MATHEMATICAL MODELS WITH DELAYS FOR GLUCOSE-INSULIN REGULATION AND APPLICATIONS IN ARTIFICIAL PANCREAS

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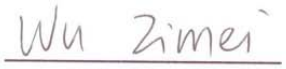
DECLARATION

I hereby declare that the thesis is my original work and it has been written by me in its entirety.

I have duly acknowledged all the sources of information which have been used in the thesis.

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



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Summary

With development of insulin, blood glucose meters and insulin delivery devices, automatic regulation of glucose level is feasible. Closed-loop insulin delivery system (also known as an artificial pancreas) could potentially be the ultimate solution for blood glucose control in diabetic patients. Three indispensable factors of a blood glucose regulation device are: glucose sensor for measuring glucose concentration, control algorithm regulating external insulin infusion, and insulin infusion device. With good knowledge of the physiology of blood glucose regulation, an accurate glucose-insulin interaction model and a safe, efficient glucose control algorithm could be developed.

Many researchers have proposed models of human glucose-insulin system to match predicted mechanism of endocrine system and investigate the underlying causes of diabetes. Optimal glucose control can be achieved by subcutaneous insulin delivery after subcutaneous glucose measurement. It is crucial to investigate dynamics of glucose and insulin in the subcutis. A new two-compartmental model with two explicit delays on hepatic glucose production and insulin secretion was applied to investigate the oscillatory behavior of glucose-insulin system when there is no external insulin delivery. Four parameters in insulin system and two delays were analyzed for their influence on glucose-insulin system; their ranges were estimated for sustaining the oscillations and discussed. Effect of these parameters on the lag between glucose and insulin in different compartments provide insights on distribution and metabolism of glucose and insulin in different compartments. Physiological delay has been demonstrated to be an important issue for effective blood glucose regulation.

Local degradation and time delay of transportation and absorption should be considered in the insulin module of the glucose-insulin system if exogenous insulin is

injected in the subcutaneous tissues. Based on the two-compartmental model, a modified model, including two absorption channels and local insulin degradation, was proposed to simulate glucose-insulin system with external insulin delivery. Two rate parameters expressing insulin transportation from subcutis to plasma compartment, two delays and two parameters expressing the dysfunction of diabetic patients were adjustable and estimated using nonlinear least squares method. Clinical data comprising glucose level, insulin injection dosage and meals was collected from diabetic inpatients. By comparing fitting results with existing model, the proposed model can mimic the dynamics of glucose and insulin. The estimated model parameters were physiologically meaningful, and provided insights on the subject's dysfunction due to diabetes.

The goal of a model predictive control (MPC) is to minimize an objective function by selecting optimal input moves. MPC has been used in glucose level regulation. Insulin dosage calculated by the MPC controller is the input to the plant (i.e., human body). Glucose level was output and feed to MPC controller. Two MPC controllers using the two-compartment model and the model including the dynamics of subcutaneous insulin were investigated, and results of glucose control were compared with that of Bergman minimal model and Hovorka model, respectively. MPC controllers using our models were demonstrated to be able to reduce occurrence of hypoglycemia and hyperglycemia, cost less insulin and better deal with glucose changes caused by unnoticed glucose disturbances.

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List of Abbreviations

CGM	Continuous glucose monitoring
CGMS	Continuous Glucose Monitoring System
EGP	Endogenous glucose production
FFA	Free fatty acid
GIR	Glucose infusion rate
HGP	Hepatic glucose production
IS	Insulin secretion
IDGU	Insulin-dependent glucose utilization
IIGU	Insulin-independent glucose utilization
ISF	Interstitial fluid
IVGTT	Intravenous glucose tolerance test
MPC	Model predictive control
MRAD	Median relative absolute difference
NRLS	Non-linear recursive least squares
ODE	Ordinary differential equations
OGTT	Oral glucose tolerance test
PD	Proportional-derivative
PID	Proportional-integral-derivative
PK	Pharmacokinetic
SC	Subcutaneous
SSE	Sum of the square error

1 Introduction

1.1 Diabetes Mellitus

Diabetes Mellitus is a common disease around the world, which can induce various systemic diseases and high mortality. The World Health Organization estimates that there are more than 180 million people suffering from diabetes, and the number may double by 2030. Diabetes can be catalogued into Type 1 and Type 2 diabetes. Type 1 diabetes, often occurring among children and young, makes up 5% to 10% of diabetes cases, and is characterized as inability of producing any insulin by their bodies. While Type 2 diabetes, usually developing in middle aged or later, is associated with high insulin resistance, which results in unused glucose cumulating in body to cause hyperglycemia and tissue damage over time .

High blood glucose level can cause high osmotic pressure in the extracellular fluid resulting in considerable cellular dehydration. Secondly, high level of glucose would cause glucose loss in the urine, which is followed by osmotic dieresis depleting fluids and electrolytes of the body. Besides, long-term high blood glucose can damage many tissues, especially blood vessels. Low glucose concentration below 45-55 mg/dL for a long interval may bring about brain function impairment, tremors and convulsions. An intensive insulin therapy can reduce the risk of complications resulted from diabetes. Hyperglycemia can be minimized and hypoglycemia can be avoided by proper insulin delivery.

