particle filters is employed to estimate the hidden states of the model. The estimated model states are used to calculate the glucose metabolic rates which in turn provide more information about the medical condition of the patients.

Another contribution of the type II diabetes model is developing a pharmacokinetic-pharmacodynamic model to study pharmaceutic impact of different medications on
diabetes treatment. A preliminary study on metformin treatment on diabetic patients is performed using the developed type II diabetes model.
Preface

This thesis entitled “Dynamic modeling of glucose metabolism for the assessment of type II diabetes mellitus” presents my research during my PhD studies at chemical and biological engineering department of the University of British Columbia. I led and performed my PhD research under the supervision of Professor K. E. Kwok and Professor R. B. Gopaluni. Contributions and collaborations to the published papers or submitted papers for publication are concisely explained in the following.


- A version of Chapter 4 has been published. O. Vahidi, R. B. Gopaluni and K. E. Kwok, “Detection of organ dysfunction in type II diabetic patients,” in American Control Conference (ACC), 2011, 2011, pp. 4769-4774. A version of Chapter 4 has been submitted for publication. O. Vahidi, R. B. Gopaluni, and K.E. Kwok, “Detection of Abnormalities in Type II Diabetic Patients Using Particle Filters,” Submitted to Mathematical Bioscience Journal, 2012. These two papers have been prepared with close collaboration of Professor Kwok and Professor Gopaluni. They also have helped in preparation of the first drafts and revision of the final draft for the published paper.

- A version of Chapter 5 is ready for submission to a journal for publication. O. Vahidi, K.E. Kwok, R. B. Gopaluni, and F. K. Knop, “A comprehensive compartmental model of blood glucose regulation for healthy and type II diabetic subjects: expansion of a former model”. This paper is prepared with the
collaboration of Professor Knop who has provided the details of requested clinical data which has been published by him in the literature. The first draft of the paper is ready and after reviewing the paper by Professor Kwok and Professor Gopaluni, the paper will be submitted.
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Nomenclature

The following nomenclature is adopted throughout the mathematical model description:

Model variables in the glucose sub-model
\( D \)  Oral glucose amount (mg)
\( G \)  Glucose concentration (mg/dl)
\( M \)  Multiplier of metabolic rates (dimensionless)
\( q \)  Glucose amount in GI tract (mg)
\( Q \)  Vascular blood flow rate (dl/min)
\( r \)  Metabolic production or consumption rate (mg/min)
\( Ra \)  Rate of glucose appearance in the blood stream (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 (l/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 (l)
\( X \)  Glucose-enhanced excitation factor (dimensionless)
\( Y \)  Intermediate variable (dimensionless)
Model variables in the glucagon sub-model

\( I \)  
Normalized glucagon concentration (dimensionless)

\( M \)  
Multiplier of metabolic rates (dimensionless)

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

\( V \)  
Volume (dl)

\( t \)  
time (min)

Model variables in the incretins sub-model

\( \Psi \)  
Incretins concentration (pmol/l)

\( r \)  
Metabolic production or consumption rate (pmol/min)

\( V \)  
Volume (dl)

\( t \)  
time (min)

First superscript

\( I \)  
Glucagon

\( \Psi \)  
Incretins

\( B \)  
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

\( I\Psi R \)  
Intestinal incretins release
Kidney glucose excretion $KGE$
Kidney insulin clearance $KIC$
Liver insulin clearance $LIC$
Metabolic glucagon clearance $MGC$
Plasma glucagon clearance $PGC$
Plasma incretins clearance $PΨC$
Pancreatic glucagon release $PGR$
Peripheral glucose uptake $PGU$
Peripheral insulin clearance $PIC$
Pancreatic insulin release $PIR$
Red blood cell glucose uptake $RBCU$

First subscripts
$A$ Hepatic artery
$B$ Brain
$G$ Gut
$H$ Heart and lungs
$L$ Liver
$P$ Periphery
$S$ Stomach
$∞$ Final steady state value

Second subscripts (if required)
$C$ Capillary space
$F$ Interstitial fluid space
$I$ Liquid
$s$ Solid
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I give my best thanks to my wife, Zahra, for all her support during my PhD studies. Far away from our country, she was the only one who could fill the absence of the rest of my family and prepared the best environment for me with love, patience and endeavor throughout the challenging days of my graduate life in Canada.
Dedication

This thesis is dedicated to the loveliest being on earth, my mother, who sacrificed herself for me, to my father for all his support, to my lovely wife and to my beloved son.
Chapter 1

Introduction

1.1 Motivation

Diabetes mellitus is a chronic disease which has affected millions of people worldwide. According to the International Diabetes Federation, data obtained from global studies shows that the number of people with diabetes mellitus in 2011 has reached 366 million and this number is expected to reach 552 million by 2030 if immediate actions are not taken [1]. In the United States, the diabetes rate raised to 11.3% in 2009 and with the current positive rate of increase, it will hit 15% in 2015 [2]. It is estimated that 4.6 million deaths are due to diabetes mellitus and currently health care spending on diabetes has reached 465 billion USD a year. The risk of death by diabetes has been decreased significantly by the discovery of insulin since 1921; however, a curable therapy for this disease is still unknown. Diabetes can lead to serious complications and even premature death, but diabetic patients may take steps to control the disease and lower the risk of its complications [3].

To have an efficient and cost effective treatment for the patients, reliable information from the patients can be helpful. 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. Alternatively, mathematical modeling is a popular approach in obtaining useful information about a disease, its effects on patients’ body and medical condition of the patients in a safe and cost effective way.
Diabetes mellitus is characterized by high levels of blood glucose caused by dysfunction of one or some organs in the body and is generally categorized into three groups: type I diabetes or insulin dependent diabetes mellitus (IDDM), type II diabetes or non insulin dependent diabetes mellitus (NIDDM), and gestational diabetes. The latter is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy which may precede development of type II diabetes. Among different types of diabetes mellitus, type II diabetes is the most common type affecting 90 to 95 percent of the diabetes population around the world [4]. Although a great majority of diabetic patients’ population belongs to type II diabetes, due to two main reasons very few works have been accomplished in mathematical modeling to study the behavior of this type of diabetes:

1- Patients with type I diabetes are in need of immediate medical attention. Due to lack of pancreatic insulin production, daily insulin doses must be supplied to the type I diabetic patients to survive while patients with type II diabetes require gradual treatment and are not in urgent need of medical attention.

2- As will be explained in detailed in next sections, pathology of type II diabetes is very complicated since it is characterized with multiple abnormalities of different body organs while the main problem of patients with type I diabetes is lack of pancreatic insulin production.

Due to the above reasons, type I diabetes has been widely the topic of many modeling and control studies, but there are very few investigations on modeling of type II diabetes mellitus. Modeling of type II diabetes can be very insightful for the treatment of this disease. The large population of type II diabetic patients with its positive rate of increase along with high costs of health care is sufficient to motivate researchers to find more efficient and cost effective methods of treatment for this disease. Although no curable therapy is available for diabetes and a permanent dietary and medical treatment is needed for type II diabetic patients, its costs, side effects and effectiveness can be optimized if reliable information is available from
the patients’ medical condition. Therefore, in this thesis, I have focused on mathematical modeling of type II diabetes in order to obtain insightful information from type II diabetes which in turn can be used in treatment of diabetes.

1.2 Thesis objectives

The objective of my Ph.D. thesis is focused on studying the physiological behavior of type II diabetic patients through mathematical modeling and computer simulation in order to evaluate the medical condition of the patients and to find suitable and optimal methods to control their blood glucose levels. This objective can be achieved in the following three steps.

1.2.1 Developing a mathematical model for type II diabetes

Development of a model for type II diabetes can be performed either by constructing a new model or by modifying an existing model. The second approach has been widely used in many studies for type I diabetes in which the type I diabetes model is developed by modifying an existing physiological model for healthy human subjects. Similarly, I have selected the second approach in developing a type II diabetes model based on a previously proposed model for healthy human subjects. This is performed into three steps. In the first step, a suitable healthy human body model is selected, in the second step the model weaknesses are eliminated if possible, and finally the selected model is adjusted and validated for type II diabetes. Results of this part of the research have been published in Biochemical Engineering Journal [5] and American Control Conference 2010 [6]. One more paper is also ready for submission to Journal of Theoretical Biology.
1.2.2 Evaluation of the medical condition of diabetic patients

The developed type II diabetes model can be used to assess glucose metabolism pathways in the subjects’ body and study any abnormal behavior of body organs in diabetic patients. The glucose metabolism assessment can be performed qualitatively and quantitatively by applying different clinical tests to the model in silico and use the simulation results for assessment. The preliminary results of qualitative glucose metabolism assessment of type II diabetic patients have been published in the American Control Conference 2011 [7]. A modified and improved version of this paper has been also submitted to the journal of medical and biological engineering.

1.2.3 Finding a suitable and optimal method to control blood glucose levels

Information obtained from the glucose metabolism assessment helps in better understanding the medical condition of the diabetic patients and provides insights for the medical doctors to administer an effective treatment for the patients. Furthermore, the type II diabetes model may be used to develop pharmacokinetic pharmacodynamic models for various medicines which allow studying the effectiveness of medicines on regulating the blood sugar. This part is not covered in my PhD research, but will be explained to provide recommendations for future works. Nevertheless, I have contributed in developing a pharmacokinetic pharmacodynamic model for metformin, a common medicine prescribed for the diabetic patients, whose preliminary results have been published in [8, 9]. I also have had another contribution in studying insulin therapy through a feedback framework for diabetic patients and its preliminary results have been published in [10].
1.2.4 Thesis outline

Chapter 2 presents a general background on glucose metabolism, diabetes mellitus, and different modeling approaches on diabetes modeling.

Chapter 3 deals with the model development for type II diabetes mellitus which includes describing the model in detailed, methodology of model development, and model results and discussions. It will be shown how the model results are generally helpful in predicting the medical condition of the patients and how obtained information can be insightful in administering a suitable treatment for the diabetic patients.

Chapter 4 presents the methodology of qualitative and quantitative assessment of glucose metabolism in each body organ. In this chapter, design of different in silico tests will be described and using them to evaluate the effects of different factor on glucose metabolism will be discussed. It will be discussed that how to estimate the unmeasured model states and how to use them in calculating the glucose metabolism in each organ.

Chapter 5 presents a structural expansion accomplished on the developed type II diabetes model and on the original healthy subject model. The model expansion includes adding a glucose absorption model to the gastrointestinal tract, adding a model of incretins hormones, a group of gastrointestinal hormones that enhances pancreatic insulin production rate, and implementing the hormonal effects of incretins on glucose regulation.

Finally, Chapter 6 summarizes the thesis and provides recommendations for future work.
Chapter 2

Background

2.1 Glucose metabolism

2.1.1 Glucose homeostasis

Required energy for the body cells is provided from catabolism of different fuel sources including carbohydrates, fats and proteins. The main source of energy for the body is carbohydrates. Glucose is a simple sugar produced from digestion of carbohydrates in the gastrointestinal tract. It is absorbed by the body cells and is used as the primary energy source. The body maintains a constant blood glucose concentration during fast by producing its own glucose endogenously through two main pathways:

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

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

Endogenous glucose produced by the liver and kidney is released into the blood stream 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 [11].
In normal (non-diabetic) subjects, blood glucose level is controlled by precise responses of several organs to any changes in circulating glucose levels, resulting in regulation of blood glucose concentration within an approximate range of 60-150 mg/dl, despite disturbances such as exercise or intake of a meal containing carbohydrates [12]. This glucose regulatory control is carried out through feedback systems reacting mainly on glucose, insulin and glucagon blood levels. Insulin and glucagon are two hormones that are secreted by the beta and alpha cells, respectively, contained in the islets of Langerhans scattered in the pancreas and play an important role in glucose homeostasis in the body. The effect of these hormones on glucose metabolism is opposite from one to another (see Figure 2.1). Insulin contributes in lowering the blood sugar level by:

1- stimulating some body cells to absorb glucose
2- suppressing endogenous glucose production
3- inhibiting glucagon secretion

Glucagon, on the other hand, contributes in increasing the blood sugar level by:

1- stimulating the liver to produce more glucose
2- inhibiting insulin secretion

When the blood sugar level is high, pancreas secretes more insulin. Secreted insulin has negative paracrine action on the alpha cells causing inhibition of glucagon secretion. Increased concentration of insulin and decreased 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 increases the blood glucose concentration.

Insulin contributes in augmenting the glucose uptake in peripheral tissues and in 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 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) [13].
2.1.2 Glucose transporter

Not all cells require insulin in order to absorb glucose. Depending on the type of the glucose transporter available on the cell, the cell may or may not need insulin for glucose absorption. Glucose transporters (GLUT) are a group of membrane proteins which facilitate the entrance of glucose through the cell membrane into the intracellular space. To date, thirteen different types of these transporters are identified [14-16]. The main four glucose transporters are:

1- GLUT1: is an insulin-independent transporter located on the cell membrane and is available predominately on tissues that do not need insulin for glucose absorption such as brain and red blood cells. They are also found on other body cells which need insulin for glucose uptake such as muscles and adipose tissues. This transporter is mainly responsible for cell basal glucose uptake.

2- GLUT2: is a bidirectional transporter which allows glucose to flow in two directions. GLUT2 also facilitates transportation of glucose in the direction of its concentration gradient which makes the cell a suitable sensor to detect blood glucose concentration. This transporter is the predominant transporter in liver and beta cells of the pancreas.

3- GLUT3: is mostly found in neurons.

4- GLUT4: is the only insulin dependent glucose transporter which is found predominantly in muscle and adipose tissue cells. Unlike other glucose transporters, GLUT4 is present in the cytosol. For absorption of glucose through GLUT4 glucose transporters, insulin must bind to the insulin receptors which are present on the cell membrane. Following a chain of intercellular signaling caused by binding insulin to its receptors, GLUT4 glucose transporters will be translocated on the cell membrane and, then, glucose is permitted to enter the intracellular space [13]. Entered glucose may be stored as glycogen through glycogenesis pathway or may be consumed to produce energy through glycolysis pathway.
2.1.3 Route of glucose entrance into the body

The route of glucose entry into the body plays an important role in maintaining the glucose homeostasis [11]. It is observed that the amount of pancreatic insulin secretion followed by an oral glucose intake is significantly greater than when the glucose is administered intravenously despite with identical increase in the blood glucose level [17-20]. This significant augmentation is associated with the secretion of a group of gastrointestinal hormones called incretins from the walls of the small intestine following the presence of carbohydrates in the lumen of small intestine. Their major contribution in glucose regulation is related to the pancreatic insulin production by stimulation of the pancreas to produce more insulin even before the elevation of the blood glucose level [20, 21]. The two main candidate hormones that fulfill criteria for an incretin are glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) gastric hormones [22-24].

2.2 Diabetes mellitus

Diabetes is characterized by high levels of blood glucose caused by the lack or insufficiency of insulin secretion in the islet beta cells of the pancreas and/or by body cell resistance against glucose and insulin. Type I diabetes is an autoimmune disease leading to the destruction of islet beta cells in the pancreas, which results in a complete halt of insulin production. Unlike type I diabetes, type II diabetes is characterized by multiple abnormalities in a number of body organs such as the liver, the pancreas, muscles and adipose tissues. These abnormalities are classified as follows.

1- Insulin resistance in peripheral tissues: As mentioned, peripheral tissues (i.e. muscle and adipose tissue cells) are dependent on insulin to absorb blood glucose. Many studies [25-33] have shown that peripheral insulin resistance and relative insulin deficiency in type II diabetic patients have
resulted in low glucose uptake rates by muscle cells and adipose tissue cells. Impairment of several factors is known to be associated with insulin residence in peripheral tissues. These factors are well reviewed in [11] and are summarized in the following:

- The number of insulin receptors
- The affinity of insulin receptors
- Insulin receptor tyrosine kinase activity
- Insulin intracellular signaling
- The number of glucose transporters
- Glucose transporter translocation on the cell membrane
- Insulin regulatory effect on hexokinase
- Insulin stimulatory effects on glycogenesis
- Insulin stimulatory effects on glycolysis

2- **Reduced hepatic glucose uptake:** Some studies have shown that insulin-induced stimulation effects on hepatic glucose uptake are impaired in type II diabetic patients, leading to reduced hepatic glucose uptake [34-39]. It is believed to be due to the impairment of insulin stimulation effect on glucose phosphorylation in the liver [39].

3- **Impaired hepatic glucose production:** Many studies have shown that hepatic glucose production rate is impaired in type II diabetic patients [28-33, 35, 36, 40-43]. Most of these studies have indicated that insulin-induced suppression of endogenous glucose production is low in diabetic patients. Basu et al. [42, 43] have demonstrated the impaired effect of insulin suppression on both pathways of endogenous glucose production (i.e. gluconeogenesis and glycogenolysis). Evaluating the glucose suppression effect on hepatic glucose production rate has indicated its normality in type II diabetic patients [44, 45].
4- **Impaired pancreatic insulin secretion**: Deficiency in the pancreatic insulin production has the key role in the development of overt diabetes [11], which means that overt diabetes does not develop unless the pancreas fails to produce insulin properly. As will be described in more detailed later, 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 early peak of insulin production and the other one is in the overall insulin secretion rate [46-50].

5- **Glucose resistance**: Alzaid et al. [41] showed that glucose-induced stimulation of glucose disposal is normal in type II diabetic patients. However, later studies by Del Prato et al. [44] and Nielsen et al. [45] have indicated that high levels of glucose concentration (particularly above 130 mg/dl) impair the glucose stimulation effect on glucose uptake in type II diabetic patients.

Diabetes mellitus treatment varies depending on the type and severity of the disease. Type I diabetic patients have permanently destroyed beta islet cells of the pancreas leading to a lack of insulin production and as such, exogenous insulin injections are, currently, the ultimate therapy. Unlike type I diabetes, blood glucose concentration in type II diabetic patients can be initially controlled by exercise and healthy dieting [51-57]; however, as the disease progresses, medication is needed. A suitable and effective treatment may be administered to synergize with the patient’s disease abnormalities. Different and probably better treatments are possible if the patient information is accurate and detailed enough. A mathematical model depicting the behavior of different organs in a particular diabetic patient may obtain information needed to determine a suitable treatment for said patient.
2.3 Mathematical modeling of diabetes mellitus

Mathematical modeling of glucose regulation has been the topic of many studies of the last fifty years starting with simple linear models by Bolie [58] and Ackerman [59]. Most of these studies (if not all) are performed on healthy human subjects. Different modeling approaches have been considered in proposed models which are well reviewed by Makroglou et al. [60], Mari [61] and Cedersund et al. [62]. One of the most popular approaches in modeling the glucose regulation in a human body is the compartmental modeling approach. In this approach, the body is divided into a number of compartments representing different organs or parts of the body. The model equations comprise mass balance equations over each compartment. The compartmental minimal model proposed by Bergman et al. [63] was one of the pioneer of this modeling approach which has been used widely in many later studies in mathematical modeling of glucose regulations and in diabetes research. This model is represented by three mass balance nonlinear differential equations over three compartments representing glucose and insulin concentrations in the body. More complicated compartmental models proposed by Cobelli [64], Sorensen [65] and Hovorka [66] have considered more compartments for better describing the behavior of different parts of the body.

The models for glucose regulation in healthy human body have been widely used in studying the physiological behavior of type I diabetic patients by adjusting the models for the patients. Using the adjusted models for type I diabetic patients, various control algorithms have been proposed to control the blood glucose level [67-74]. Model adjustment for type I diabetes mellitus is not a complex problem. Since type I diabetic patients have no insulin production, without changing the model structure, simply the insulin production rate term of the healthy subject’s model should be set to zero and then, the model is ready to be used for type I diabetes.
Although type II diabetes is associated with multiple abnormalities, a similar approach can be used to develop a model for type II diabetes. Nevertheless, using the similar approach for type II diabetes modeling is not as simple as type I diabetes modeling. As described in the previous section, in spite of abnormal functioning of different body organs which leads to the deterioration of glucose homeostasis in type II diabetes, all body organs are still functioning. Therefore, to adjust the healthy human subject’s model for type II diabetes, no structural modification is needed. These abnormalities target the glucose metabolic rates in some organs and the secretion rates of glucose regulatory hormones (such as pancreatic insulin secretion). Therefore, in order to adjust the healthy human subject’s model for type II diabetes, it is sufficient to modify the model parameters. This approach has been used by Dalla Man et al. [75]. In this thesis, I have used a similar approach in developing the type II diabetes model. Searching through the literature, no other approach for developing a model to represent the glucose regulation for type II diabetic patients was located.

2.4 Evaluation of the medical status of diabetic patients

Evaluation of abnormalities associated with diabetic patients is commonly performed by assessing the glucose metabolism in different body organs during different clinical tests. A brief explanation of some of these clinical tests is presented in the following. More details will be provided in next chapters.

1- **Oral glucose tolerance test (OGTT):** In this test, a glass of dissolved glucose in water is given and blood samples are taken afterwards to determine how body is able to clear glucose from the blood. The dose of glucose may vary from 50 g to 100 g depending on different standards.

2- **Euglycemic hyperinsulinemic clamp (EHIC):** In this test the plasma insulin concentration is elevated and clamped at a high level by a continuous infusion rate of insulin. Meanwhile, the plasma glucose level is maintained at
its normal levels by continuous glucose infusion with variable rate based on a negative feedback principle. At steady states, the amount of glucose infusion is equal to the whole body glucose uptake rate and therefore is a measure of whole body insulin sensitivity.

3- **Hyperglycemic clamp (HGC):** In this test glucose concentration is elevated to a high value by a continuous infusion rate of glucose and no insulin injection is performed. At steady states, the rate of glucose infusion is a measure of pancreatic insulin secretion rate along with glucose metabolism capability.

4- **Intravenous glucose tolerance test (IVGTT):** In this test glucose is infused intravenously into the body and following the injection, variation of glucose concentration is measured from blood samples taken from the subject. Similar to the OGTT test, measurements of glucose concentration show how the body clears glucose from the body.

5- **Insulin suppression test:** Similar to the EHIC test, this test is used to measure insulin sensitivity. In this test, endogenous secretion of glucose and insulin is suppressed by injection of somatostatin. Simultaneously, a constant rate of glucose and insulin is infused intravenously. Blood samples are taken from the subject in specific times during the test. At steady states, the plasma insulin concentration is almost the same for all subjects while the plasma glucose concentrations varies depending on the level of resistance of the subject’s body to infused insulin. The higher the value of the steady state glucose concentration the higher the body resistance to the infused insulin.

Qualitative and quantitative evaluation of abnormal behavior of diabetic patients has been the topic of many investigations. Based on the results of the clinical tests, different indices have been defined in the literature to quantify the medical condition of healthy and diabetic patients. Insulin sensitivity index, the ability of insulin to stimulate the body glucose disposal, and glucose effectiveness index, the ability of glucose per se to mediate its own disposal, are two common indices
defined in the literature. Many different definitions for these two indices are reported in the literature. Direct measurement of insulin sensitivity index via euglycemic hyperinsulinemic clamp technique is proposed in [76, 77] and via IST test is proposed in [78-80]. Indirect measurement of insulin sensitivity and glucose effectiveness indices via frequently sampled intravenous glucose tolerance test (FSIVGTT) are proposed in [81-87]. In this method, the results of FSIVGTT test is used to determine the parameters of the minimal model [63] and then, obtained parameters are used to define insulin sensitivity and glucose effectiveness indices. Different surrogate indices for insulin sensitivity have been also defined in the literature using fasting insulin and glucose measurements. Two well-known surrogate indices for insulin sensitivity from fasting insulin and glucose measurements are homeostasis model assessment (HOMA) [88-90] and quantitative insulin sensitivity check index (QUICKI) [77, 91-94]. There are other surrogate indices for insulin sensitivity obtained from OGTT test results such as Matsuda index [95], Stumvoll index [96], Avignon index [97], oral glucose insulin sensitivity index [98], Gutt index [99], and Belfiore index [100] in which different sampling protocols has been considered during OGTT test.

2.5 Type II diabetes treatment

As mentioned before, there is no curable therapy for diabetes mellitus. Nevertheless, high blood sugar of type II diabetic patients can be controlled by regular exercise and healthy dieting at early stages of diabetes, however, as the disease progresses, medication is needed. Since multiple abnormalities leads to high sugar levels in type II diabetes, information obtained from the model can firstly identify the source of these abnormalities and secondly the severity of them. This information can suggest a suitable therapy for the patients.

In my current research, I will not consider the effects of exercise and different diets on the patients and I assume that the patients need medication in order to control
their blood glucose levels. Various drugs are produced and prescribed for type II diabetic patients such as insulin, sulfonylureas, meglitinides, biguanides and thiazolidinediones which trigger specific part of the body. Based on the type and severity of abnormalities of any diabetic patient, specific type of medication is administered.

The type II diabetes model can be further used to develop pharmacokinetic pharmacodynamic (PK-PD) models for any type of medication. The term “pharmacokinetics” refers to a branch of pharmacology that studies the fate of an external substance administered to a live organism. The term “pharmacodynamic” refers to another branch of pharmacology in which the biochemical and physiological effects of a medicine on a live organism is examined. Therefore, this type of modeling approach allows studying the mutual effects of different medications on type II diabetic patients. It provides insights for medical doctors to prescribe a suitable and effective medication for the patients and decrease the risk of administering wrong medication for the patients.
In this chapter, a detailed description of mathematical model development for type II diabetes mellitus is provided. My approach in doing this is similar to what has been previously done for various type I diabetes models which is developing a model based on a former model proposed for healthy human body. This is performed into two steps. In the first step, a suitable healthy human body model is selected. A wide variety of mathematical models have been proposed for healthy human subjects. Since dysfunctioning of different organs leads to high blood glucose level in type II diabetic patients, a model which describes the behavior of the associated organs can be suitable for type II diabetes model development. Among the models available in the literature, the Sorensen model [65] meets the requirements needed for the model development. In the second step, the model is adjusted and validated for type II diabetes using available clinical data of diabetic patients. To do this, I have selected certain model parameters for estimation based on abnormalities associated with type II diabetic patients. Selected model parameters are then estimated via solving a nonlinear optimization problem. Results of this part of the research have been published in Biochemical Engineering Journal [5] and American Control Conference 2010 [6].

### 3.1 The Sorensen model

The compartmental model of glucose-insulin interactions in a healthy body selected in this research has been developed by Guyton et al [101] and later modified by Sorensen [65]. This model considers individual compartments for organs associated in diabetes research including the liver, pancreas, muscles and adipose tissues
which makes it suitable for type II diabetes model development. In the Sorensen model the regulatory effects of insulin and glucagon hormones on glucose metabolism are considered. The Sorensen model contains three main sub-models representing variations of blood glucose, insulin and glucagon concentrations in different part of the body. Each sub-model is divided into individual number of compartments representing a specific part or organ of a human body. The number of compartments in each sub-model is determined by the significance of the organ's job in maintaining the respective solute concentrations.

Considering the circulatory system, 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. To model the glucose regulation in whole human body organs, major organs which contribute significantly in glucose production and consumption are considered and therefore, the circulatory system can be simplified as shown in Figure 3.1. A number of compartments are assigned to these organs in the Sorensen compartmental model which will be described later.

General assumptions included into the Sorensen model are:

1- Hormonal effects of epinephrine, cortisol, and growth hormone are neglected.
2- Physiology of changes in amino acid and free fatty acid substrate levels are not considered.
3- The physiologic parameters such as blood flow rates and capillary space volumes are selected to represent a typical 70 Kg adult male.
3.1.1 Compartments

In compartmental modeling approach, a compartment represents an organ or a specific part of the human body. A graphical representation of a typical compartment of the Sorensen model is shown in Figure 3.2. 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. The capillary space is fed in by arterial blood inflow and drained by venous blood outflow. The blood components may diffuse through capillary walls to 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. Due to the following reasons, 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:

1- The capillary wall may be 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 3.3 a).

2- The permeability of the capillary wall may be high enough for a solute which leads to a fast equilibrium of the capillary blood and the interstitial fluid spaces. In this case, two spaces are considered as one combined sub-compartment with uniform solute concentration (Figure 3.3 b).

3- 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, in which case two spaces are combined and considered as one sub-compartment with uniform solute concentration (Figure 3.3 c).

4- 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 and, therefore, all three spaces are combined and considered as one space with uniform solute concentration (Figure 3.3 d).
Figure 3.3: Simplified configurations of physiological compartments

5- The rate of solute transport across the cell membrane is not restricted by the concentration of the solute in the intracellular fluid space. In this case the intracellular space is omitted (Figure 3.3 e).
### 3.1.2 Glucose sub-model

A schematic representation of the glucose sub-model is depicted in Figure 3.4.

![Figure 3.4: Schematic diagram of glucose sub-model](image)

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 3.4 represent the blood flow direction. Mass balance equation over each sub-compartment results in eight ordinary differential equations constituting the glucose sub-model:
\[
V_{BC}^G \frac{dG_{BC}}{dt} = Q_B^G (G_H - G_{BC}) - \frac{V_{BF}^G}{T_B^G} (G_{BC} - G_{BF})
\]
3.1

\[
V_{BF}^G \frac{dG_{BF}}{dt} = \frac{V_{BF}^G}{T_B^G} (G_{BC} - G_{BF}) - r_{BGU}
\]
3.2

\[
V_{H}^G \frac{dG_{H}}{dt} = Q_B^G G_{BC} + Q_L^G G_L + Q_K^G G_K + Q_P^G G_{PC} - Q_H^G G_H - r_{RBCU}
\]
3.3

\[
V_{G}^G \frac{dG_{G}}{dt} = Q_G^G (G_H - G_G) - r_{GGU}
\]
3.4

\[
V_{L}^G \frac{dG_{L}}{dt} = Q_A^G G_H + Q_H^G G_G - Q_L^G G_L + r_{HGP} - r_{HGU}
\]
3.5

\[
V_{K}^G \frac{dG_{K}}{dt} = Q_K^G (G_H - G_K) - r_{KGE}
\]
3.6

\[
V_{PC}^G \frac{dG_{PC}}{dt} = Q_P^G (G_H - G_{PC}) - \frac{V_{PF}^G}{T_P^G} (G_{PC} - G_{PF})
\]
3.7

\[
V_{PF}^G \frac{dG_{PF}}{dt} = \frac{V_{PF}^G}{T_P^G} (G_{PC} - G_{PF}) - r_{PGU}
\]
3.8

Glucose metabolic rates shown in above equations have the following general representation:

\[
r = M^I(t) M^G(t) M^R(t) r^R
\]
3.9

where \( M \) reflects the multiplicative effect of each substance on the metabolic rate which means that each substrate affects glucose metabolism independently and in a multiplicative format. The multipliers are potentially time dependant. Most of them have the following general form:
\[ M^C = a + b \tanh[c(C/C^b - d)] \]  \hspace{1cm} 3.10

where \( a, b, c \) and \( d \) are the parameters of the model, \( C \) is the concentration of the substance and \( C^b \) is the concentration of the substance at basal condition.

Glucose metabolic rates are calculated from the following equations:

\[ r_{BGU} = 70 \]  \hspace{1cm} 3.11

\[ r_{RBCU} = 10 \]  \hspace{1cm} 3.12

\[ r_{GGU} = 20 \]  \hspace{1cm} 3.13

\[ r_{PGU} = M_{PGU}^I M_{PGU}^G r_{PGU}^B \]  \hspace{1cm} 3.14

\[ r_{PGU}^B = 35 \]  \hspace{1cm} 3.15

\[ M_{PGU}^I = 7.03 + 6.52 \tanh[0.338(l_{PF}/l_{PF}^B - 5.82)] \]  \hspace{1cm} 3.16

\[ M_{PGU}^G = G_{PF}/G_{PF}^B \]  \hspace{1cm} 3.17

\[ r_{HGP} = M_{HGP}^I M_{HGP}^G M_{HGP}^G r_{HGP}^B \]  \hspace{1cm} 3.18

\[ r_{HGP}^B = 35 \]  \hspace{1cm} 3.19

\[ \frac{d}{dt} M_{HGP}^I = 0.04(M_{HGP}^{I\infty} - M_{HGP}^I) \]  \hspace{1cm} 3.20

\[ M_{HGP}^{I\infty} = 1.21 - 1.14 \tanh[1.66(l_{L}/l_{L}^B - 0.89)] \]  \hspace{1cm} 3.21
\[ M_{HGP}^C = 1.42 - 1.41 \tanh[0.62(G_L/G_L^B - 0.497)] \] 3.22

\[ M_{HGP} = 2.7 \tanh[0.39 \Gamma / \Gamma^B] - f \] 3.23

\[ \frac{d}{dt} f = 0.0154 \left[ \frac{2.7 \tanh[0.39 \Gamma / \Gamma^B] - 1}{2} \right] - f \] 3.24

\[ r_{HGU} = M_{HGU}^{I_H}M_{HGU}^{G^C} r_{HGU}^B \] 3.25

\[ r_{HGU}^B = 20 \] 3.26

\[ \frac{d}{dt} M_{HGU}^{I_H} = 0.04(M_{HGU}^{I_H} - M_{HGU}^I) \] 3.27

\[ M_{HGU}^{I_H} = 2.0 \tanh[0.55 I_L/I_L^B] \] 3.28

\[ M_{HGU}^C = 5.66 + 5.66 \tanh[2.44(G_L/G_L^B - 1.48)] \] 3.29

\[ r_{KGE} = 71 + 71 \tanh[0.11(G_K - 460)] \quad 0 \leq G_K < 460 \] 3.30

\[ r_{KGE} = 71 + 71 \tanh[0.11(G_K - 460)] \quad G_K \geq 460 \]

As above equations show some of the multipliers are time dependant (e.g. 3.20, 3.23 and 3.27).

As equation 3.17 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:

\[ M_{FGU}^G = a(G_{FG}/G_{FG}^B) + b \] 3.31
where $a$ and $b$ are the parameters of glucose multiplier of peripheral glucose uptake rate.

### 3.1.3 Insulin sub-model

A schematic representation of the insulin sub-model is depicted in Figure 3.5. In this sub-model, the body is divided into seven compartments: brain; liver; heart and lungs; periphery (muscles and adipose tissues); gastrointestinal (GI) tract (the stomach and intestinal system); kidney; and pancreas. The sub-model equations comprise mass balance equation over each sub-compartment except for the pancreas compartment. Since pancreatic insulin production is a complex mechanism...
which cannot be described by simple mass balance equations, a separate model is considered for the pancreas.