The conventional therapy of diabetes is multiple subcutaneous insulin injections using long or short acting insulin analogues after glucose level measurement by glucose monitor. Insulin pen devices can make insulin delivery more convenient. There are some

other routes of insulin delivery such as inhaled insulin, orally administered insulin, transdermal insulin delivery and so on. Continuous subcutaneous insulin infusion using external insulin pump has been applied to regulate blood glucose concentration. In the past decades, some continuous or semi-continuous glucose monitors and insulin infusion pumps have received approval, both of which promote the development of closed-loop insulin delivery system. A closed-loop insulin delivery system relying on a continuous glucose sensor, insulin infusion pump and an advanced control algorithm can be developed to control blood glucose concentration automatically.

The control algorithm can optimize insulin dose to be delivered to the patient by insulin pump in order to maintain glucose concentration within the normal range. Proportional-integral-derivative (PID) method to control blood glucose level has attracted interests of many researchers [4-7]. Difference between measured glucose level and reference value multiplied by proportional constant, integrated over a period of time, and its derivative are used to control the insulin input. Although the simple control approach is easy to implement, it cannot provide insight into the physiological meaning of the metabolic system, and human expertise is needed to ensure the successful operation, which restricts greatly the functioning of this approach. Due to the complexity of nonlinear dynamics of glucose-insulin metabolic system, model predictive control (MPC) taking advantage of detailed process models and information regarding process constraints or limitations is more advantageous in regulating blood glucose concentration. Advanced control algorithm is one of the three important factors developing closed-loop insulin delivery system and has been established to aid in the diabetes treatment.

1.2 Closed-Loop Insulin Delivery System

The closed-loop insulin delivery system, which is also called artificial pancreas, is composed of three essential components: a stable glucose sensor for measuring the glucose concentration, a control system regulating external insulin infusion based on the glucose-insulin system and a safe and stable insulin infusion device [1].

1.2.1 Types of Closed-Loop Insulin Delivery System

There are two ways to divide the closed-loop insulin delivery system: way of prandial insulin delivery and the body interface. Glucose excursion by meals is a great challenge to closed-loop insulin delivery system. In a closed-loop insulin delivery system, insulin is delivered fully automatically without knowledge of exercise or meals' time, size or composites, and it is only based on the evaluation and prediction of the measured glucose level. In a closed-loop insulin delivery system with meal announcement, the system is informed of the time and size of the meals and gives out advised prandial insulin bolus to deliver [2]. There is also a hybrid approach which delivers up to 50% of bolus insulin and leaves the remaining to be delivered during the feedback.

There are three types of closed-loop insulin delivery system according to the body interface: sc-sc system (subcutaneous glucose sensing and subcutaneous insulin delivery), iv-ip system (intravenous glucose sensing and intraperitoneal insulin delivery), and iv-iv system (intravenous glucose sensing and intravenous insulin delivery). Insulin delivery via subcutaneous route has advantages over intravenous or intraperitoneal route: low incidence of infection, less pain and discomfort and ease of administration. The sc-sc system is easy and safe to implement though it results in insulin absorption delay. The iv-iv system is usable under some situations such as surgical operations, for critically ill and

research investigation. However, this approach is high invasiveness due to the need of vascular access for the glucose sensing and insulin delivery. Up to now, there are a few prototypes developed and tested under limiting clinical conditions.

1.2.2 Prototypes of Closed-Loop Insulin Delivery System in Market

Median relative absolute difference (MRAD) is often used to evaluate the performance of the continuous glucose monitoring (CGM). Freestyle Navigator CGM (Abbott Diabetes Care, Alameda, CA, US) is reported to achieve an average MRAD of 14% [2]. Continuous Glucose Monitoring System (CGMS, Medtronic Minimed, Northridge, CA, US) [3] is reported with slightly higher MRAD than Freestyle Navigator CGM, and DexCom Seven STS [4] with an MRAD of 11.4%. The three CGMs can be used for 3, 5, and 7 days in a closed-loop insulin delivery system, respectively.

The earliest closed-loop insulin delivery system was the Biostator, Glucose-Controlled Insulin Infusion System, introduced in 1977, which was an iv-iv system using a glucose oxidase sensor to measure the glucose level in the blood and peristaltic pump to deliver insulin and glucose intravenously. The control algorithm of Biostator is oversimplified. After Biostator, Shichiri's group developed a wearable artificial pancreas named STG-22 (Nikkiso Co. Ltd., Japan) [5] using the sc-sc route and sc-ip route, and the microdialysis type glucose sensor in the system can work up to 7 days.

Medtronic Minimed developed an external physiologic insulin delivery [6] employing the CGMS (Medtronic Minimed, Northridge, CA, US) and the Medtronic 511 Paradigm Pump with a PID controller [7]. Studies using the system is performed on dogs [8] and 10 subjects with Type 1 diabetes [6]. Glucose level keeps in the range 3.9-10

mmol/L 75% of the time applying closed-loop treatment, compared with that of 63% for open-loop treatment.

Roche Diagnostics developed a sc-sc semi-closed-loop prototype with meal announcement employing subcutaneous continuous glucose monitor (SCGM1, Roche Diagnostics GmbH, Germany) which can monitor glucose level for 4-5 days [9]. Insulin bolus was administrated every 10 min, which is determined by an "empirical algorithm" based on clinical observations. The system was tested on twelve Type 1 diabetic subjects over 32 hours. It was shown that the algorithm can reach near-target glucose level and reduce the number of hypoglycemia interventions. 60% of SCGM1 readings were in the range 5-8.3 mmol/L compared to that of 45% under self-directed treatment. An European Commission funded project Advanced Insulin Infusion using a Control Loop [10] also developed a sc-sc semi-closed-loop with meal announcement, which is composed of a minimally invasive glucose monitor system, an insulin pump (Disetronic D-Tron) and a PocketPC computer. An adaptive nonlinear MPC is applied in the system.

The Renard group developed an implantable insulin delivery system employing a long-term sensor system [11, 12] which is an intravenous enzymatic oxygen-based sensor by Medtronic Minimed (Northridge, CA, US) implantable in the superior vena cava. The pump, implementing Proportional-derivative (PD) control, is implanted in the abdominal wall and delivers insulin intraperitoneally. The system implemented test on four elderly Type 1 diabetes subjects over 2 days and for 84.1% time glucose level is in the range of 4.4-13.3 mmol/L [1].

The sc-sc system will gain wide applications in the near future due to its safety and convenience to implement and maintain. However, there are two physiological factors

affecting the performance of a sc-sc system. One is the delay between insulin delivery and sensed glucose lowering. It would take some time for the glucose level to go down after the insulin delivery; therefore, subjects using insulin pumps should be alerted insulin overdosing due to insulin administrations in a close sequence, which is followed by hypoglycemia. The other factor is the inter-subject variability of insulin delivery. Actually, developing a "one size fits all" closed-loop system is difficult due to some factors such as age, gender, body mass index, physical exercise or some other diseases. For the same person, insulin needs are different day-to-day or even hour-to-hour because of some physiological or physical reasons. The problem of insulin absorption delay can be solved by including the delay in the model of glucose-insulin metabolic system. The second factor causes problem for all the closed-loop insulin delivery systems, which is expected to be improved by advanced control algorithm such as MPC.

1.3 Motivation and Scopes

Subcutaneous glucose monitoring and insulin delivery is advantageous over the other two approaches for closed-loop insulin delivery system. Therefore, subcutaneous tissue is to become the main measurement site of glucose sensor and administration sit of exogenous insulin. It is therefore important to understand the kinetics interactions of glucose and insulin between plasma and subcutaneous tissues.

The timing and amplitude difference of plasma glucose and glucose in interstitial fluid (ISF) may reflect the variation of glucose uptake, utilization and elimination in blood, ISF and cells [13]. Besides, the lag and amplitude difference are also characteristics of insulin kinetics between plasma and ISF. However, in most current

studies, glucose [14-18] and insulin [15, 18] are considered as a one-compartment model during the study of the physiological processes. The ignorance of the lag and amplitude difference of glucose in the two compartments would result in loose control of glucose level to cause hyper- or hypoglycemia. Therefore, a new two-compartment model is developed to express the glucose and insulin metabolic system.

The new two-compartment model aims to study the physiological phenomenon and pathology in diabetes by analyzing the changes of glucose and insulin level, lags existing in the glucose-insulin system and the effect of model parameters on the oscillatory behavior of glucose-insulin system. Using the proposed mathematical model, the effect of the model parameters on blood glucose regulation is investigated. Some key issues are analyzed from the perspective of physiology and pathology:

- Effect of model parameters on the oscillatory behavior of the glucose-insulin system.
- Pathological relations of parameters' change with some diseases related to abnormal glucose level.
- Influence of model parameters on the interactions of glucose and insulin between plasma and ISF compartment regarding physiological lags and amplitude differences.

The two-compartment model without considering external insulin injection/ infusion is developed and analyzed physiologically. For diabetic patients, external insulin injected subcutaneously is administered to the two-compartment model to simulate the metabolism of glucose and insulin. It is the first model to include the dynamics of injected insulin into the glucose-insulin model for type 2 diabetic patients. This model

considering the dynamics of injected insulin provides insights on the dynamics of human blood glucose regulation, and helps derive control algorithms for treatment of diabetic patients. The following points were studied:

- In order to model insulin absorption delay in the sc-sc insulin delivery system, the ISF compartment of insulin in the two-compartment model aforementioned was separated into three compartments considering insulin degradation at the injection site and two insulin absorption channels.
- Six model parameters value were estimated by fitting the model with injected insulin to clinical data of diabetic patients, and the fitting result of our model is compared with that of Hovorka model.
- The six model parameters were discussed physiologically and pathologically considering the situations of the diabetic subjects.
- MPC controller was investigated using the two-compartment model and the modified model with subcutaneous insulin, and compared the control performance with that of using Bergman minimal model and Hovorka model, respectively. The glucose curves and insulin dosages in the simulations of the models were compared accordingly to evaluate the performance of glucose control.

1.4 Thesis Organization

The aim of this thesis is to study the oscillatory behavior of glucose and insulin and assess the feasibility of using the model to control blood glucose concentration for diabetic patient. A detailed model of glucose-insulin system is indispensable to achieve this. Chapter 2 introduces some established mathematical models of glucose-insulin

system. In chapter 3, a two-compartment model was developed and analyzed physiologically to investigate the oscillatory behaviors of glucose and insulin. The two-compartment model was modified to simulate the dynamics of insulin injected subcutaneously in Chapter 4. The model parameters in the modified model were estimated using the clinical data of diabetic subjects and discussed and related to diabetes. MPC controllers were developed in Chapter 5 using the two-compartment model and the modified model with injected insulin. The control performance of the two models was compared with that of Bergamn minimal model and Hovorka model, respectively. Simulation results addressed the challenges in using the current models to design a closed-loop insulin delivery system. A discussion on the future modeling of glucose-insulin system was introduced in Chapter 6. Further investigation of virtual patient model is necessary with the growing understanding of diabetes.