Mass balance equations over each sub-compartment results in the following equations:

\[
V_B^l \frac{dI_B^l}{dt} = Q_B^l (I_H^l - I_B^l) \tag{3.32}
\]

\[
V_H^l \frac{dI_H^l}{dt} = Q_B^l I_B^l + Q_L^l I_L^l + Q_K^l I_K^l + Q_P^l I_P^l - Q_H^l I_H^l \tag{3.33}
\]

\[
V_G^l \frac{dI_G^l}{dt} = Q_G^l (I_H^l - I_G^l) \tag{3.34}
\]

\[
V_L^l \frac{dI_L^l}{dt} = Q_A^l I_H^l + Q_G^l I_G^l - Q_L^l I_L^l + r_{PIR} - r_{LIC} \tag{3.35}
\]

\[
V_K^l \frac{dI_K^l}{dt} = Q_K^l (I_H^l - I_K^l) - r_{KIC} \tag{3.36}
\]

\[
V_{PC}^l \frac{dI_{PC}^l}{dt} = Q_P^l (I_H^l - I_{PC}^l) - \frac{V_{PF}^l}{T_P} (I_{PC}^l - I_{PF}^l) \tag{3.37}
\]

\[
V_{PF}^l \frac{dI_{PF}^l}{dt} = \frac{V_{PF}^l}{T_P} (I_{PC}^l - I_{PF}^l) - r_{PIC} \tag{3.38}
\]

The insulin consumption rates are calculated from the following equations:

\[
r_{LIC} = 0.4 [Q_A^l I_H^l + Q_G^l I_G^l + r_{PIR}] \tag{3.39}
\]

\[
r_{KIC} = 0.3 Q_K^l I_K \tag{3.40}
\]
Figure 3.6: Biphasic response of a healthy pancreas to a glucose concentration step change

As mentioned before, Sorensen has used a separate model to simulate the pancreatic insulin release. Pancreatic insulin release is mainly stimulated by changes in blood glucose concentration. A healthy pancreas has a biphasic insulin release pattern in response to a glucose concentration step change (see Figure 3.6) with a sharp release of insulin for about 5-10 min (constituting the first phase) followed by a gradual increase of insulin release rate (constituting the second phase) [102].

The pancreatic insulin release model used in the Sorensen model has been proposed by Landahl and Grodsky [103]. The graphical representation of Landahl and Grodsky's model is depicted in Figure 3.7. The aim of Landahl and Grodsky's model is to mimic the biphasic behavior of pancreatic insulin secretion in response to a glucose stimulus.
The schematic diagram of the Landahl and Grodsky’s model is shown in Figure 3.7. This model is a two-compartment model in which a small labile insulin compartment is assumed to exchange insulin with a large storage compartment. The rate at which insulin flows into the labile compartment is regulated by a glucose-stimulated factor, $P$. The rate of insulin secretion, $S$, is dependent 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 pancreas model equations include mass balance equations over its compartments and correlations between variables. The mass balance equation over each compartment results in:
\[
\frac{dm}{dt} = K'm_S - Km + \gamma P - S
\]  
\[3.42\]

\[
\frac{dm_S}{dt} = Km' - K'm_S - \gamma P
\]  
\[3.43\]

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:

\[ K'm_S = Km_0 \]  
\[3.44\]

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

\[
\frac{dP}{dt} = \alpha(P_\infty - P)
\]  
\[3.45\]

\[
\frac{dR}{dt} = \beta(X - R)
\]  
\[3.46\]

\[ S = [N_1Y + N_2(X - R)]m \quad X > R \]  
\[3.47\]

\[ S = N_1Ym \quad X \leq R \]  
\[3.47\]

\[ P_\infty = Y = X^{1.11} \]  
\[3.48\]

\[ X = \frac{G_H^{3.27}}{132^{3.27} + 5.93G_H^{3.02}} \]  
\[3.49\]

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

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

\[ \nu^r \frac{d \Gamma}{dt} = r_{PFR} - r_{PFC} \]  

3.50

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

\[ r_{PFC} = 9.1 \Gamma \]  

3.51

\[ r_{PFR} = M_{PFR}^G M_{PFR}^I r_{PFR}^B \]  

3.52

\[ M_{PFR}^G = 1.31 - 0.61 \tanh [1.06(G_H / G_H^B - 0.47)] \]  

3.53

\[ M_{PFR}^I = 2.93 - 2.09 \tanh [4.18(I_H / I_H^B - 0.62)] \]  

3.54

\[ r_{PFR}^B = 9.1 \]  

3.55

The model parameters are summarized in Table 3.1.
### Table 3.1: The model parameters

<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>13.8 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_{G}^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>15.1 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_{p}^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_L^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_{PC}^I )</td>
<td>0.74 l</td>
</tr>
<tr>
<td>( Q_L^I )</td>
<td>0.90 l/min</td>
</tr>
<tr>
<td>( V_{PF}^I )</td>
<td>6.74 l</td>
</tr>
<tr>
<td>( V^I )</td>
<td>99.3 dl</td>
</tr>
</tbody>
</table>
3.2 Type II diabetes model

To build a model for type II diabetes, in the second step, the selected healthy human body model should be modified for type II diabetic patients according to the abnormalities associated with the patients. This may be done by estimating the model parameters using the available clinical data for type II diabetic patients through a nonlinear optimization problem.

3.2.1 Abnormalities of type II diabetic patients

As mentioned in section 2.2, malfunctioning of different organs leads to high level of blood glucose in type II diabetic patients. These abnormalities are summarized in the following:

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

3.2.2 Selection of model parameters for estimation

The Sorensen model has many parameters; of which, a few need to be estimated. Some of these parameters, such as capillary space volumes and blood flow rates, are physiological factors that are predetermined by a person’s physical body. Since such values have no impact on abnormalities of diabetic patients, they are not considered for parameter estimation and, therefore, remain constant for both diabetic and healthy subjects. The rest of the parameters are in equations representing metabolic rates of glucose, insulin and glucagon besides the parameters of the pancreas model.
Based on abnormalities associated with type II diabetes, some of remaining parameters are selected for estimation.

Based on abnormalities of type II diabetic patients, parameters which are capable for parameter estimation are within the insulin secretion rate and glucose metabolic rates. Considering the functional defects of the liver, peripheral tissues and pancreas, as previously described, nineteen parameters of the Sorensen model are chosen for estimation. As equation 3.10 shows, multipliers which represent multiplicative effects of glucose, insulin and glucagon on glucose metabolic rates have four parameters. Out of nineteen selected parameters, twelve of which are chosen from the insulin multiplier parameters in peripheral glucose uptake rate, hepatic glucose uptake rate and hepatic glucose production rate; and five of which are chosen 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

### Table 3.2: 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 (equation 3.47)</td>
</tr>
</tbody>
</table>
parameter estimation. Table 3.2 summarizes the abnormalities associated with type II diabetes and their corresponding model equations whose parameters are selected for estimation.

### 3.2.3 Nonlinear optimization problem

I have used a set of available clinical data to estimate the parameters of the model by solving a nonlinear optimization problem. I have employed MATLAB environment to solve the optimization problem. The model parameters are estimated through an iterative optimization algorithm which uses a sequential quadratic programming (SQP) method for solving the constrained optimization problem. In each iteration, the new values of the estimated parameters are used to solve the model equations.

The objective function of the optimization problem is to minimize sum deviation of model results from the clinical data for both healthy and diabetic subjects. The best model parameters result in the closest model results to the clinical data. The clinical data set which has been used for the parameter estimation is obtained from a set of frequent blood samples taken from the peripheral tissues during a clinical test. It comprises peripheral glucose and insulin concentrations. The following equation represents the objective function of the optimization problem:

\[
\min_\theta \sum_{i=1}^{n} \left( |G_{PC}^i - G_{PC_c}^i| + |I_{PC}^i - I_{PC_c}^i| \right)
\]

where \(G_{PC}^i\) and \(I_{PC}^i\) are peripheral glucose and insulin concentrations at time \(i\) obtained from the model, respectively; \(G_{PC_c}^i\) and \(I_{PC_c}^i\) are the corresponding clinical measurements; \(n\) is the size of clinical data set; and \(\Theta\) is the vector of selected model parameters.
This optimization problem contains three constraints for the insulin multipliers in peripheral glucose uptake rate, hepatic glucose uptake rate, and hepatic glucose production rate; and one constraint for the glucose multiplier in hepatic glucose uptake rate. These constraints express that the value of the multiplier must be set to 1 at basal conditions. Considering equation 3.10, the general form of the constraints is:

\[ 1 = a + b \tanh[c(1 - d)] \quad 3.57 \]

These constraints can be combined with their corresponding multipliers and no longer be considered as constraints:

\[ M^C = \frac{(a + b \tanh[c(c^{B}/c - d)])}{a + b \tanh[c(1 - d)]} \quad 3.58 \]

For glucose multiplier of peripheral glucose uptake rate (equation 3.31) same constraint is also considered as follows:

\[ 1 = a(1) + b \quad 3.59 \]

Therefore, if only \( a \) is estimated and \( b \) is calculated from above equation, the above constraint is satisfied.

Another constraint for all parameters is that they must remain positive during all calculations.

### 3.2.4 Clinical data set

Different sets of clinical data for type II diabetic patients have been published in literature. Presently, a set of frequently sampled insulin-modified intravenous glucose tolerance test (FSIGT) data, published by Nagasaka et al. [104], has been used to estimate the model parameters. The data set comprises 26 blood samples obtained from eleven non-obese Japanese type II diabetic patients up to 180
minutes. In this test, 0.3 g/kg of isotopically labeled glucose bolus was injected intravenously into the body of the patients followed by a 5 min, 20 mU/kg intravenous insulin infusion after 20 min. Blood samples were frequently taken up to 180 min after the glucose bolus injection. In this study, the basal conditions of diabetic patients were measured at $4.5 \pm 0.4$ mU/l and $117 \pm 7$ mg/dl for peripheral insulin and glucose concentrations, respectively.

### 3.2.5 Parameter estimation results

The parameter estimation results for glucose sub-model are shown in Table 3.3. For the insulin sub-model, the estimation results are $N_1=0.00595$ and $N_2=0.0467$.

| Table 3.3: Parameter estimation results for the glucose sub-model |
|-----------------|---|---|---|---|
|                | $a$ | $b$ | $c$ | $d$ |
| $M_{PGU}^I$     | 2.551 | 1.66 | 0.69 | 3.454 |
| $M_{HPG}^I$     | 1.173 | 1.073 | 0.993 | 1.164 |
| $M_{HGP}^{iso}$ | 0.662 | 0.731 | 0.985 | 0.493 |
| $M_{HGU}^{G}$   | 1.855 | 1.85 | 2.047 | 1.244 |
| $M_{PGU}^{G}$   | 0.897 | 0.103 | - | - |

According to the glucose concentration profile (Figure 3.8 a), injecting the body with a bolus of glucose increases the blood glucose concentration very quickly. As the glucose bolus spreads throughout the body, the glucose uptake rate of body organs increases, resulting in a drop in blood glucose concentrations from 3 min to 10 min. At this point, the glucose concentration gradually decreases until it reaches the steady state amount. As shown, the model estimation results are acceptable for the early peak in glucose concentration and for the model’s overall trend. However, since blood circulation effects are not considered in the structure of the model, there is a discrepancy between the model results and the clinical data during the initial phase. As for the insulin concentration (Figure 3.8 b), the estimated parameters for the insulin profile are acceptable.
3.2.6 Abnormality evaluation of current diabetic patients

Abnormal functioning of organs, such as the liver, pancreas, muscles, and adipose tissues, in utilizing blood glucose results in high blood glucose concentration in diabetic patients. Glucose metabolic rates in the liver, muscles, and adipose tissues may be used to predict the response of these organs during blood glucose concentration changes. In the case of the pancreas, the pancreatic insulin secretion rate is able to predict the behavior of the pancreas in response to glucose stimulus.
Therefore, by comparing the glucose metabolic rate of different organs and the insulin secretion rate in the pancreas with their corresponding rates in a healthy body, the level of organ malfunction in a diabetic patient may be determined.

To perform the comparison, dynamic simulation of a healthy subject has been completed using the Sorensen model. The basal condition for peripheral glucose and insulin concentrations are reported at $91 \pm 8 \text{ mg/dl}$ and $5.1 \pm 0.3 \text{ mU/l}$, respectively [104].

The simulation results of a healthy human subject for peripheral glucose and insulin concentrations are shown in Figure 3.9. The injection of a glucose bolus into a

![Figure 3.9: Peripheral insulin and glucose concentration profiles in the FSIGT test, type II diabetic patients (−) and healthy subjects (---)](image-url)
healthy body rapidly increases the pancreatic insulin secretion rate as well as the peripheral insulin concentrations. Whereas in diabetic patients, because of reduced early phase response of the pancreas and lower insulin production rates, the insulin concentration does not increase significantly.

The glucose concentration profiles indicate a larger early peak of glucose concentration in diabetic patients compared to healthy people. The glucose peak in a diabetic patient is 360 mg/dl, while the corresponding amount for a healthy person is 315 mg/dl. As the overall trend shows, the rate of glucose concentration decrease is significantly lower in diabetic patients than in healthy people. The overall resulting trend in diabetic patients is characterized by a higher early peak and higher glucose concentrations because of higher basal glucose concentration, higher hepatic glucose production rate, and lower peripheral and hepatic glucose uptake rates.

### 3.2.6.1 Peripheral glucose uptake

Peripheral glucose uptake rate profiles for both diabetic patients and healthy subjects are shown in Figure 3.10 (a). The insulin and glucose multipliers of peripheral glucose uptake rate versus normalized peripheral insulin and glucose concentrations for both subject groups are indicated Figure 3.10 (b), (c).

As Figure 3.10 (b) shows, insulin effect on peripheral glucose uptake rate is lowered a little in low peripheral insulin concentrations and significantly in high peripheral insulin concentrations. Similarly, the glucose stimulation effect per se on peripheral glucose uptake rate is decreased (see Figure 3.10 (c)).
Figure 3.10: Peripheral glucose uptake rate during the FSI GT test, (b) insulin and (c) glucose multipliers in peripheral glucose uptake rate versus normalized peripheral insulin and glucose concentrations, type II diabetic patients (−) and healthy subjects (−−)
According to Figure 3.10 (a), after injecting the glucose bolus, the peripheral glucose uptake rate increases significantly in the normal body, while in diabetic patients because of low insulin concentrations as well as insulin resistance no remarkable increase in glucose uptake rate is seen. The level of insulin resistance in peripheral tissues and its effect on peripheral glucose uptake rate is much better revealed by injection of exogenous insulin at time 20 min. At time 20 min, the peripheral insulin concentration is increased with almost identical magnitude for both diabetic patients and healthy subjects, but the increment of peripheral glucose uptake rate in diabetic patients is about half of the corresponding increment in healthy subjects. As such, even when blood insulin concentration is high, the glucose uptake rate in peripheral tissues is low for diabetic patients. It suggests existence of high levels of insulin resistance in peripheral tissues of those particular diabetic patients. As this figure shows, since all basal metabolic rates are assumed to be identical for diabetic patients and healthy subjects, the final value of peripheral glucose uptake rate converges to an identical value for both groups.

### 3.2.6.2 Hepatic glucose production rate

Figure 3.11 (a) shows the hepatic glucose production rate profile for diabetic and healthy subjects. Insulin multiplier of hepatic glucose production rate versus hepatic insulin concentration is also shown in Figure 3.11 (b). As can be seen, the insulin suppression effect on hepatic glucose production is delayed when the hepatic insulin concentration is above the hepatic insulin basal concentration (i.e. when the normalized hepatic insulin concentration is higher than 1). However, its final suppression effect is similar to that of healthy subjects. Since the insulin concentrations in the clinical data set were greater than the basal concentration, the estimated parameters for concentrations lower than basal condition may not be accurate.
As Figure 3.11 (a) shows, the hepatic glucose production rate sharply decreases when glucose concentration increases both in diabetic patients and healthy people. In diabetic patients, this is caused by normal glucose suppression effects on the hepatic glucose production. However, since the insulin secretion rate is low and its suppression effects on endogenous glucose production are impaired, in spite of the higher peak of glucose concentration, during the first few minutes the hepatic glucose production rate remains at a higher level with respect to that of healthy subjects. The gradual decrease in plasma glucose concentration as well as the decrease in insulin concentration from time 25 to 40 min mark results in an increasing of hepatic glucose production from the 40 min onwards in both diabetic

![Graph A](image1.png)

![Graph B](image2.png)

Figure 3.11: Hepatic glucose production rate during the FSIGT test, (b) the functionality of insulin multiplier in hepatic glucose production rate versus normalized hepatic insulin concentration, type II diabetic patients (−−) and healthy subjects (−−)
patients and healthy subjects. Much like the analysis of the peripheral glucose uptake rate, the final value of hepatic glucose production rate is the same both in diabetic patients and the normal body.

### 3.2.6.3 Hepatic glucose uptake rate

Hepatic glucose uptake rate profiles for both diabetic patients and healthy subjects are shown in Figure 3.12 (a). The insulin and glucose multipliers of hepatic glucose uptake rate versus normalized hepatic insulin and glucose concentrations for both subject groups are indicated Figure 3.12 (b) and (c).

Figure 3.12 (b) and (c) suggests that both insulin-induced and glucose-induced stimulation of hepatic glucose uptake rate are impaired in diabetic patients. Although glucose concentration levels are much higher in diabetic patients, the hepatic glucose uptake rate in healthy people is remarkably higher than that of diabetic patients, as indicated in Figure 3.12 (a).