2 Review of Virtual Patient Models

Since the development of the concept of “artificial pancreas”, there have been many researchers studying on the modeling of glucose-insulin regulation system in order to understand the mechanism of endocrine system and causes of diabetes and develop a safe, efficient glucose control device to relieve the suffering of the diabetes patients. These virtual patient models promote the development of advanced control algorithm to regulate glucose concentration and investigation of the pathophysiology of diabetes.

Most mathematical models of glucose-insulin system are based on the idea of compartment. When compartmental model is applied to describe the metabolic system composed of a series of interconnected compartments, there are several specifications needed to be illustrated: compartment number, input and removal sites, and mathematical relations of interdependences and controls [19].

The glucose-insulin regulatory system is a complex system controlled by many cerebral signals and hormones; up to now, there has not been a model which can express all the interactions of glucose and insulin in the human body. Even, there is much physiological phenomenon in human being body which still cannot be explained by researchers. Some models developed during the last few decades are introduced in this chapter. The advantages and shortcomings of the glucose-insulin models are reviewed in [20-22].

Virtual patient models can be catalogued into two groups. One is the pharmacokinetic (PK) model, in which absorption and clearance kinetics are expressed, and some compartments are determined related to the elimination and absorption. The other type is the physiological models in which organ system is considered as a

compartment, and mass balance of each organ is written by considering convection due to metabolic processes, and diffusion between blood and organ cells. The PK models are easier to identify from experimental data compared with the second type.

The early PK model developed by Bolie consisted of one linear equation for insulin and one for glucose [23]. First order rate equations were used to express absorption and elimination kinetics. This model was modified by Ackerman et al. [24] by involving insulin and other hormones in glucose regulation together as a single variable. The glucose regulatory system is still oversimplified due to the fact that insulin or hormone secretion is more complex than a first order process.

A two-compartment model for insulin in normal and diabetic patients was developed by Frost et al. [25]. Insulin secretion rate was considered as an exponential function of glucose for normal subjects and zero for diabetic subjects. Insulin elimination was expressed by a nonlinear saturation function of insulin for normal subjects and a first order process for diabetic subjects.

A three-compartment model was proposed by Sherwin et al. [26] in which a central compartment exchanged insulin continuously with other two compartments. Insulin appearance and elimination from each compartment were modeled as first order kinetics. Another three-compartment model developed by Cerasi [27] is similar to Sherwin model. It comprised six ordinary differential equations (ODE) to describe physiological insulin secretion. The three-compartment model proposed by Insel et al. [28] included one nonlinear term to take into account the effect of insulin on glucose uptake.

A two-compartment model describing glucose and its regulatory hormones was developed and validated with data from intravenous glucose tolerance tests (IVGTT) and

oral glucose tolerance tests (OGTT) in [29]. A nonlinear model of free fatty acid glucose metabolism was proposed for normal subjects in [30]. The system, consisting of 15 states, 36 metabolic equations and 22 parameters, comprised of glucose, insulin, epinephrine, glucagon, growth hormone and free fatty acid models.

A new model of glucose-insulin system in normal humans was present to describe the physiological events occurring after a meal in [31]. The glucose-insulin system consisting of 12 states was decomposed into glucose and insulin subsystem both expressed by two compartments. 35 model parameters were estimated for normal and Type 2 diabetic patients by fitting the mean data of normal subject database undergoing a triple tracer meal protocol.

The Automated Insulin Dosage Advisor on the website (http://www.2aida.net/) is a three-compartment model expressing glucose and insulin dynamics. The insulin dynamics in the model was driven by subcutaneous insulin injection. The model, proposed as an educational tool, was originally designed to study the use of different insulin analogues on the insulin therapy and the effect of different meal sizes on the rate of gastric emptying in the system.

The second type of virtual patient models describes biochemical dynamics at each important organ site. The organs with significant appearance or clearance of glucose and insulin are selected as main compartments. Foster et al. [32] proposed one model of this type assuming glucose compartment for blood, muscle and liver, and assuming a compartment each for insulin, glucagon and fatty acid. Guyton et al. modified Foster model by adding a central organs compartment to the glucose model, including diffusion in the transport equations, and making insulin secretion more complex [33].

Sorensen [20] divided the central organs compartment into brain and gut compartment and included the effect of glucagon. This model consisted of six-compartment: brain, heart and lungs, liver, gut, kidney and peripheral tissues. The dynamics in the ISF and capillary fluid were detailed in the compartment of brain and peripheral tissues. Glucose meal disturbance was directly input into the gut along with the intravenous delivery of insulin and arterial blood glucose measurement. The model consisting of 21 states and 22 metabolic functions described the dynamics of glucose, insulin and glucagon. Puckett [34] proposed a new model similar to Sorensen model, however it did not include glucagon and removed transport terms besides metabolic sinks and sources.

A kinetic model of glucose regulation system was developed and validated in [35] with 6 parameters to identify. The four states in this model expressed the insulin and glucose concentration, overall endogenous glucose balance and the peripheral insulin-dependent glucose utilization (IDGU).

Cobelli et al. [14] proposed a nonlinear model consisting of glucose, insulin and glucagon subsystems. There were 9 states, 23 metabolic functions and 46 parameters in this model. Glucose and glucagon subsystem were modeled using a single compartment respectively, and insulin subsystem was expressed as a five-compartment model. There were 7 ODEs and 23 metabolic functions to describe the glucose-insulin-glucagon system.

Although Sorensen's model is widely used in glucose control, it has also been criticized for not accurately representing observed glucose change [22]. In addition, model parameters must be estimated accurately to ensure the simulation results. However, the accuracy of physiological model is lowered due to the large numbers of model

parameters compared with PK models. Model parameters are estimated by comparing simulation responses with glucose and insulin data, and selecting the parameter set that has the minimal sum of squared residuals. Therefore, lower order models can be estimated with a single set of glucose or insulin data, which is an advantage over larger models.

Three virtual patient models will be highlighted in the following sections. The Bergman, Sturis and Hovorka models are all PK models and used in following chapters. All the three models have some common limitations although the structures of the models are different:

1. The counter-regulatory hormones (e.g., glucagon, epinephrine, etc.) have profound effect on the change of glucose and insulin. The effect of these hormones in the body is not taken into account in the models.
2. Some physiological factors such as stress or sickness can greatly affect the dynamics of glucose and insulin in the human body.
3. Exercise or some other physical activities can affect the metabolism of glucose significantly, which further compound the modeling of glucose-insulin system. This factor is ignored in the three models.
4. The models do not consider the variations in the absorption of different foods.

2.1 Bergman Minimal Model

Minimal model suggested by Bergman et al [36] with low-order was for estimation of insulin sensitivity and glucose effectiveness. It is widely applied in clinical studies and mathematical modeling of glucoregulation studies. A revised model was developed by Cobelli et al. [37] to estimate glucose clearance and insulin sensitivity. Minimal model

was improved in [38] to represent glucose subsystem using two compartments. Hovorka et al. [39] added three glucose and insulin subcompartments to extend the original minimal model. Some other modified models are proposed as well [40, 41]. Most models were glucocentric and ignored the effect of free fatty acid (FFA). Roy et al. [42] extended the Bergman minimal model by including plasma FFA dynamics focusing on Type 1 diabetic patients.

A schematic of the Bergman minimal model is shown in Figure 2.1. The minimal model, compatible with some known physiological facts, can simulate the glucose-insulin system with minimal identifiable parameters and is computationally suitable for parameter estimation and real-time control.

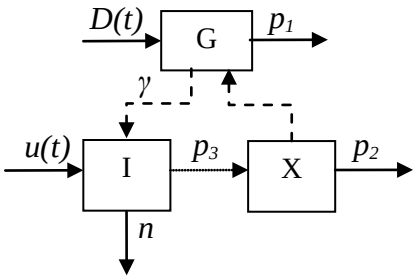

Figure 2.1. Block diagram of the minimal model. The solid arrows represent material flow, the dashed arrows imply the interactions between compartments, and the dotted arrow presents the effect of plasma insulin on the remote compartment.

As shown in Figure 2.1, Bergman's minimal model consists of a glucose compartment *G*, a remote insulin compartment *X* and an plasma insulin compartment *I*. Glucose uptake is influenced by plasma insulin through a remote compartment. The model is composed of three differential equations:

$$\begin{aligned} \dot{G}(t) &= -p_1[G(t)-G_b]-X(t)G(t)+D(t), G(0)=G_0, \\ \dot{X}(t) &= -p_2X(t)+p_3[I(t)-I_b], X(0)=0, \\ \dot{I}(t) &= \gamma[G(t)-h]^+ - n[I(t)-I_b]+u(t), I(0)=I_0, \end{aligned} \tag{2.1}$$

where G and I are concentration of plasma glucose (mg/dL) and plasma insulin (mU/L), respectively. G_b and I_b are the basal levels of plasma glucose and insulin, accordingly. X is proportional to the insulin level in the plasma compartment (min^{-1}). It is introduced to account for the accelerating glucose disappearance into the periphery and liver, and inhibiting hepatic glucose production (HGP).

Plasma glucose level decays at a rate (p_1: min^{-1}) proportional to the difference between the plasma glucose level $G(t)$ and the basal glucose level G_b. If the plasma glucose level is below the basal glucose level, glucose enters into plasma, and glucose leaves plasma if plasma glucose level is above the basal glucose level. The second term, $-X(t)G(t)$ describes an additional mechanism via which glucose disappears from plasma by the clearance effect of insulin in the remote compartment. $D(t)$ is glucose intake rate due to a meal disturbance (mg/min). The change rate of glucose is the difference between net hepatic glucose production and the utilization of glucose by the tissues and organs. Glucose uptake within glucose space to peripheral and hepatic tissues is mediated by the remote insulin compartment. The insulin dynamics of the model is driven by an intravenous infusion of insulin to the system.

Remote-compartment insulin disappears at a rate (p_2: min^{-1}) proportional to itself, and enters at a rate (p_3: min^{-2} (mU/L)) proportional to the difference between plasma insulin level $I(t)$ and basal insulin level I_b. Insulin enters plasma compartment from pancreas at the rate of γ [(mU/L)min^{-1}(mg/dL)$^{-1}$] with glucose level above h (mg/dL) and disappears at a rate (n: min^{-1}) proportional to its concentration. $u(t)$ is the exogenous insulin infusion rate (mU/min).