Early increases in glucose and insulin concentrations result in rapid increase of the hepatic glucose uptake rate both in healthy people and in diabetic patients. After the glucose concentration peaks, the glucose multiplier effect on hepatic glucose uptake rate reverses. Since the insulin effect in diabetic patients is impaired, hepatic glucose uptake rate decreases gradually after the glucose peak. In healthy subjects, high insulin concentrations along with the transient time effect on insulin concentration result in increasing the glucose uptake rate until 10 min, which then starts decreasing, as shown in Figure 3.12 (a). The hepatic glucose uptake rate continues its decreasing trend until the glucose concentration reaches its normal value. The final value of hepatic glucose uptake rate converges to the same amount in both diabetic patients and healthy people, analogous to the peripheral glucose uptake rate and hepatic glucose production rate results.
Figure 3.12: Hepatic glucose uptake rate during the FSIGT test, (b) insulin and (c) glucose multipliers in hepatic glucose uptake rate versus normalized hepatic insulin and glucose concentrations, type II diabetic patients (−) and healthy subjects (−−)
3.2.6.4 Pancreatic insulin production rate

Figure 3.13 shows the pancreatic insulin secretion rate during the FSIGT test. As seen in Figure 3.13 (a), the early secretion rate of pancreatic insulin increases very fast within 2 min. As the figure shows, the early peak pancreatic insulin secretion rate of diabetic patients is significantly lowered. The model shows that the final glucose concentration of diabetic patients is higher than healthy people, while the final value of insulin production rate is lower in diabetic patients. It is consistent with the fact that overall insulin production is lower in diabetic patients.

Figure 3.13: Insulin secretion rate during the FSIGT test, (a) 0-10 min, (b) 10-180 min, type II diabetic patients (−) and healthy subjects (−−)
Chapter 4

Diabetic Abnormalities Assessment

In previous chapter, my approach in development of a mathematical model for type II diabetes mellitus was described. After developing the type II diabetes model, it is time to obtain more information from the model. Since the model represents the physiological behavior of diabetic patients, obtained information provides insights of abnormalities associated with the patients which in turn helps coming up with more efficient treatments. At the end of the previous chapter, some general evaluations have been accomplished using the model; however, since multiple abnormalities exist in diabetic patients, accomplished evaluations were not sufficient in differentiation of associated organ dysfunctioning.

In this chapter, a strategy to detect and differentiate possible abnormalities of body organs of type II diabetic patients is proposed. Several *in silico* clinical trials are performed on the developed type II diabetes model. Since pancreatic insulin secretion rate and glucose metabolic rates of different organs represents the functional behavior of the corresponding organ, calculated values of these rates are analyzed and compared with the corresponding rates calculated from a healthy subject model to detect possible abnormalities. These rates are calculated from local estimated values of glucose and insulin concentrations obtained from the model. Estimation of the concentrations in different body organs are carried out through a Sequential Monte Carlo filtering method called particle filters. The results show that the proposed strategy is capable of detecting deficiencies in hepatic and peripheral glucose disposal, endogenous glucose production and pancreatic insulin secretion. The information provided by this strategy can potentially be used to tailor patient dietary requirements and/or select appropriate medications for the patients.
This chapter is organized as follows: Firstly, the mathematical model preparation for including a state estimation method will be described followed by the state estimation method which is a Sequential Monte Carlo filtering method called particle filters will be explained. Then, designed in silico clinical trials will be described and finally how to evaluate the abnormalities of diabetic patients by applying in silico clinical trials.

4.1 Mathematical model preparation

The mathematical model of type II diabetes developed in previous chapter will be used to detect possible abnormal behavior of body organs such as the liver, pancreas and peripheral tissues in type II diabetic patients. Comparing type II diabetes model results with those of healthy subjects may reflect abnormalities of diabetic patients. Since abnormalities of type II diabetes target glucose metabolic rates in the liver and peripheral tissues as well as the pancreatic insulin secretion rate, these rates are considered for comparison and detection. However, calculating the amount of glucose metabolic rates and the pancreatic insulin secretion rate requires glucose and insulin measurements from different parts of the body. Since taking blood samples from all parts of the body (except peripheral tissues) is clinically impossible, glucose and insulin concentrations around or inside different organ systems are just not measurable. An alternative is to estimate these concentrations using available measurements from peripheral tissues along with a mathematical model and a filtering algorithm. Therefore, I have employed a particle filtering algorithm along with the mathematical model to estimate glucose and insulin concentrations in different parts of the body. Description of particle filtering algorithm is provided in the next section.

In order to include particle filtering method in the diabetic model, the model must be discretized. To discretize the model, any discretization method is possible to be
used. I have simply used the fixed-step backward difference approximation since it was accurate enough to discretize the model. The following equation represents general discretization using fixed-step backward difference approximation:

\[
\frac{dy}{dx} \sim \frac{y_i - y_{i-1}}{\Delta x}
\]  

4.1

The above equation is applied to all ordinary differential equations. The model can be then rewritten in state space general form as follows:

\[
x_k = f(x_{k-1}, u_{k-1}, \theta) + v_k
\]  

4.2

\[
y_k = g(x_k, u_k, \theta) + \omega_k
\]

where:

- \(f\) is the state function representing equations (3.1) to (3.8), (3.20), (3.24), (3.27), (3.32) to (3.38), (3.42), (3.45), (3.46), and (3.50)).
- \(g\) is the measurement dynamic function representing equations (3.7) and (3.37).
- \(k\) is the sampling time index.
- \(x_k\) is the vector of states.
- \(u_k\) is the vector of inputs.
- \(y_k\) is the vector of measurements.
- \(\theta\) is the vector of model parameters which are constant values.
- \(v_k\) and \(\omega_k\) are state and measurement noise sequences with known probability density functions with zero mean. Since all real systems normally incorporate different environmental noises affecting the measurements and also mathematical models normally have some uncertainties, these noise sequences are added to the model states and outputs to address usual measurement noises and also model uncertainties.

Since the mathematical model has 22 ordinary differential equations, the size of vector \(x_k\) is 22. Peripheral glucose and insulin concentrations are two model outputs
corresponding to the common measurements of clinical trials and therefore, the size of the vector of outputs is 2. Model inputs are intravenous glucose and insulin infusion rates and therefore, the size of vector $u_k$ is 2.

## 4.2 State estimation

In control theory, state estimator or state observer is a series of mathematical calculations included in a mathematical model of a real system in which provides estimation of model internal states given measurements of input and output from the real system. In most real systems, not all physical states are measureable due to various inherent restrictions. For instance, taking blood samples from many internal body organs in order to obtain measurements of blood glucose and insulin concentrations are extremely difficult, dangerous for the subjects and in most of the times clinically impossible. However, having this type of information is necessary in evaluating the behavior of body organs.

Particle filtering algorithm is a powerful state estimation method whose accuracy is independent on the degree of model nonlinearity and is able to be improved by increasing the number of particles – unlike Kalman filter. I have used particle filtering algorithm as a state estimator method to estimate the hidden states of the type II diabetic model. The model states comprise mainly the glucose and insulin concentrations from all sub-compartments. The estimated values of these concentrations will be used to calculate the glucose and insulin production and consumption rates in different body organs.

### 4.2.1 Particle filters, a Sequential Monte Carlo method

Sequential Monte Carlo (SMC) approach is a recursive Bayesian estimation method for nonlinear and non-Gaussian filtering problems. The basic framework of the SMC approach is presented below.
4.2.1.1 Recursive Bayesian estimation

The SMC approach in filtering problems (Bayesian method) is based on calculating the probability density function (PDF) of model states at current time step $k$ (i.e. $x_k$), given a sequence of measurements from initial time step up to current time step $k$ (i.e. $y_{1:k} = \{y_1, y_2, \ldots, y_k\}$). The Bayesian solution to this filtering problem is to calculate the PDF of $x_k$ given $y_{1:k}$, $p(x_k|y_{1:k})$, for each iteration. The density $p(x_k|y_{1:k})$ is calculated recursively into two steps - prediction step and an update step. In the prediction step, the PDF of $x_k$ is calculated given the sequence of the measurements up to time $k-1$ through the following equation:

$$p(x_k|y_{1,k-1}) = \int p(x_k|x_{k-1})p(x_{k-1}|y_{1,k-1})dx_{k-1} \quad 4.3$$

Then, the density $p(x_k|y_{1:k})$ is updated via following equation:

$$p(x_k|y_{1,k-1}) = \frac{p(y_k|x_k)p(x_k|y_{1,k-1})}{p(y_k|y_{1,k-1})} \quad 4.4$$

The PDF of the initial time step, $p(x_0|y_0)$, is assumed to be known. Equations (4.3) and (4.4) have analytical solutions only for linear processes with Gaussian noise. In most cases the integrals in equation (4.3) are complex and intractable. For general non-linear, non-Gaussian systems described by equations (4.1) and (4.2), there is no simple way to proceed. The Sequential Monte Carlo algorithms make these complex integrals tractable through the use of efficient sampling strategies [105, 106].

4.2.1.2 Sequential Monte Carlo

Gordon et al [107] introduced Sequential Monte Carlo methods for the first time in 1993 and later on, the SMC algorithm has been further developed and adapted to many different applications [106]. It has appeared in the literature in different names such as bootstrap filtering [107], particle filtering [108] and interacting particle approximations [109]. The basic idea of SMC follows the framework of
Bayesian recursive estimation described above. In this approach the recursive computation of relevant probability distributions is accomplished using the concept of importance sampling and approximation of probability distributions by a set of random samples with associated weights.

Considering the model equations represented by equations (4.1) and (4.2), the Bayesian recursive estimation is applied via a SMC algorithm instead of analytically solving the equations (4.3) and (4.4). At each time step \( k \), two pieces of information are required for estimating the PDF: the samples \( x^i_k \) and their associated weights \( w^i_k \). Samples \( x^i_k \) are assumed to be generated from a known PDF called importance density function, \( q(x_k|y_{1:k}) \). Then, the corresponding weights of the samples are calculated from the following equation:

\[
\begin{align*}
    w^i_k &= \frac{p(x^i_k|y_{1:k})}{q(x^i_k|y_{1:k})} \\
    &= \frac{p(x^i_k|y_{1:k})}{q(x^i_k|x_{k-1},y_{1:k-1})} \quad (4.5)
\end{align*}
\]

and the weights after normalization are:

\[
\begin{align*}
    w^i_k &= \frac{w^i_k}{\sum_{i=1}^{N} w^i_k} \\
    &= \frac{w^i_k}{\sum_{i=1}^{N} w^i_k} \quad (4.6)
\end{align*}
\]

where \( N \) is the number of particles used. If the importance density function is chosen to be factorized such that:

\[
q(x_k|y_{1:k}) = q(x_k|x_{k-1},y_k)q(x_{k-1}|y_{1:k-1}) \quad (4.7)
\]

then the samples at time step \( k \), \( x^i_k \sim q(x_k|y_{1:k}) \), are computed by augmenting the existing samples, \( x^i_{k-1} \sim q(x_{k-1}|y_{1:k-1}) \), and the new samples, \( x^i_k \sim q(x_{k}|x_{k-1},y_{1:k}) \). The corresponding weights are updated using the following equation:

\[
\begin{align*}
    w^i_k &\propto w^i_{k-1} \frac{p(y_k|x^i_k)p(x^i_k|x^i_{k-1})}{q(x^i_k|x^i_{k-1},y_{1:k})} \\
    &= \frac{p(y_k|x^i_k)p(x^i_k|x^i_{k-1})}{q(x^i_k|x^i_{k-1},y_{1:k})} \quad (4.8)
\end{align*}
\]

In common cases when only a filtered estimate of \( p(x_k|y_{1:k}) \) is required, it is useful to assume that:
and then, the importance density only depends on $x_{k-1}$ and $y_k$. Under this assumption, equation (8) can be rewritten as:

$$w_k^i \propto w_{k-1}^i \frac{p(y_k|x_k^i)p(x_k^i|x_{k-1}^i)}{q(x_k^i|x_{k-1}^i,y_k)}$$

and the filtered density $p(x_k|y_{1:k})$ can be approximated by the following equation:

$$p(x_k|y_{1:k}) \approx \sum_{i=1}^{N} w_k^i \delta(x_k - x_k^i)$$

where $\delta$ is the Dirac delta function, $x_k^i$ is the $i$th particle that approximates the distribution, and the coefficient $w_k^i$ is the corresponding weight. As $N \to \infty$, the above density approximation approaches the true filtered density $p(x_k|y_{1:k})$.

For type II diabetes model, I have assumed that state and measurement noises have a Gaussian probability density function and affect the model in a linear manner. Therefore, the importance density function, $q(x_k|y_{1:k})$, and model states density functions, $p(x_k|y_{1:k})$, are chosen to be Gaussian.

### 4.3 In silico clinical trials

In silico clinical trials that I have designed for evaluation of abnormalities of type II diabetic patients are based on available real clinical trials common in diabetes research. In section 2.4, some of the common clinical trials usually employed in diabetes research are briefly described. Two of these clinical trials are euglycemic hyperinsulinemic clamp test and hyperglycemic clamp test proposed by Defronzo et al. [76] in 1979 and have been widely used in several studies. I have applied these two tests with some modifications to the developed model of type II diabetes in computer environment. The same tests have also been applied to the Sorensen model to obtain similar data from a healthy individual. Comparing the glucose
metabolic rates and pancreatic insulin secretion rate of diabetic patients with those obtained from healthy subjects will provide insight into any possible organ deficiencies in the patients. In the following section, the original clinical trials proposed by Defronzo et al. [76] are described and then, required modifications to the trials will be explained.

4.3.1 Euglycemic hyperinsulinemic clamp test

4.3.1.1 Original euglycemic hyperinsulinemic clamp test

This test was developed by Defronzo et al. [76] in 1979. In this test, the plasma insulin concentration is raised and clamped at around 100 mU/l by a continuous infusion of insulin. At the same time, the plasma glucose concentration is kept constant at basal levels by glucose injection via a negative feedback principle. High insulin concentration suppresses endogenous glucose production rate to almost zero. Therefore, at steady state conditions, the rate of glucose infusion is equal to the rate of glucose uptake by all body tissues and is therefore a measure of the body insulin sensitivity. This is the only information obtainable from the original test proposed by Defronzo et al.

4.3.1.2 In silico euglycemic hyperinsulinemic clamp test

During the euglycemic hyperinsulinemic clamp test further physiological information could be obtained if measurements of glucose metabolic rates in different body organs were available. However, these metabolic rates are not clinically measureable since taking blood sample from all internal body organs are clinically impossible. They are, however, calculable from the mathematical modeling results. To calculate these rates, insulin and glucose concentrations from corresponding body organs are needed. From the mathematical model, the estimated values of glucose and insulin concentrations are used to calculate the glucose metabolic rates in different organs which in turn will allow determining the
sensitivity of individual organs to insulin. The estimation of glucose and insulin concentrations is performed by particle filtering estimation method.

The additional information obtainable via in silico euglycemic hyperinsulinemic clamp test is as follows:

1- The calculated value of hepatic glucose metabolic rate indicates the insulin mediated effect on hepatic glucose uptake rate as well as its suppression effect on hepatic glucose production rate.
2- The calculated value of peripheral glucose metabolic rate shows the insulin mediated effect on peripheral glucose uptake rate.

4.3.2 Hyperglycemic clamp test

4.3.2.1 Original hyperglycemic clamp test

This test was also proposed by Defronzo et al. [76] in 1979. In the original hyperglycemic clamp test, the plasma glucose concentration is raised and maintained at 125 mg/dl above basal levels by a continuous infusion of glucose. At this steady hyperglycemia level, the amount of glucose infusion rate can be regarded as a measure of how well body cells metabolize glucose and how well the pancreas supplies the required insulin for glucose metabolism. These two general pieces of information are obtainable from the original hyperglycemic clamp test.

4.3.2.2 In silico hyperglycemic clamp test

Similar to the euglycemic clamp test, further physiological information could be obtained from the hyperglycemic clamp test if clinical measurements of the pancreatic insulin secretion rate and glucose metabolic rates in different organs were available. However, these rates are not clinically measureable, but fortunately calculable from the mathematical modeling results. To calculate these rates, I have
used the estimated values of insulin and glucose concentrations obtained from the mathematical modeling results along with particle filtering algorithm. The calculated rates will allow us to detect possible abnormalities of body organs.

During the hyperglycemia condition, four additional important pieces of physiological information are obtainable if the numerical values of the glucose metabolic rates and the pancreatic insulin secretion rate are available:

1. The calculated value of hepatic glucose metabolic rate reflects the glucose suppression effect on hepatic glucose production rate and the glucose stimulation effect on hepatic glucose uptake rate.
2. The calculated value of peripheral glucose metabolic rate shows the glucose stimulation effect on peripheral glucose uptake rate.
3. The calculated value of pancreatic insulin secretion rate indicates the early peak magnitude of the pancreatic insulin production rate.
4. The calculated value of pancreatic insulin secretion rate also indicates the overall production rate of the pancreatic insulin.

However, due to some reasons described in the following section, only the latter can be evaluated from the results of in silico hyperglycemic clamp test in its original scheme (which was proposed by Defronzo et al.). To obtain the rest of the information, some modifications are needed to be made to the test in its original scheme.