Though its wide application, a major limitation was reported that glucose production cannot separate from its disposal. The indices insulin sensitivity and glucose effectiveness describe not only the effect of glucose and insulin on the glucose utilization but also the inhibitory effect on the glucose production [43]. Other limitations include poor precision of parameter estimation and unsatisfactory reproducibility of the index insulin sensitivity. Although these limitations, the model has been validated extensively on human patients.

2.2 Sturis Model

Oscillatory behavior of glucose and insulin in human body has been revealed from in vivo and in vitro experiments. Ultradian oscillation of plasma glucose and insulin concentration with large amplitude in humans has been observed after meal ingestion, oral glucose, constant intravenous glucose infusion and continuous enteral nutrition. A three-compartment model including major metabolic processes in glucose regulation was proposed to determine whether the oscillations resulted from the feedback loops between glucose and insulin [44], as shown in Figure 2.2. Two major negative feedbacks in the model, both including the stimulatory effect of glucose on insulin secretion (IS), describe the effect of insulin on glucose production and glucose utilization, respectively.

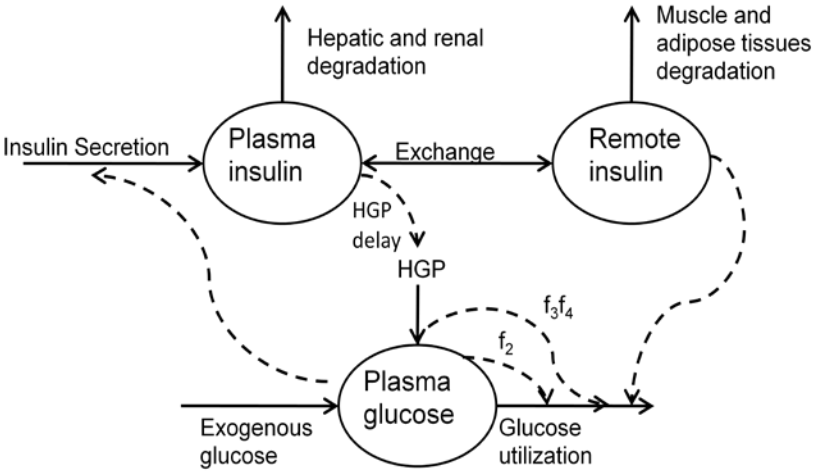

Figure 2.2. Flow diagram of Sturis model. Solid arrows represent exchange rate, flows of input and output; dashed arrows represent metabolic relationship between compartments.

The model has three main states: amount of glucose in the glucose space, amount of plasma insulin and amount of insulin in the ISF. The model equations are shown as following:

$$\begin{aligned} dx/dt &= f_1(z) - E(x/V_1 - y/V_2) - x/t_1, \\ dy/dt &= E(x/V_1 - y/V_2) - y/t_2, \\ dz/dt &= f_5(h_3) + I - f_2(z) - f_3(z)\, f_4(y), \\ dh_1/dt &= 3(x - h_1)/t_3, \\ dh_2/dt &= 3(h_1 - h_2)/t_3, \\ dh_3/dt &= 3(h_2 - h_3)/t_3, \end{aligned} \tag{2.2}$$

where x (mU) and y (mU) are the insulin amount in plasma and ISF, respectively; and z is glucose amount in glucose space (mg). The variables h_1, h_2 and h_3 express the delay between plasma insulin and HGP. f_1 and f_5 denote IS and HGP, respectively. f_2 and f_3f_4 describe insulin-independent glucose utilization (IIGU) and IDGU, respectively.

The metabolic functions are shown in Eq. 2.3; definition and value of model parameters are listed in Table 2.1.

$$
\begin{aligned}
&f_1(z) = 209/[1+\exp(-z/300V_3+6.6)],\\
&f_2(h_3) = 72[1-\exp(-z/144V_3)],\\
&f_3(z) = 0.01z/V_3,\\
&f_4(y) = 4+90/[1+\exp(-1.772\log(y(1/V_2+1/Et_2))+7.76)],\\
&f_5(h_3) = 180/\{1+\exp[0.29(h_3/V_1-7.5)]\}.
\end{aligned}
\tag{2.3}
$$

Table 2.1. Definition and value of Sturis model parameters.

Parameter	Definition	Value
E	Rate constant for insulin exchange between plasma and remote compartment	0.2 L/min
I	Exogenous glucose delivery rate	216 mg/min
t_1	Time constant for plasma insulin degradation	6 min
t_2	Time constant for remote insulin degradation	100 min
t_3	Delay time between insulin and glucose production	36 min
V_1	Volume of insulin distribution in the plasma	3 L
V_2	Volume of remote insulin compartment	11 L
V_3	Volume of glucose space	10 L

2.3 Hovorka Model

In a similar manner with Bergman model, Hovorka et al. [45] proposed a nonlinear model to develop model predictive controller in subjects with Type 1 diabetes. The compartment model includes submodels expressing absorption of subcutaneously administered short-acting insulin Lispro and gut absorption. The model outline is shown in Figure 2.3.