4.3.2.3 Modified in silico hyperglycemic clamp test

Abnormalities of peripheral and hepatic glucose uptake in type II diabetic patients are primarily due to three possible different factors:

1. Insulin resistance.
2- Low insulin concentration level.
3- Impaired stimulation effect of glucose per se on its own uptake (glucose resistance).

In previous section, it was described how to assess insulin resistance impact on peripheral and hepatic glucose uptake rate via in silico euglycemic hyperinsulinemic clamp test. As mentioned, during that test, the glucose concentration is clamped at its basal level and the insulin concentration is clamped at 100 mU/l. Therefore, the second factor (i.e. the insulin concentration level) is made identical for diabetic and healthy subjects and the third factor (i.e. glucose resistance) is kept unchanged. Hence, the insulin resistance became assessable without any interference. However, in the original hyperglycemic clamp test by DeFronzo et al., all these three factors may contribute in lowering the blood glucose disposal rate and, therefore, they cannot be evaluated independently.

In order to assess the third factor (i.e. glucose resistance) independently, some modifications are needed for the original hyperglycemic clamp test. To keep the effect of insulin concentration on glucose uptake rate identical for both diabetic and healthy subjects, the insulin concentration must be clamped at an identical value during the hyperglycemic clamp test. On the other hand, to exclude the effect of insulin resistance on glucose disposal rate, it must be kept identical comparing to a reference point. I have proposed the modification of original hyperglycemic clamp test by clamping the insulin concentrations at the same value as in euglycemic hyperinsulinemic clamp test (i.e. 100 mU/l). Now, the results of the modified hyperglycemic clamp test compared with those of the euglycemic hyperinsulinemic clamp test can only reflect the stimulation effect of the glucose per se on the hepatic and peripheral glucose uptake rates without interference of other two factors because:
1- The insulin concentrations of both diabetic and healthy subjects are clamped at an identical level.

2- Since the insulin concentrations are again clamped at 100 mU/l, the insulin resistance effect remains unchanged comparing to the euglycemic hyperinsulinemic clamp test.

Due to the same reasoning, glucose and insulin suppression effects on hepatic glucose production rate cannot be independently differentiated by the original hyperglycemic clamp test results. Therefore, the same modification is made to the original hyperglycemic test (i.e. clamping the insulin concentrations at 100 mU/l and comparing the results with those of the euglycemic hyperinsulinemic clamp test) to evaluate the suppression effect of the glucose per se on hepatic glucose production.

In order to evaluate the magnitude of the early peak of pancreatic insulin secretion rate, the original hyperglycemic clamp test cannot be used as well. In the original test, to clamp the glucose levels at 125 mg/dl higher than the basal level, two different glucose infusion rates are required for type II diabetic patients and healthy subjects due to the abnormalities associated with the diabetic patients, whereas the correct comparison of the pancreatic insulin production rate at the early phase can be performed when the same amount of glucose infusion rate is injected to both groups to provide an identical glucose stimulus. Therefore, a separate in silico hyperglycemic clamp test with identical amount of glucose infusion for both groups is needed to be performed.

Due to above reasons, to obtain the four aforementioned pieces of physiological information, I have simulated three different hyperglycemic clamp tests for both type II diabetic patients and healthy subjects. In the first test, the original hyperglycemic clamp test is performed and the overall rate of the pancreatic insulin secretion is evaluated. In the second test, the hyperglycemic clamp test with
clamped insulin concentrations at 100 mU/l is performed and the glucose stimulation effect on hepatic/peripheral glucose uptake rates and the glucose suppression effect on hepatic glucose production rate are assessed. Finally, the hyperglycemic clamp test with identical glucose infusion rates for both diabetic patients and healthy subjects is performed and the early peak magnitude of the pancreatic insulin secretion rate is evaluated.

### 4.4 Results and discussion

Results of one euglycemic hyperinsulinemic clamp test and three hyperglycemic clamp tests are indicated and discussed here. All *in silico* tests are performed using the type II diabetic model and their results are compared with the simulation results of the Sorensen model in order to detect possible abnormalities of type II diabetic patients. The basal conditions of diabetic and healthy subjects are determined from Nagasaka et al. [104]. I had used the clinical data provided by Nagasaka et al. to develop the type II diabetes model in my previous work [5]. The peripheral insulin and glucose concentrations at the basal condition for the diabetic group were reported to be $4.5 \pm 0.4$ mU/l and $117 \pm 7$ mg/dl, respectively. The corresponding concentrations reported for healthy subjects were $5.1 \pm 0.3$ mU/l and $91 \pm 8$ mg/dl, respectively. The particle filtering algorithm was implemented with 30 particles in all tests.

#### 4.4.1 *In silico* euglycemic hyperinsulinemic clamp test

To perform euglycemic hyperinsulinemic clamp test, the insulin infusion rate is set to 76.87 mU/min and 72.26 mU/min, and the glucose infusion rate is set to 255.8 mg/min and 489.1 mg/min for diabetic patients and healthy subjects, respectively. These values are obtained by trial and error to maintain insulin concentrations at 100 mU/l and glucose concentrations at its basal value (see Figure 4.1).
Figure 4.1: Peripheral insulin and glucose concentrations profiles during *in silico* euglycemic hyperinsulinemic clamp test, type II diabetic patients (−−) and healthy subjects (--).

Figure 4.3 indicates variations of glucose metabolic rates in the liver and peripheral tissues during the test. As shown in Figure 4.3 (c), the hepatic glucose production rate is significantly decreased due to hyperinsulinemia for both groups and therefore, the glucose infusion rate is approximately equal to the net glucose uptake rate of the whole body. The glucose infusion rate shows that the overall sensitivity of the diabetic patients’ body to the insulin is less than that of the healthy subjects by approximately 68%. It reflects high insulin resistance in body tissues of this group of diabetic patients.
To maintain the insulin concentrations at 100 mU/l, the required rate of insulin infusion for diabetic subjects is a bit higher than that of the healthy subjects. This difference is due to the deficiency of pancreatic insulin secretion in diabetic patients which requires more infusion rate of exogenous insulin to maintain identical insulin concentrations for both groups (see Figure 4.2 which indicates the pancreatic insulin secretion rate during the test).

Figure 4.3 shows the peripheral and hepatic glucose metabolic rates during the test. The glucose metabolic rates in diabetic group show abnormal behavior of these organs at hyperinsulinemia. According to Figure 4.3 (a), the peripheral glucose uptake rate in diabetic patients is approximately 66% less than that of healthy subjects. Similarly, the hepatic glucose uptake rate of the diabetic group is 83% less than that of healthy subjects (see Figure 4.3 (b)).

Figure 4.3 (c) indicates that the insulin-induced suppression of hepatic glucose production at hyperinsulinemia condition is normal in the group of diabetic patients. This result agrees with the previous results reported by Defronzo et al. [30] which show fairly normal hepatic glucose production rate for the diabetic patients whose fasting plasma glucose level is lower than 140 mg/dl. The results are...
Figure 4.3: Peripheral and hepatic glucose metabolic rates during in silico euglycemic hyperinsulinemic clamp test, type II diabetic patients (−−) and healthy subjects (−).

also in agreement with the discussion by Defronzo [11] which indicates normal suppression of hepatic glucose production due to hyperinsulinemia over physiological range.
4.4.2 *In silico* hyperglycemic clamp test

4.4.2.1 First hyperglycemic clamp test

In this test, the *in silico* hyperglycemic clamp test in its original scheme is performed and glucose concentrations are clamped at 125 mg/dl above their basal levels. The glucose infusion rate is set to 311.3 mg/min and 1229 mg/min for diabetic patients and healthy subjects, respectively. These values are obtained by trial and error to maintain the peripheral glucose concentrations at 125 mg/dl above the basal level for both groups (see Figure 4.4).

![Graphs showing peripheral insulin and glucose concentrations](image)

**Figure 4.4:** Peripheral insulin and glucose concentrations profiles during the first *in silico* hyperglycemic clamp test, type II diabetic patients (−−) and healthy subjects (−−−)
The glucose infusion rate of the diabetic group shows that the whole body absorption of glucose is significantly low with respect to that of healthy subjects. In the previous section, euglycemic hyperinsulinemic clamp test indicated that this group of patients has high resistance against insulin. In the current test, high insulin resistance of the diabetic group is supplemented by low plasma insulin concentration (due to the deficiencies in the pancreatic insulin secretion) and low stimulation effect of glucose per se on its own uptake. These three factors all together have resulted in significantly low overall body glucose uptake rate by approximately 85% in the diabetic group less than that of healthy subjects.

Simulation results of the first *in silico* hyperglycemic clamp test indicate a severe deficiency of overall pancreatic insulin production. Figure 4.5 shows the pancreatic insulin secretion during the test. As this figure shows, the overall rate of the pancreatic insulin secretion is significantly lower in diabetic patients with respect to that of healthy subjects by approximately 75% which in turn results in lower peripheral insulin concentrations (Figure 4.4 (a)).

The peripheral and hepatic glucose metabolic rates are shown in Figure 4.6. As Figure 4.6 (a) and (b) show, peripheral and hepatic glucose uptake rates are
Figure 4.6: Peripheral and hepatic glucose metabolic rates during the first \textit{in silico} hyperglycemic clamp test, type II diabetic patients (−) and healthy subjects (···)

significantly lowered in the diabetic group with respect to those of the healthy group. It suggests sever deficiency of these organs/tissues; however, since combination of multiple abnormalities may have resulted in such deficiencies, this
test cannot differentiate them. As Figure 4.5 shows, pancreatic insulin secretion rate is significantly impaired in the diabetic group which has led to low insulin concentration (see Figure 4.4 (a)). On the other hand, the previous test demonstrated severe insulin resistance in the liver and peripheral tissues of the diabetic group. Moreover, these patients may be also resistant against glucose (which cannot be diagnosed by the previous and the current tests). Therefore, this test can only detect the pancreatic insulin production deficiency just from the insulin concentration and pancreatic insulin secretion rate profiles. The second in silico hyperglycemic clamp test will be accomplished for the detection of glucose resistance.
4.4.2.2 Second hyperglycemic clamp test

In the second hyperglycemic clamp test, the glucose concentration is clamped at 125 mg/dl above its basal level and the insulin concentration is clamped at 100 mU/l for both diabetic and healthy subjects. The insulin infusion rate is set to 70.11 mU/min and 48.45 mU/min, and the glucose infusion rate is set to 470.9 mg/min and 1372 mg/min for diabetic patients and healthy subjects, respectively. These values are obtained by trial and error to maintain insulin concentrations at 100 mU/l and glucose concentrations at 125 mg/dl above their basal values (see Figure 4.7).

As the infusion rates show, glucose infusion rate for diabetic patients is approximately 73% less than that of healthy subjects. The corresponding value in

Figure 4.7 Peripheral insulin and glucose concentrations profiles during the second in silico hyperglycemic clamp test, type II diabetic patients (−−) and healthy subjects (−−)
the previous test was 85%. This relative increase in glucose infusion rate (and equivalently glucose uptake rate) is due to compensation of required insulin by infusing exogenous insulin and maintaining the insulin concentrations at a high level (100 mU/l). Nevertheless, the glucose infusion rate (and equivalently glucose uptake rate) is still significantly low in the diabetic group with respect to that of healthy subjects. It reflects high insulin resistance and probably glucose resistance (which the latter means impaired stimulation effect of the glucose per se on its own uptake).

Figure 4.8 shows the insulin infusion rate during the second hyperglycemic clamp test. The exogenous insulin infusion rate is also significantly lower in the diabetic group with respect to that of the healthy group which is also in agreement with the results of the previous tests.

Variations of glucose metabolic rates in the liver and peripheral tissues during the second hyperglycemic clamp test are shown in Figure 4.9. Considering the euglycemic hyperinsulinemic clamp test results (Figure 4.3 (a) and (b)) as the reference point and comparing them with current test results (Figure 4.9 (a) and (b)) indicates that in healthy subjects, clamping the peripheral glucose level at 125 mg/dl higher than the basal level causes increasing the peripheral glucose uptake.
rate and hepatic glucose uptake rate by 2.38 and 9.12 times, respectively, while the corresponding values for diabetic patients are 1.94 and 4.02 times. Since the insulin concentration is clamped at 100 mU/l during both tests, insulin hormonal effects on

Figure 4.9: Peripheral and hepatic glucose metabolic rates during the first in silico hyperglycemic clamp test, type II diabetic patients (−) and healthy subjects (−−)
the metabolic rates remain unchanged. Also, since the insulin concentration is kept identical for both tests, the patients’ body resistance against insulin remains unchanged for both tests. Therefore, the only remaining reason for the current deficiencies in glucose metabolic rates is the glucose resistance in those organs/tissues. These results show that peripheral glucose uptake rate and hepatic glucose uptake rate are approximately 19% and 56% less in diabetic patients with respect to those of the healthy subjects due to the glucose resistance.

Figure 4.9 (c) indicates that hepatic glucose production rate is suppressed at the same level in diabetic patients with respect to that of healthy subjects which suggests that the glucose suppression effect on hepatic glucose production rate is normal in diabetic patients.

### 4.4.2.3 Third hyperglycemic clamp test

In the third hyperglycemic clamp test, the glucose infusion rate is set to 500 mg/min for both diabetic and healthy subjects to provide identical glucose stimulation. Figure 4.10 shows initial 110 min of the third *in silico* hyperglycemic clamp test. As Figure 4.10 shows, the magnitude of the early peak of the pancreatic insulin secretion rate is less than that of healthy subjects by approximately 65%.

![Figure 4.10: Pancreatic insulin secretion rate during the third in silico hyperglycemic clamp test, type II diabetic patients (−−) and healthy subjects (−−−)](image-url)
Chapter 5

Mathematical Model Expansion

In two previous chapters, developing a type II diabetes model and explaining how to use the developed model to evaluate the possible abnormalities of type II diabetic patients were discussed. In this chapter, model expansion accomplished on the diabetic model in order to eliminate its drawbacks is presented.

5.1 The main drawback of the model and its solution

As mentioned before, the route of glucose entry into the body plays an important role in maintaining the glucose homeostasis. It is observed that the amount of pancreatic insulin secretion followed by an oral glucose intake is about two to three times greater than the pancreatic secretion amount after intravenous glucose injection in spite of identical increase in the blood glucose level [17-20]. This significant augmentation is known to be associated with the secretion of a group of gastrointestinal hormones called incretins from the walls of the small intestine following the presence of carbohydrates in the lumen of small intestine. Their major contribution in glucose regulation is related to the pancreatic insulin production by stimulation of the pancreas to produce more insulin even before the elevation of the blood glucose level [20, 21]. The two main candidate hormones that fulfill criteria for an incretin are glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) gastric hormones [22-24].

Perhaps the main drawback of the Sorensen model is its assumption on the route of glucose entrance to the body which has limited its applications. The Sorensen model is only able to handle intravenous glucose injection while the oral glucose entrance
is the normal route for glucose entrance into the body. Based on this limitation, the model structure is designed and all model parameters are set. On the other hand, availability of the clinical data is the most important issue for the parameter estimation modeling approach and many of available clinical data are based on the oral glucose test. Since the Sorensen model is incapable of handling the oral glucose intake, this type of clinical data cannot be used for this modeling approach.

To eliminate this drawback, it is sufficient to include the glucose absorption process in gastrointestinal tract. To do this, I have added a model of glucose absorption in the gastrointestinal tract proposed by Dalla Man et al. [110] to the Sorensen model. By including the model of gut glucose absorption into the Sorensen model, the variations of blood glucose concentration resulted from oral glucose intake will be determined. However, the hormonal effect of incretins in boosting pancreatic insulin secretion is not taken into account yet. To include the stimulation effects of incretins on pancreatic insulin secretion, firstly, another model which represents the production and secretion of incretins into the blood circulation is required and secondly, the hormonal effect of incretins on the pancreas in boosting its insulin secretion needs to be taken into account. To do this, firstly, I have added a two-compartment model to the Sorensen model to simulate the release of intestinal incretins followed by the presence of carbohydrate in the small intestine. Secondly, the hormonal effects of the incretins on the pancreatic insulin secretion are considered by modifying the equations calculating the pancreatic insulin release in the Sorensen model.

After incorporating the two aforementioned models into the Sorensen model, the resulted model parameters need to be estimated for healthy and type II diabetic subjects. I have used one set of clinical data to estimate the parameters of the resulted model through solving an optimization problem. Then, the model with new parameters is validated using another set of clinical data from the same subjects. The estimation of model parameters and validation of model results have been
carried out for both healthy subjects and type II diabetic patients. The estimation results show acceptable precision of the model parameters estimation and the validation results demonstrate the capability of the model in accurate prediction of the body response during the clinical tests.

5.2 Methodology

As mentioned above, to eliminate the limitation of the Sorensen model on the route of glucose entrance to the body and to make the model able to handle oral glucose intake, I have added two models to the Sorensen model, one for representing the oral glucose absorption into the gastrointestinal tract and another one for representing the release of incretins into the blood circulation followed by oral glucose intake. Also, the stimulatory hormonal effect of incretins on the pancreatic insulin secretion is implemented by few modifications into the Sorensen model structure. After attaching the glucose absorption model and the incretins model to the Sorensen model and making some modifications into the Sorensen model, the parameters of the resulted model are estimated through solving a nonlinear optimization problem using available clinical data for both healthy and type II diabetic subjects.

Details of the methodology are explained in the following.

5.2.1 The integrated mathematical model

5.2.1.1 The Sorensen model

The Sorensen model in detailed is discussed in section 3.1. Describing concisely, the Sorensen model contains three main sub-models representing variation of glucose, insulin and glucagon concentrations in the circulatory system. Each sub-model is divided into individual number of compartments representing a specific part or
organ of a human body. The number of compartments in each sub-model is determined by the significance of the organ’s job in maintaining the respective solute concentrations. The Sorensen model equations comprise mass balance equations over each sub-compartment except for the pancreas which has a separate model proposed by Landahl and Grodsky [103].

5.2.1.2 The model of glucose absorption in the GI tract

Modeling of glucose absorption in the gastrointestinal tract has been the topic of many researches and several models are proposed in the literature for it [110-115]. In most of these models, it is tried to follow the generic profile of glucose absorption in the gastrointestinal tract. Among the proposed models, I have chosen the model proposed by Dalla Man et al. [110]. It is a detailed compartmental model whose superiority is proved by Dalla Man et al. [110] over the older models in terms of prediction of ingested glucose appearance trajectory in the blood and better precision in estimation of its parameters. The compartmental configuration of this model helps in developing the incretins model more realistically which will be discussed in next section.

The schematic diagram of the Dalla Man et al. model is shown in Figure 5.1. This model has three compartments, two compartments for the stomach (one for the solid phase and one for the liquid phase) and one compartment for the intestine. As shown in Figure 5.1, following the oral glucose intake, glucose enters the stomach in the solid form. After the digestion, it turns into the liquid form and then, enters the small intestine and eventually absorbed to the blood circulation.

Figure 5.2 indicates the connection of the glucose absorption model with the Sorensen model. As the solid arrow shows in Figure 5.2 the glucose absorption model is placed into the gut compartment of the glucose sub-model and is responsible for calculation of the glucose appearance rate into the blood stream.
Figure 5.1: Schematic diagram of Dalla Man et al. model for glucose absorption in the GI tract

following an oral glucose intake. The calculated value of the glucose appearance rate is added as a source of glucose into the equation 3.4 which represents the mass balance over the gut compartment of the glucose sub-model.
The equations of the glucose absorption model comprise mass balance equations over each compartment as follows:

\[
\frac{dq_{ss}}{dt} = -k_{12}q_{ss} + D\delta(t) \tag{5.1}
\]

\[
\frac{dq_{sl}}{dt} = -k_{empt}q_{ss} + k_{12}q_{sl} \tag{5.2}
\]

\[
\frac{dq_{int}}{dt} = -k_{abs}q_{int} + k_{empt}q_{sl} \tag{5.3}
\]

\[
k_{empt} = k_{min} + \frac{k_{max} - k_{min}}{2} \left\{ \tanh[\varphi_1(q_{ss} + q_{sl} - x_1D)] - \tanh[\varphi_2(q_{ss} + q_{sl} - x_2D)] + 2 \right\} \tag{5.4}
\]
\[
\varphi_1 = \frac{5}{2D(1 - x_1)} 
\]
5.5

\[
\varphi_2 = \frac{5}{2Dx_2} 
\]
5.6

\[
Ra = f k_{abs} q_{int} 
\]
5.7

where \( \delta(t) \) is the impulse function. \( x_1, x_2 \) and \( f \) are constant and their values are given in.

Table 5.1: The glucose absorption model constants

<table>
<thead>
<tr>
<th>( f )</th>
<th>( x_1 )</th>
<th>( x_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>0.82</td>
<td>0.00236</td>
</tr>
</tbody>
</table>

\( Ra \) in equation 5.7 is the calculated rate of glucose appearance in the bloodstream. This term is added to the equation 3.4 and equation 3.4 is rewritten as follows:

\[
V_G^G \frac{dG_G}{dt} = Q_G^G (G_H - G_G) - \tau_{GGU} + Ra 
\]
5.8

5.2.1.3 The incretins model

I have modified and used a model initially proposed by Alvehag [116] to simulate the release of incretins from the walls of small intestine followed by the presence of glucose in the duodenum, the first section of the small intestine. Figure 5.2 indicates the connection of the incretins model with the Sorensen model and the glucose absorption model. As the solid arrow in Figure 5.2 shows, this model is added to the Sorensen model as one sub-model along with the other three main sub-models.

Similar to the glucagon sub-model, the incretins sub-model also has one compartment. Its equations comprise two ordinary differential equations, one represents the production of the incretins followed by the presence of the glucose in
the small intestine and the other one represents the mass balance over the compartment.

As mentioned before, the glucose absorption model proposed by Dalla Man et al. [110] allows a more realistic model design for the incretins model. Figure 5.2 indicates the connection of the incretins model with the glucose absorption model. Considering the compartmental configuration of the Dalla Man et al. model which comprises a compartment for the small intestine, the incretins production is calculated from the following differential equation:

\[
\frac{d\psi}{dt} = \zeta k_{empt}q_{s2} - r_{\psi P} \tag{5.9}
\]

where \(\psi\) is the amount of produced incretins, \(k_{empt}q_{s2}\) is the rate of glucose entrance to the small intestine, \(r_{\psi P}\) is the rate of incretins absorption into the blood stream, and \(\zeta\) is a constant. \(r_{\psi P}\) is calculated from the following equation:

\[
r_{\psi P} = \frac{\psi}{\tau_{\psi}} \tag{5.10}
\]

where \(\tau_{\psi}\) is the time constant of the incretins absorption process into the blood stream. The mass balance equation over the incretins compartment results in:

\[
V^\psi \frac{d\psi}{dt} = r_{\psi P} - r_{p\psi C} \tag{5.11}
\]

where \(V^\psi = 11.31 l\) is the incretins distribution volume, \(\psi\) is the blood incretins concentration and \(r_{p\psi C}\) the rate of plasma incretins clearance which depends on the incretins concentration. The clearance rate is calculated from the following equation:

\[
r_{p\psi C} = r_{M\psi C} \psi \tag{5.12}
\]

where \(r_{M\psi C}\) is the mean incretins clearance rate and is a constant.
5.2.1.4 The hormonal effects of incretins on pancreatic insulin secretion

As mentioned few structural modifications are needed to include the hormonal effects of incretins on pancreatic insulin secretion. These modifications are implemented into the pancreas compartment of the insulin sub-model (see Figure 5.2). Considering the Landahl and Grodsky [103] model for the pancreas, it is assumed that incretins stimulate the pancreatic insulin secretion directly in a linear manner and indirectly through enhancing the liable compartment filling factor ($P$) [116]. Therefore, equations 3.47 and 3.48 can be rewritten:

\[
S = [N_1 Y + N_2 (X - R) + \xi_1 \Psi]m \quad X > R
\]
(5.13)

\[
S = (N_1 Y + \xi_1 \Psi)m \quad X \leq R
\]

\[
P_\infty = Y = X^{1.11} + \xi_2 \Psi
\]
(5.14)

where $\xi_1$ and $\xi_1$ are constants.

5.2.2 Parameters of the integrated mathematical model

Similar to the model development for type II diabetes described in Chapter 3, not all model parameters need to be estimated. There is a group of model parameters which are predetermined by a person’s physical characteristics such as blood flow rates, volume of capillary fluid space, volume of interstitial fluid space, etc. These model parameters are assumed to be identical for a typical 70 kg subject and independent to his/her health condition. Values of these parameters are given for a typical 70 Kg person in Table 3.1. Another group of model parameters are in equations representing the production and consumption rates of glucose, insulin, glucagon and incretins in different organs. Since functionality of the body organs may differ from a subject to another one, these parameters may have different numerical values in different individuals. Some of these parameters have been
selected for parameter estimation. The selected model parameters for parameter estimation are presented in the following.

5.2.2.1 The glucose sub-model

From the glucose sub-model, parameters of the glucose metabolic rates and some parameters of the glucose absorption model have been considered for the parameter estimation. As the model equations in Chapter 3 shows, the glucose metabolic rates in the glucose sub-model has the general form of equation 3.9 and the multipliers have the general form of equation 3.10. Considering equation 3.10, $a$, $b$, $c$ and $d$ are the parameters of the glucose metabolic rates. To reduce the number of parameters for estimation $c$ and $d$ are selected for the parameter estimation and $a$ and $b$ are considered to be unchanged.

The glucose absorption model equations are represented by equations 5.1 to 5.7. The model parameters that have been chosen for parameter estimation are $k_{12}$, $k_{min}$ and $k_{abs}$.

5.2.2.2 The insulin sub-model

From the insulin sub-model, some parameters from the pancreas model have been chosen for parameter estimation. The pancreas model is represented by equations 3.42 to 3.49 from which $N_1$, $N_2$, $K$, $\gamma$, $\alpha$ and $\beta$ are selected for parameter estimation.

The hormonal effects of incretins on the pancreatic insulin production are included in equations 5.13 and 5.14. The parameters representing the hormonal effects of incretins on the pancreatic insulin secretion rate are $\xi_1$ and $\xi_2$ which are considered for parameter estimation.
5.2.2.3 The incretins sub-model

The incretins sub-model is represented by equations 5.9 to 5.12. It has three parameters (i.e. $\zeta$, $\tau_\psi$ and $r_{M\Psi_C}$) which all of them are selected for the parameter estimation.

5.2.3 Nonlinear optimization problem

I have used two sets of available clinical data to estimate the parameters of the integrated mathematical model through solving a nonlinear optimization problem. MATLAB environment is employed to solve the optimization problem. The MATLAB programming code used for mathematical modeling are provided in Appendix B. The model parameters are estimated through an iterative optimization algorithm which uses a sequential quadratic programming (SQP) method for solving the constrained optimization problem. In each iteration, the new values of the estimated parameters are used to solve the model equations.

The objective function of the optimization problem is the deviation of model results from the clinical data for both healthy and diabetic subjects. The best model parameters result in the closest model results to the clinical data. The clinical data set which has been used for the parameter estimation is obtained from a set of frequent blood samples taken from the peripheral tissues during a clinical test. It comprises peripheral glucose, insulin and incretins concentrations. The following equation represents the objective function of the optimization problem:

$$\min_\theta \sum_{i=1}^{n} \left( \left( G_{PC_m}^i \right)^2 + \left( I_{PC_m}^i \right)^2 + \left( \Psi_m^i \right)^2 \right)$$

where $\Psi_m^i$ is the incretins concentration and $G_{PC_m}^i$ and $I_{PC_m}^i$ are peripheral glucose and insulin concentrations respectively all obtained at time $i$ from the model; $\Psi_C^i$. 
$G_{PC_c}^l$ and $I_{PC_c}^l$ are corresponding clinical measurements; $n$ is the size of clinical data set; and $\Theta$ is the vector of model parameters.

Similar constraints as presented in section 3.2.3 are also considered for the current optimization problem.

5.2.4 Clinical data

The clinical data sets used here are from the clinical tests performed by Knop et al. [117]. Ten type II diabetic patients (eight men and two women) and ten healthy subjects (eight men and two women) have been selected for the tests. Two different clinical tests are performed on the subjects. A 50 g glucose tolerance test (OGTT test) is performed in the first test and 17 blood samples are taken from the subjects during the test. In the second test, isoglycemic intravenous glucose infusion test (IIVGIT test) is carried out, aimed at copying the plasma glucose profile obtained from the first test. 20 blood samples are taken from the subjects during the second test. Details about the experiments and the subjects’ characteristics are available in [117]. Since the Sorensen model is proposed for a typical 70 kg subject and the clinical data sets which I am working with are from subjects with different body weights, all clinical data is scaled to a 70 kg body weight. The numerical values of the clinical data sets are provided at the end of this chapter.

The information included in data sets are peripheral glucose, insulin and incretins (GLP-1 plus GIP) concentrations. The data from both tests are used for estimating the parameters of the model and validating the model results as follows:

- From the IIVGIT test:
  - Incretins concentrations are not used since no secretion of incretins occurs during the IIVGIT test.
Insulin concentrations are used to estimate the parameters of the pancreas model.
Glucose concentrations are used to validate the model results with new values of the estimated model parameters.

- From the OGTT test:
  - The rest of the integrated model parameters including the parameters of the incretins sub-model, the parameters of the glucose sub-model which also comprises the parameters of the glucose absorption model and the parameters representing the hormonal effects of incretins on the pancreatic insulin production are all estimated using OGTT test data set.

5.2.5 Steady state solution

By adding the model of glucose absorption and the incretins model to the Sorensen model, the integrated mathematical model will have a set of 27 ordinary differential equations (ODE). The initial values for solving the ODEs are calculated by solving the model equations at steady state conditions. To do this, the time derivative terms of the ODEs are set to zero and the metabolic rates are assumed to be at the basal rates. For glucose and insulin sub-models, this results in two sets of decoupled algebraic equations - one for the glucose sub-model and one for the insulin sub-model. To solve the resulting sets of algebraic equations, two unknown variables, one for glucose concentration in the glucose sub-model and one for insulin concentration in the insulin sub-model, needed to be set. Since the clinical data includes the measured values of peripheral insulin and glucose concentrations at time zero, these values in the model are set to their measured values for the steady state solution. For glucagon sub-model, since only the normalized value of glucagon concentration is used in the Sorensen model equations, its basal value is arbitrarily chosen for the steady state condition as it does not affect the simulation. For the
incretins sub-model, the incretins concentrations are considered to be zero at steady states and all clinical data for the incretins concentrations are subtracted from the measured basal incretins concentration.
5.3 Results and discussion

5.3.1 Healthy subjects

The parameter estimation results for healthy subjects are shown in Figure 5.3 and Figure 5.4. Figure 5.3 indicate variations of the peripheral glucose and incretins concentrations during the OGTT test and Figure 5.4 indicates peripheral insulin concentration and pancreatic insulin secretion rate profiles during OGTT and IIVGIT tests. The parameter estimation results look acceptable for the overall trends except

![Figure 5.3: Peripheral glucose and incretins concentration for healthy subjects during the OGTT test, model results (−) and clinical data (●)](image-url)
Figure 5.4: Peripheral insulin concentration and pancreatic insulin secretion rate profiles for healthy subjects during the OGTT test (model results (−), clinical data (●)) and the IIVGIT test (model results (--), clinical data (×)) for the last minutes of the insulin and glucose profiles. This discrepancy is due to the mathematical characteristics of the model. The mathematical solution of the ordinary differential equations ends to the basal concentrations of insulin and glucose (as mentioned in section 5.2.5, at steady state condition all rates and concentrations are at basal level), while the experimental glucose and insulin concentrations end to the values a bit below the basal concentrations which usually take a while to return to their basal levels.
As Figure 5.4 (a) shows, peripheral insulin concentration followed by oral glucose intake is significantly higher than the peripheral insulin concentration followed by intravenous glucose injection. Also, as indicated in Figure 5.4 (b), the amount of pancreatic insulin secretion during the OGTT test is about three times higher with respect to that of IIVGIT test. This is due to the hormonal impact of incretins on the pancreatic insulin production followed by oral glucose intake which boosts the insulin production rate by three times comparing with the same rate when glucose is administered intravenously.

The model results are validated with the remaining clinical data which is the peripheral glucose concentration during the IIVGIT test. The validation results are shown in Figure 5.5. As it is shown, the mathematical model is able to predict the peripheral glucose concentration profile with sufficient accuracy. The model prediction results are a bit off at the last minutes of the test which is due to the mathematical characteristics of the model. As mentioned above, the mathematical solution of ODEs ends to the steady state concentrations of insulin and glucose which are at basal levels, while the experimental glucose and insulin concentrations
end to the values a bit below the basal concentrations which usually take a while to return to their basal levels.

Figure 5.6 shows the total glucose uptake amount for different parts of the body and Figure 5.7 indicates the total exogenous and endogenous glucose supplied to the healthy subjects’ body. Splanchnic area comprises the digestive system and the liver. The summation of glucose uptake amount from the brain, heart and lungs, kidney, and red blood cells are indicated as “other glucose uptake” in Figure 5.6. This summation is almost constant and independent to the type of test [65]. All numerical values in Figure 5.6 and Figure 5.7 are calculated by integrating the rates up to 140 min. As Figure 5.3 to Figure 5.5 show, for both OGTT and IIVGIT tests, the blood glucose, insulin and incretins concentrations return to their basal levels approximately within 140 min and variations of the metabolic rates occur within this period. This period is selected to reduce the effects of constant metabolic rates (e.g. the brain glucose uptake rate) on the accuracy of metabolic rates analysis.
According to Figure 5.6 the splanchnic glucose uptake amount followed by oral glucose intake is significantly higher than when glucose is administered intravenously. Regardless of constant glucose uptake amount from some body organs, the splanchnic area accounts for the majority of the blood glucose disposal during the OGTT test with respect to the peripheral tissues, while this roll is reversed during the IIVGIT test and the peripheral tissues accounts for much more glucose absorption with respect to the splanchnic area. According to Figure 5.7, during the IIVGIT test, the required amount of infused glucose to copy the blood glucose profile resulted from the OGTT test is approximately half of the glucose amount taken orally for the OGTT test. This is due to the secretion of incretins which push the pancreas to produce more insulin for faster glucose disposal from the blood stream during OGTT test. These model predictions are all in agreement with the reports by Defronzo [11] for healthy subjects.