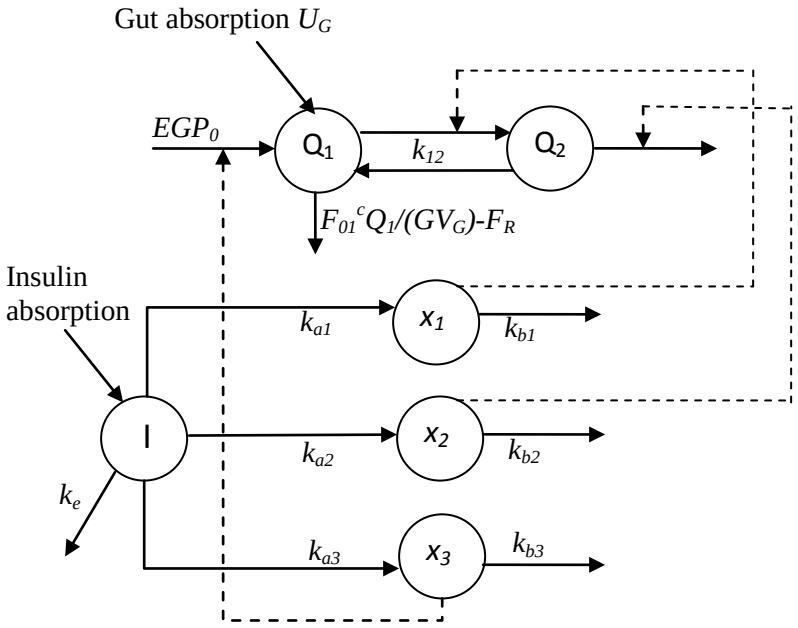

Figure 2.3. Compartment model of glucose-insulin system proposed by Hovorka et al.. Solid arrows represent exchange rate, flows of input and output; and dashed arrows represent insulin action on glucose metabolism.

The model comprises a glucose subsystem (glucose absorption, distribution and disposal), an insulin subsystem (insulin absorption, distribution and disposal) and an insulin action subsystem (insulin action on glucose transport, disposal and endogenous production). The model equations of glucose subsystem are shown by Eq. 2.4:

$$
\begin{aligned}
&dQ_1(t)/dt = -[F_{01}^c(t) + x_1(t)Q_1(t)] + k_{12}Q_2(t) - F_R(t) + U_G(t) + EGP_0[1 - x_3(t)],\\
&dQ_2(t)/dt = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t), \qquad G(t) = Q_1(t)/V_G,\\
&dS_1(t)/dt = u(t) - S_1(t)/t_{\max,I},\\
&dS_2(t)/dt = [S_1(t) - S_2(t)]/t_{\max,I},\\
&dI(t)/dt = S_2(t)/V_I t_{\max,I} - k_e I(t),\\
&dx_1(t)/dt = -k_{a1}x_1(t) + k_{b1}I(t),\\
&dx_2(t)/dt = -k_{a2}x_2(t) + k_{b2}I(t),\\
&dx_3(t)/dt = -k_{a3}x_3(t) + k_{b3}I(t).
\end{aligned}
\tag{2.4}
$$

The functions of metabolic processes are shown in Eq. 2.5. The definition of the state variables and model parameters are listed in Table 2.2 and Table 2.3, respectively.

$$
\begin{aligned}
F_{01}^{c}(t) &= \begin{cases} F_{01}, & G \geq 4.5\ mmol/L \\ F_{01}G(t)/4.5, & G < 4.5\ mmol/L \end{cases} \\
\mathrm{F_R(t)} &= \begin{cases} 0.003(G(t)-9)V_G, & G \geq 9\ mmol/L \\ 0, & G < 9 mmol/L \end{cases} \\
\mathrm{U_G(t)} &= \mathrm{D_G A_G t e^{-t/t\,max,G}} / t_{\max,G}^{2}.
\end{aligned}
\tag{2.5}
$$

Table 2.2. Definition of Hovorka model variables.

Variable	Definition	Unit
G	Plasma glucose concentration	mmol/L
Q_1	Glucose mass in accessible compartment	mmol
Q_2	Glucose mass in non-accessible compartment	mmol
F_{01}	Insulin-independent glucose flux	mmol/(Lmin)
F_R	Renal glucose clearance	mmol/(Lmin)
U_G	Glucose absorption rate	mmol/(Lmin)
I	Plasma insulin concentration	mU/L
x_1	Insulin action on glucose transport	min^{-1}
x_2	Insulin action on glucose uptake	min^{-1}
x_3	Insulin action on glucose production	min^{-1}

Table 2.3. Definition and value of Hovorka model parameters.

Parameter	Definition	Value
k_{12}	Transfer rate from non-accessible to accessible compartment	0.066 min^{-1}
k_{a1}	Deactivation rate	0.006 min^{-1}
k_{a2}	Deactivation rate	0.06 min^{-1}
k_{a3}	Deactivation rate	0.03 min^{-1}
k_{b1}	Activation rate	3.07e-5 min^{-1}
k_{b2}	Activation rate	4.92e-5 min^{-1}
k_{b3}	Activation rate	1.56e-4 min^{-1}
k_e	Insulin elimination rate from plasma	0.138 min^{-1}
V_I	Insulin distribution volume	0.12 L/kg
V_G	Glucose distribution volume	0.16 L/kg
D_G	Amount of carbohydrates digested	N.A.
A_G	Carbohydrate bioavailability	0.8
$t_{max,G}$	Time-to-maximum of carbohydrate absorption	40 min
EGP_0	Endogenous glucose production extrapolated to zero insulin concentration	0.0161 mmol kg^{-1} min^{-1}
F_{01}	Non-insulin-dependent glucose flux	0.0097 mmol kg^{-1} min^{-1}
$t_{max,I}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	55 min

2.4 Summary

The Bergman, Sturis, and Hovroka models use different approaches to model the dynamics of glucose-insulin system. In order to improve the control algorithm of glucose regulation and hence the diabetes treatment, virtual patient models have to be refined continually for further understanding of the pathology and physiology of diabetes. In Chapter 3, a refined two-compartment model based on the Sturis model is proposed to explore the oscillatory behavior of glucose-insulin system and the relation of the oscillations and diabetes.