The numerical values of the estimated parameters are provided in Table 5.2, Table 5.3 and Table 5.4.
Table 5.2: Parameter estimation results for glucose metabolic rates (healthy subjects)

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<td>$M_{PGU}^d$</td>
<td>2.03</td>
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Table 5.3: Parameter estimation results for glucose absorption model (healthy subjects)

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<td>$k_{abs} (min^{-1})$</td>
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Table 5.4: Parameter estimation results for insulin sub-model (healthy subjects)

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</thead>
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<tr>
<td>$K (min^{-1})$</td>
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<td>$N_1 (min^{-1})$</td>
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<tr>
<td>$N_2 (min^{-1})$</td>
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<td>$\gamma (U/min)$</td>
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<td>$\xi_1 (l/pmol)$</td>
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<td>$\xi_2 (l/pmol.min)$</td>
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</tr>
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</table>
5.3.2 Type II diabetic patients

The parameter estimation results for type II diabetic patients are shown in Figure 5.8 and Figure 5.9. Figure 5.8 shows variations of the peripheral glucose and incretins concentrations during the OGTT test and Figure 5.9 indicates variations of peripheral insulin concentration during OGTT and IIVGIT tests. Similar to the healthy subjects, the parameter estimation results look acceptable for the overall trends.

Figure 5.8: Peripheral glucose and incretins concentration for type II diabetic subjects during the OGTT test, model results (−) and clinical data (●)
As Figure 5.8 and Figure 5.9 show, in spite of high blood glucose concentration peak in diabetic subjects with respect to that of healthy subjects, the peak of insulin concentration in diabetic patients is about half of the peak insulin concentration in healthy subjects. It suggests a high deficiency of the diabetic patients' pancreas in producing required insulin to reduce the blood sugar level. Nevertheless, like healthy subjects, peripheral insulin concentration followed by oral glucose intake is significantly higher than the peripheral insulin concentration followed by intravenous glucose injection (see Figure 5.8 (a)). Also, as indicated in Figure 5.8

**Figure 5.9:** Peripheral insulin concentration and pancreatic insulin secretion rate profiles for type II diabetic subjects during the OGTT test (model results (−), clinical data (●)) and the IIVGIT test (model results (--), clinical data (×))
Figure 5.10: Peripheral glucose concentration profile for type II diabetic subjects during the IIVGIT test, model results (–) and clinical data (●).

(b), the amount of pancreatic insulin secretion during the OGGTT test is about two times higher with respect to that of IIVGIT test. This is due to the hormonal impact of incretins on the pancreatic insulin production followed by oral glucose intake which boosts the insulin production rate by two times comparing with the same rate when glucose is administered intravenously. It suggests that the hormonal effect of incretins on this group of diabetic patients is fairly normal comparing to the healthy subjects explained in section 5.3.1.

The model results are validated with the remaining clinical data which is the peripheral glucose concentration during the IIVGIT test. The validation results are shown in Figure 5.10. As it is shown, although the model prediction results overestimate the blood glucose concentration profile, the overall model prediction is acceptable and the mathematical model is able to predict the peripheral glucose concentration profile with sufficient accuracy.

Figure 5.11 shows the total glucose uptake amount for different parts of the body and Figure 5.12 indicates the total exogenous and endogenous glucose supplied to the diabetic subjects' body. Splanchnic area comprises the digestive system and the
liver. The summation of glucose uptake amount from the brain, heart and lungs, kidney, and red blood cells are indicated as “other glucose uptake” in Figure 5.11. This summation is almost constant and independent to the type of test [65]. All numerical values in Figure 5.11 and Figure 5.12 are calculated by integrating the rates up to 240 min.

Unlike healthy subjects, due to the multiple abnormalities of diabetes mellitus, the glucose uptake amounts by different organs of the diabetic group are defected. As Figure 5.12 shows, exogenous glucose amounts for IIVGIT and OGTT tests are approximately the same and the route of glucose entrance doesn’t affect the glucose disposal from the blood stream. Although the hormonal effects of incretins looks fairly normal in stimulating the pancreas to secret more insulin (see Figure 5.9), however, due to the high insulin resistance in the liver and peripheral tissues, the blood glucose disposal is blunted and almost independent to the route of glucose entrance.
Figure 5.12: The total exogenous and endogenous glucose supplied to the healthy subjects’ body during OGTT and IIVGIT tests

Same conclusion is also obtained from the glucose uptake amount by the splanchnic area and peripheral tissues shown in Figure 5.11. Results also show high glucose resistance in splanchnic area. During the OGTT test, the glucose concentration at blood streams of splanchnic area is higher with respect to the glucose concentration present at the peripheral tissues. As Figure 5.11 shows, in spite of higher glucose concentration, the contribution of the splanchnic area in blood glucose disposal during the OGTT test is not significant compared to the peripheral tissues and also compared to the corresponding amount during the IIVGIT test, while in healthy subjects, the splanchnic area is responsible for the major blood glucose disposal during the OGTT test. These model predictions are all in agreement with the abnormalities associated with diabetic patients categorized in the introduction section.

The numerical values of the estimated parameters are provided in Table 5.5, Table 5.6 and Table 5.7. The numerical values of the clinical data sets taken from 10 healthy and 10 diabetic subjects used in this chapter are provided in 0.
## Table 5.5: Parameter estimation results for glucose metabolic rates (Diabetic subjects)

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<tr>
<th>Multiplier</th>
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<td>$M_{RGU}^5$</td>
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<td>1.5485</td>
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## Table 5.6: Parameter estimation results for glucose absorption model (Diabetic subjects)

<table>
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<tr>
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<th>Value</th>
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<td>$k_{12}$ (min$^{-1}$)</td>
<td>0.0783</td>
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<tr>
<td>$k_{\text{min}}$ (min$^{-1}$)</td>
<td>0</td>
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<td>$k_{\text{max}}$ (min$^{-1}$)</td>
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<tr>
<td>$k_{\text{abs}}$ (min$^{-1}$)</td>
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## Table 5.7: Parameter estimation results for insulin sub-model (Diabetic subjects)

<table>
<thead>
<tr>
<th>Parameter</th>
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<td>$\alpha$ (min$^{-1}$)</td>
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<td>$K$ (min$^{-1}$)</td>
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<td>$N_1$ (min$^{-1}$)</td>
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<td>$N_2$ (min$^{-1}$)</td>
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<td>$\gamma$ (U/min)</td>
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<td>$\xi_2$ (l/pmol.min)</td>
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Chapter 6

Conclusions and Recommendations

6.1 Summary

The thesis is summarized into the following main outcomes.

6.1.1 Type II diabetes mathematical modeling

Chapter 3 presented the mathematical model developed for type II diabetes mellitus. The developed model was based on a former detailed compartmental model proposed for healthy subjects by Sorensen [65]. In compartmental modeling approach, a number of compartments are considered to represent body organs. The Sorensen model considers individual compartments for organs associated in diabetes research including the liver, pancreas, muscles and adipose tissues which makes it suitable for type II diabetes model development. This model considers the interactions of three substances, glucose, insulin and glucagon on regulating the blood sugar. The model contains three main sub-models representing variations of blood glucose, insulin and glucagon concentrations in different part of the body. Each sub-model is divided into individual number of compartments representing a specific part or organ of a human body. The number of compartments in each sub-model is determined by the significance of the organ’s job in maintaining the respective solute concentrations.

After selecting a suitable model structure, to develop the model for type II diabetes, the Sorensen model was modified for type II diabetic patients according to the abnormalities associated with the patients. The modification carried out by
estimating the model parameters using the available clinical data for type II diabetic patients through a nonlinear optimization problem. Based on the abnormalities of diabetic patients, some of the Sorensen model parameters were selected for parameter estimation. By solving of a nonlinear optimization problem whose objective function is the deviation of model results from the clinical data taken from the diabetic patients, the new model parameters for type II diabetes were obtained. Then, the resulted model with its new estimated parameters was a mathematical representation of those diabetic patients.

At the end of Chapter 3 a general qualitative evaluation of diabetic abnormalities was accomplished using the model simulation results. Glucose metabolic rates along with their associated multipliers as well as pancreatic insulin secretion rate were evaluated and compared with corresponding rates of healthy subjects. The comparison indicated dysfunctioning of different body organs of diabetic patients such as the liver, pancreas and peripheral tissues which had led to their high blood sugar.

6.1.2 Assessment of abnormalities associated with type II diabetic patients

Since multiple abnormalities exist in diabetic patients, the evaluations carried out at the end of Chapter 3 were not sufficient in differentiation of associated organ dysfunctioning and further assessments were needed. In Chapter 4, a strategy to detect and differentiate possible abnormalities of body organs of type II diabetic patients was proposed. Several in silico clinical trials were designed and performed on the developed type II diabetes model to detect the dysfunctioning of different body organs independently. The comparison of calculated values of pancreatic insulin secretion rate and glucose metabolic rates of diabetic patients with those of healthy subjects was considered to be the basis of detection.
To calculate these rates, numerical values of glucose and insulin concentrations from the model were needed. On the other hand, to accommodate the model uncertainties and measurement noises, noise effects were included into the states and outputs of the model. Existence of these noises makes the numerical values of concentrations uncertain. Therefore a Sequential Monte Carlo filtering method called particle filters was used to reduce the effects of noise on numerical values of concentrations estimated from the model. The simulation results of designed *in silico* trial indicated that the proposed strategy was able to differentiate the abnormalities of type II diabetic patients and was capable of detecting deficiencies of body organs independently.

### 6.1.3 Type II diabetes model expansion

Chapter 5 presented the main drawback of the Sorensen model (and in turn the developed type II diabetes model) and proposed a solution for it. The main drawback of the Sorensen model is its limitation on the route of glucose entrance to the body which is restricted to the intravenous glucose injection, while the oral glucose entrance is the normal route for glucose entrance into the body. Based on this limitation, the Sorensen model structure is designed and all model parameters are set. On the other hand, availability of the clinical data is the most important issue for the parameter estimation modeling approach and many of available clinical data are based on the oral glucose test. Since the Sorensen model is incapable of handling the oral glucose intake, this type of clinical data cannot be used for this modeling approach.

To eliminate this drawback, I modified the model structure to accommodate the oral glucose intake. I included the glucose absorption process in gastrointestinal tract by adding a model of glucose absorption in the gastrointestinal tract proposed by Dalla Man et al. [110] to the Sorensen model. By including the model of gut glucose absorption into the Sorensen model, the variations of blood glucose concentration
resulted from oral glucose intake would be determined. To include the hormonal effects of incretins on boosting pancreatic insulin secretion, I added a two compartment model of incretins production to the Sorensen model in order to simulate the variations of incretins concentrations in blood circulatory system. Then, I made a modification into the pancreas model to include the hormonal effects of produced incretins on pancreatic insulin secretion rate. After adding the two models into the Sorensen model, the parameters of the new model needed to be estimated. I used one set of clinical data to estimate the parameters of the new model with the same methodology presented in Chapter 3. Then, the new model results with new parameters were validated using another set of clinical data from the same subjects. The estimation of model parameters and validation of model results were carried out for both healthy and diabetic subjects. The estimation results indicated acceptable precision of the model parameters estimation and the validation results demonstrated the capability of the model in accurate prediction of the body response during the clinical tests.

6.2 Recommendations for future works

6.2.1 Quantitative assessment of abnormalities of diabetic patients

As summarized above, Chapter 4 presented somehow a quantitative assessment of type II diabetic patients by comparing the glucose metabolic rates in different organs and pancreatic insulin secretion rate with those of healthy subjects. The accomplished assessment was able to indicate existence of abnormal behavior of some organs in type II diabetic patients. However, the assessment made for the diabetic patients required the comparison of the metabolic rates with the corresponding rates of healthy subjects. It is possible to define a number of indices to quantitatively assess the abnormalities associated with diabetic subjects without
direct comparison to the corresponding values of healthy subjects. As explained in section 2.4, many indices have defined in the literature to quantify the medical condition of healthy and diabetic patients such as insulin sensitivity index, glucose effectiveness index, QUICKI, HOMA, etc. The numerical value of these indices represents firstly the medical condition of the patients and secondly the severity of possible abnormal behavior. The numerical value of the indices solely carries sufficient information with no need to compare with other values. Some of these indices (e.g. insulin sensitivity index and glucose effectiveness index) are defined based on a mathematical model results. One recommendation for future works is to define several indices from the developed type II diabetes model to quantitatively assess the physiological behavior of different body organs. The numerical value of the defined indices will solely express the medical condition of different body organs and no comparison is needed.

6.2.2 Development of a pharmacokinetic pharmacodynamic model

To lower the blood sugar level, various medications are available for type II diabetic subjects such as insulin, sulfonylureas, meglitinides, biguanides and thiazolidinediones which trigger specific part of the body. Based on the type and severity of abnormalities of any diabetic patient, specific type of medication is administered. These medications are commercialized and commonly prescribed for the patients. Since medications usually trigger specific body organs, the information obtained from the developed type II diabetes model would be helpful in prescribing a suitable medication for the patients. It will increase the chance of prescribing an efficient medication for the patients in a safe and cost effective way.

In addition to above benefit of type II diabetes model, development of pharmacokinetic-pharmacodynamic (PK-PD) models for different medicines is another benefit of the developed type II diabetes model. The term “pharmacokinetics” refers to a branch of pharmacology that studies the fate of an
external substance administered to a live organism. The term “pharmacodynamic” refers to another branch of pharmacology in which the biochemical and physiological effects of a medicine on a live organism is examined. As its definition shows, PK-PD models study the effect of different medicines on the body organs and vice versa. These models provide the opportunity to study the effect of medications on the patients safely without any administration which may be harmful for the patients.

To develop a PK-PD model, a similar approach described in Chapter 5 can be used. A pharmacokinetic model can be attached to the type II diabetes model which represents how the medication is distributed into the body organs and consumed by them. For the pharmacodynamic part, structural modification should be implemented into the type II diabetes model to represent the effects of the medication on body organs. I have contributed in developing a pharmacokinetic pharmacodynamic model for metformin whose preliminary results have been published in [8, 9]. Metformin is an oral medication in the biguanides class which suppresses hepatic glucose production and increases peripheral glucose uptake. Similarly, PK-PD models for other medications can be developed for studying the effects of them on lowering the blood sugar level.
References

[1] International Diabetes Federation, "One adult in ten will have diabetes by 2030," 2011.


[34] B. Ludvik, J. J. Nolan, A. Roberts, J. Baloga, M. Joyce, J. M. Bell and J. M. Olefsky, "Evidence for decreased splanchnic glucose uptake after oral glucose administration


Appendices

Appendix A  Clinical data sets

The numerical values of the clinical data sets used in the fifth chapter are provided here in detailed. These values are normalized by the body weight of the subjects shown in Table 6.1 and Table 6.9.

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Table 6.1: Gender and body weight of healthy subjects

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### Table 6.3: Normalized GIP concentration data set (pmol/l) of healthy subjects for OGTT test

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### Table 6.4: Normalized peripheral glucose concentration data set (mmol/l) of healthy subjects for OGTT test

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Table 6.7: Normalized peripheral glucose concentration data set (mmol/l) of healthy subjects for IVGIT test

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### Table 6.10: Normalized GLP-1 concentration data set (pmol/l) of diabetic subjects for OGTT test

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### Table 6.11: Normalized GIP concentration data set (pmol/l) of diabetic subjects for OGTT test

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Table 6.12: Normalized peripheral glucose concentration data set (mmol/I) of diabetic subjects for OGTT test

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Table 6.15: Normalized peripheral insulin concentration data set (pmol /l) of diabetic subjects for IVGTT test

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Appendix B  Computer programming code

The computer programming code used for computer simulation is provided in this Appendix. As mentioned, MATLAB environment has been employed for all computer simulations.

The computer code for developing the mathematical modeling of type II diabetes is written in multiple m-files. As mentioned, a nonlinear optimization problem has been established and solved in order to estimate the model parameters. The detailed information regarding the development of type II diabetes model is provided in section 3.2 and for the expanded model is provided in section 5.2.

The main routine where the optimization problem is defined is as follows:

```matlab
global UU VV AAA BBB CCC DDD EEE KKK LLL NNN
global AA BB CC DD EE FF GG HH II JJ KK LL MM NN OO PP QQ RR SS TT FFF GGG HHH III;
global WW XX YY;
load CoefficientsDiabetic
fmincon('myfun_Glucose',[0.0970 2.7521 1.0385 0.7121 2 0.3648 3.2606 0.0031 2.0304 1.5485 0 0.0412 0.0783 0.1 30.1404 28.1048 177.9610 0.0027 0.0001],[0.05 1 0.3 0.05 1 0.3 0.4 0 1.7 1.2 0 0.02 0.03 0.03 25 23 150 0.001 0],[0.2 5 4 1 2 1.2 3.5 0.2 2.5 1.6 0.01 0.1 0.1 0.1 35 35 200 0.005 0.001]);

The subroutine "myfun_Glucose" is:

```matlab
function f = myfun_Glucose (x)

global UU VV AAA BBB CCC DDD EEE KKK LLL NNN
global AA BB CC DD EE FF GG HH II JJ KK LL MM NN OO PP QQ RR SS TT FFF GGG HHH III;
global WW XX YY;
```
CC = x(1);
DD = x(2);
HHH = x(3);
III = x(4);
GG = x(5);
HH = x(6);
KK = x(7);
LL = x(8);
OO = x(9);
PP = x(10);
AAA = x(11);
BBB = x(12);
CCC = x(13);
DDD = x(14);
WW = x(15);
XX = x(16);
YY = x(17);
UU = x(18);
VV = x(19);

load GlucoseOGTTData;
load InsulinOGTTData;
load Incretins;

Basal_Condition();
load SS_Con;

[t,y] = ode15s('Dynamic',[0 5 10 15 20 30 45 50 60 70 90 120 150 180 240],[X' Q P I 0 0 0 0 0]);

y1=[y(1,7);y(2,7);y(3,7);y(4,7);y(5,7);y(6,7);y(7,7);y(9,7);y(10,7);y(11,7);y(12,7);y(13,7);y(14,7);y(15,7);y(16,7)];
y2 = [y(1,27);y(4,27);y(6,27);y(8,27);y(10,27);y(12,27);y(13,27);y(14,27);y(15,27);y(16,27)];
y3=[y(1,17);y(3,17);y(5,17);y(6,17);y(7,17);y(9,17);y(10,17);y(11,17);y(12,17);y(13,17);y(14,17);y(15,17);y(16,17)];
\[ f = 0; \]
\[ \text{for } i = 1:\text{size}(s,1) \]
\[ \quad f = f + \text{abs}(s(i,2)-y1(i))^2; \]
\[ \text{end} \]
\[ \text{for } i = 1:\text{size}(\text{Incretins},1) \]
\[ \quad f = f + \text{abs}((\text{Incretins}(i,2)-y2(i))^2; \]
\[ \text{end} \]
\[ \text{for } i = 1:\text{size}(r,1) \]
\[ \quad f = f + \text{abs}((r(i,2)-y3(i))^1.5)^2; \]
\[ \text{end} \]

The subroutine "Basal\_Condition" is:

```matlab
function Basal\_Condition()
    global AA BB CC DD EE FF GG HH II JJ KK LL MM NN OO PP QQ RR SS TT KKK NNN;
    GPC\_B = 153.4;
    rPGU = 35; rBGU = 70; rGGU = 20; rHGP = 155; rHGU = 20;
    QGP = 15.1; QGA = 2.5; QGB = 5.9; QGG = 10.1; QGL = 12.6;
    VBT = 4.5; VPT = 63;
    TGP = 5; TB = 2.1;

    GHC\_B = GPC\_B+rPGU/QGP;
    GKC\_B = GHC\_B;
    GBC\_B = GHC\_B-rBGU/QGB;
    GSC\_B = GHC\_B-rGGU/QGG;
    GLC\_B = (QGA*GHC\_B+QGG*GSC\_B+rHGP-rHGU)/QGL;
    GBT\_B = GBC\_B-rBGU*TB/VBT;
    GPT\_B = GPC\_B-rBGU*TGP/VPT;
    IPC\_B = 5.9;

    FPIC = 0.15; FKIC = 0.3; FLIC = 0.4;
    QIP = 1.05; QIH = 3.12; QIB = 0.45; QIK = 0.72; QIL = 0.9; QIG = 0.72; QIA = 0.18;
    TIP = 20;
    VPT = 6.3;
```

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GAMA = KKK;
K = NNN;
Q0 = 6.33;
M1 = QQ;

IHC_B = IPC_B/(1-FPIC);
IKC_B = IHC_B*(1-FKIC);
IBC_B = IHC_B;
ISC_B = IHC_B;
IPT_B = IPC_B-(QIP*TIP*(IHC_B-IPC_B)/VPT);
ILC_B = (QIH*IHC_B-QIB*IHC_B-QIK*IKC_B-QIP*IPC_B)/QIL;
rPIR_B = QIL*ILC_B/(1-FLIC)-QIG*ISC_B-QIA*IHC_B;
X_B = GHC_B^3.27/(8.595611e6+5.93*GHC_B^3.02);
P_Inf_B = X_B^1.11;
Y_B = P_Inf_B;
P_B = P_Inf_B;
I_B = X_B;
Q_B = (K*Q0+GAMA*P_Inf_B)/(K+M1*Y_B);
S_B = M1*Y_B*Q_B;

save Basal_Condition GBC_B GBT_B GHC_B GSC_B GLC_B GKC_B GPC_B GPT_B IBC_B IHC_B ISC_B ILC_B IKC_B IPC_B IPT_B rPIR_B X_B S_B P_Inf_B Y_B Q_B

X = [GBC_B GBT_B GHC_B GSC_B GLC_B GKC_B GPC_B GPT_B 1 0 1 IBC_B IHC_B ISC_B ILC_B IKC_B IPC_B IPT_B 1];

P = P_B;
I = I_B;
Q = Q_B;

save SS_Con X P I Q

------------------------------------------------------------------------------------------------------------

The subroutine “Dynamic” which contains main model equations is:
function sys = Dynamic(t,x)

global UU VV AAA BBB CCC DDD EEE KKK LLL NNN
global AA BB CC DD EE FF GG HH II JJ KK LL MM NN OO PP QQ RR SS TT FFF GGG HHH III;
global WW XX YY;

vbc=3.5;vbt=4.5;vhc=13.8;vsc=11.2;vlc=25.1;vkc=6.6;vpc=10.4;vpt=63;
VBC=0.265;VHC=0.985;VSC=0.945;VLC=1.14;VKC=0.505;VPC=0.735;VPT=6.3;
VN=113.1;FPNC=9.1;
FKC=0.3;FPC=0.15;FLC=0.4;
qb=5.9;qh=43.7;qs=10.1;ql=12.6;qa=2.5;qk=10.1;qp=15.1;
QB=0.45;QH=3.12;QS=0.72;QL=0.9;QK=0.72;QA=0.18;QP=1.05;
TB=2.1;TPG=5;TPI=20;
rBGU=70;rRBCU=10;rSGU=20;rSIA=0;

% Input for OGTT test
rVI = 0;
rIVG = 0;
if t <= 1
    rMeal = 1;
else
    rMeal = 0;
end

% Input for IIVGIT test
% if t <= 15
%     rIVG = 4.7;
% elseif t > 15 && t <= 30
%     rIVG = 8.62;
% elseif t > 30 && t <= 45
%     rIVG = 10.62;
% elseif t > 45 && t <= 60
%     rIVG = 8.02;
% elseif t > 60 && t <= 75
%     rIVG = 5.38;
% elseif t > 75 && t <= 90

rIVG = 3.26;
% elseif t > 90 && t <= 105
% rIVG = 2.24;
% elseif t > 105 && t <= 120
% rIVG = 0.82;
% elseif t > 120 && t <= 135
% rIVG = 0.48;
% elseif t > 135 && t <= 150
% rIVG = 0.10;
% elseif t > 150 && t <= 165
% rIVG = 0.07;
% else
% rIVG = 0;
% end
%
% rIVG = rIVG/15*1000;
% rVI = 0;
% rMeal = 0;

GBC = x(1);
GBT = x(2);
GHC = x(3);
GSC = x(4);
GLC = x(5);
GKC = x(6);
GPC = x(7);
GPT = x(8);
AIHGP = x(9);
ANHGP = x(10);
AIHGU = x(11);
IBC = x(12);
IHC = x(13);
ISC = x(14);
ILC = x(15);
IKC = x(16);
IPC = x(17);
IPT = x(18);
N = x(19);
Q = x(20);
P = x(21);
I = x(22);

Inc = x(26);
IncC = x(27);

load Basal_Condition

M1 = QQ;
M2 = RR;

ALPHA = LLL;
K = NNN;
GAMA = KKK;
BETA = 0.931;
Q0 = 6.33;
fi1 = UU;
fi2 = VV;
X1 = GHC^3.27/(8.595611e6+5.93*GHC^3.02);
P_INF = X1^1.11+fi1*IncC;
Y = X1^1.11+fi1*IncC;
if X1>I
    S = (M1*Y+M2*(X1-I)+fi2*IncC)*Q;
else
    S = (M1*Y+fi2*IncC)*Q;
end

Qsto1 = x(23); % mg
Qsto2 = x(24); % mg
Qgut = x(25); % mg

Kmin = AAA; % 1/min
Kmax = BBB; % 1/min
\[ Kgri = CCC; \quad \% 1/\text{min} \]
\[ Kabs = DDD; \quad \% 1/\text{min} \]
\[ f = 0.9; \]
\[ a = 0.00013; \quad b = 0.82; \quad c = 0.00236; \quad d = 0.01; \]
\[ D = 50000; \quad \% \text{mg} \]

\[ \alpha = 5/(2*D*(1-b)); \]
\[ \beta = 5/(2*D*c); \]
\[ Qsto = Qsto1+Qsto2; \]
\[ Kempt = Kmin+(Kmax-Kmin)/2*(\tanh(\alpha*(Qsto-b*D))+\tanh(\beta*(Qsto-c*D))+2); \]
\[ Ra = f*Kabs*Qgut; \]

\[ \text{sys}(23) = -Kgri*Qsto1+D*rMeal; \]
\[ \text{sys}(24) = -Kempt*Qsto2+Kgri*Qsto1; \]
\[ \text{sys}(25) = -Kabs*Qgut+Kempt*Qsto2; \]
\[ \text{sys}(4) = ((\text{GHC-GSC})*(qs/vsc))+(Ra/vsc)-(rSGU/vsc); \quad \% \text{Stomach} \]

\[ \text{sys}(26) = WW*Kempt*Qsto2-Inc/XX; \]
\[ \text{sys}(27) = (Inc/XX-YY*IncC)/(VN/10); \]

\[ rPIR = S/S_B*rPIR_B; \]

\[ FFF = 1.425; \]
\[ GGG = 1.406; \]
\[ \text{Denom5} = FFF-GGG*\tanh(HHH*(1-III)); \]
\[ \text{if} \quad \text{Denom5} < 0.01 \quad \text{then} \]
\[ \quad \text{Denom5} = 0.01; \]
\[ \text{end} \]
\[ \text{Num5} = FFF-GGG*\tanh(HHH*(GLC/GLC_B-III)); \]
\[ \text{if} \quad \text{Num5} > = 0 \quad \text{then} \]
\[ \quad rHGP = 155*AIHGP*((2.7*\tanh(0.388*N))-ANHGP)*(FFF-GGG*\tanh(HHH*(GLC/GLC_B-III)))/\text{Denom5}; \]
\[ \text{else} \]
\[ \quad rHGP = 0; \]
\[ \text{end} \]
Denom4 = (MM+NN*tanh(OO*(1-PP)));  
if Denom4 < 0.1  
    Denom4 = 0.1;  
end  
Num4 = MM+(NN*tanh(OO*(IPT/IPT_B-PP)));  
if Num4 >= 0  
    rHGU = 20*AIHGU*(MM+(NN*tanh(OO*(GLC/GLC_B-PP))))/Denom4;  
else  
    rHGU = 0;  
end  

if GKC < 460  
    rKGE=71+(71*tanh(0.011*(GKC-460))));  
else  
    rKGE=-330+0.872*GKC;  
end  

Denom1 = (AA+BB*tanh(CC*(1-DD)));  
if Denom1 < 0.1  
    Denom1 = 0.1;  
end  
Num1 = AA+(BB*tanh(CC*(IPT/IPT_B-DD)));  
TT = 1-SS;  
if Num1 >= 0  
    rPGU = (35*(SS*GPT/GPT_B+TT))*(AA+(BB*tanh(CC*(IPT/IPT_B-DD))))/Denom1;  
else  
    rPGU = 0;  
end  

rKIC = FKC*IKC*QK;  
rPIC = IPT/(((1-FPC)/(FPC*QP))-(TPI/VPT));  
rLIC = FLC*(((IHC*QA)+(ISC*QS)+rPIR);  
rPNR = (1.3102-(0.61016*tanh(1.0571*((IHC/IHC_B)-0.46981))))*(2.9285-(2.095*tanh(4.18*((GHC/GHC_B)-0.6191))));
\[ \text{sys}(1) = \frac{((\text{GHC} - \text{GBC}) \cdot (\text{qb} / \text{vbc})) - ((\text{GBC} - \text{GBT}) \cdot \text{vbt})}{(\text{TB} \cdot \text{vbc})}; \quad \% \text{Brain Capillary} \]
\[ \text{sys}(2) = \frac{((\text{GBC} - \text{GBT}) \cdot \text{rBGU} / \text{vbt})}{(\text{TB})}; \quad \% \text{Brain Interstitial} \]
\[ \text{sys}(3) = \frac{((\text{GBC} \cdot \text{qb}) + (\text{GLC} \cdot \text{ql}) + (\text{GKC} \cdot \text{qk}) + (\text{GPC} \cdot \text{qp}) - (\text{GHC} \cdot \text{qh}) - \text{rRBCU})}{(\text{vhc})} + \frac{\text{rIVG}}{(\text{vhc})}; \quad \% \text{Heart} \]
\[ \text{sys}(5) = \frac{(\text{rHGP} / \text{vlc}) - (\text{rHGU} / \text{vlc}) + (((\text{GHC} \cdot \text{qa}) + (\text{GSC} \cdot \text{qs}) - (\text{GLC} \cdot \text{ql})) / \text{vlc})}{(\text{TB})}; \quad \% \text{Liver} \]
\[ \text{sys}(6) = \frac{((\text{GHC} - \text{GKC}) \cdot \text{qk} / \text{vkc}) - (\text{rKGE} / \text{vkc})}{(\text{TB})}; \quad \% \text{Kidney} \]
\[ \text{sys}(7) = \frac{((\text{GHC} - \text{GPC}) \cdot \text{qp} / \text{vpc}) + ((\text{GPC} - \text{GPT}) \cdot \text{vpt})}{(\text{TPG} \cdot \text{vpc})}; \quad \% \text{Periphery Capillary} \]
\[ \text{sys}(8) = \frac{((\text{GPC} - \text{GPT}) / \text{TPG}) - (\text{rPGU} / \text{vpt})}{(\text{TB})}; \quad \% \text{Capillary Interstitial} \]

\[ \text{Denom2} = (\text{EE} - (\text{FF} \cdot \tanh(\text{GG} \cdot (1 - \text{HH}))); \]
\[ \text{if} \quad \text{Denom2} < 0.1 \]
\[ \quad \text{Denom2} = 0.1; \]
\[ \text{end} \]
\[ \text{Num2} = \text{EE} - (\text{FF} \cdot \tanh(\text{GG} \cdot (\text{ILC} / \text{ILC_B} - \text{HH}))); \]
\[ \text{if} \quad \text{Num2} \geq 0 \]
\[ \quad \text{sys}(9) = \frac{(1/25) \cdot ((\text{EE} - (\text{FF} \cdot \tanh(\text{GG} \cdot (\text{ILC} / \text{ILC_B} - \text{HH})))) / \text{Denom2} - \text{AIHGP})}{(\text{TB})}; \]
\[ \text{else} \]
\[ \quad \text{sys}(9) = (1/25) \cdot (-\text{AIHGP}); \]
\[ \text{end} \]

\[ \text{sys}(10) = \frac{(1/65) \cdot ((1.35 \cdot \tanh(0.388 \cdot N)) - 0.5 - \text{ANHGP})}{(\text{TB})}; \]

\[ \text{Denom3} = (\text{II} + \text{JJ} \cdot \tanh(\text{KK} \cdot (1 - \text{LL}))); \]
\[ \text{if} \quad \text{Denom3} < 0.1 \]
\[ \quad \text{Denom3} = 0.1; \]
\[ \text{end} \]
\[ \text{Num3} = \frac{(\text{II} + \text{JJ} \cdot \tanh(\text{KK} \cdot (\text{ILC} / \text{ILC_B} - \text{LL})))}{(\text{TB})}; \]
\[ \text{if} \quad \text{Num3} \geq 0 \]
\[ \quad \text{sys}(11) = \frac{(1/25) \cdot ((\text{II} + \text{JJ} \cdot \tanh(\text{KK} \cdot (\text{ILC} / \text{ILC_B} - \text{LL})))) / \text{Denom3} - \text{AIHGU})}{(\text{TB})}; \]
\[ \text{else} \]
\[ \quad \text{sys}(11) = (1/25) \cdot (-\text{AIHGU}); \]
\[ \text{end} \]

\[ \text{sys}(12) = \frac{(\text{IHC} - \text{IBC}) \cdot \text{QB} / \text{VBC}}{(\text{TB})}; \quad \% \text{Brain} \]
\[ \text{sys}(13) = \frac{(\text{IBC} \cdot \text{QB}) + (\text{ILC} \cdot \text{QL}) + (\text{IKC} \cdot \text{QK}) + (\text{IPC} \cdot \text{QP}) - (\text{IHC} \cdot \text{QH})}{(\text{VHC})} + \text{rIVI} / \text{VHC}; \quad \% \text{Heart} \]
\[ \text{sys}(14) = \frac{(\text{IHC} - \text{ISC}) \cdot \text{QS} / \text{VSC}}{(\text{TB})}; \quad \% \text{Stomach (Gut)} \]
sys(15) = (((IHC*QA)+(ISC*QS)-(ILC*QL))/VLC)+((rPIR-rLIC)/VLC); %+rIVI/VLC; % Liver
sys(16) = ((IHC-IKC)*QK/VKC)-(rKIC/VKC); % Kidney
sys(17) = ((IHC-IPC)*QP/VPC)-((IPC-IPT)*VPT/(TPI*VPC)); % Periphery Capillary
sys(18) = ((IPC-IPT)/TPI)+((rSIA-rPIC)/VPT); % Periphery Interstitial
sys(19) = (rPNR-N)*FPNC/VN;
sys(20) = K*(Q0-Q)+GAMA*P-S;
sys(21) = ALPHA*(P_INF-P);
sys(22) = BETA*(X1-I);

sys = sys'