3 Model of Glucose – Insulin System with Delays

Researchers have studied the oscillatory behavior of the insulin, glucose and other hormones for decades. Two delays are suggested to be relevant to the oscillations of glucose and insulin as well as some lags existing to affect the regulation of glucose concentration. Hepatic glucose production delay and insulin secretion delay are two delays studied mostly by the researchers. Some lags are observed such as the lags between plasma glucose and glucose in the ISF, between plasma glucose and plasma insulin, between plasma insulin and ISF insulin, and between IDGU and ISF insulin. Glucose level is regulated by these variables and four negative feedback loops among them (refer to Figure 2.A in [44]). Insulin action delay and the feedback loop in the glucose-insulin system may be key factors of stimulating the oscillations [15, 44].

3.1 Periodic Oscillation of Insulin

Periodic oscillation is one of the most significant characteristics of insulin secretion. It can pulsate at different amplitudes and periodicities (Figure 3.1) [44]. Oscillation of insulin secretion can be divided into rapid oscillation and ultradian oscillation.

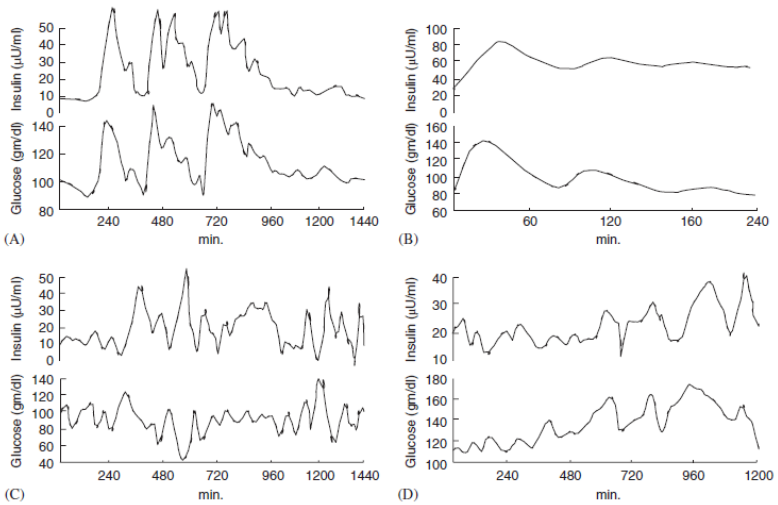

Figure 3.1. Different amplitudes and periodicities of insulin and glucose for different glucose infusion rates: (A) meal ingestion; (B) oral glucose intake; (C) continuous enteral nutrition; (D) constant glucose infusion.

3.1.1 Rapid Oscillation

The rapid oscillations of insulin, plasma glucose and glucagon concentration have been observed in overnight fasting monkeys [46]. A mean period of 9 min for the insulin, plasma glucose and glucagon was proposed. Larger amplitudes for insulin and glucagon were reported to be ten and five times greater than glucose.

Concurrent oscillations of glucose and insulin was reported with averaging period of 13 min in normal men in [47]. Plasma was sampled from ten normal subjects every two minutes between one and two hours in this study. In five subjects with regular cycle of basal plasma insulin, the average concentration of plasma glucose led plasma insulin for 2 min. For the less regular subjects, a two-minute lead of plasma glucose to rise before the insulin rise was demonstrated. It was proposed that negative feedback loop between the liver and the pancreatic beta cells regulated the basal plasma insulin and glucose.

In order to examine whether the hormone cycles could be sustained without the influences of liver or central nerves, isolated canine pancreas was perfused in vitro [48]. Sustained regular cycles of insulin secretion, glucagon and somatostatin were observed for over 200 min under constant infusion of glucose. The average periods for insulin, glucagon and somatostain were 10 min, 8.6 min and 10 min, respectively. Based on the experiments results, there might be a pacemaker or a driving oscillator of hormone secretion within the pancreas to produce the in-vitro cycles.

Pancreas was suggested to be possibly a driver or Zeitgeber of the glucose-insulin interaction system [48, 49]. The results of in vivo and in vitro experiments were compared to study the causes of the oscillations [50]. Samples were taken every minute from the portal vein of the dog and from the isolated perfused pancreas in vitro. The data from the experiments was in agreement with the proposal in [48] supporting that there was a pacemaker within the pancreas to regulate the insulin secretion. The amplitude of the oscillation was suggested to be mediated by vagal nerves as well [50].

3.1.2 Ultradian Oscillation

Ultradian oscillation is regarded as characteristic of intact organism and may be inherent to the glucose-insulin feedback system. Some studies on oscillatory behavior of glucose and insulin under different situations are listed in Table 3.1.

Table 3.1. Studies on the oscillatory behavior of glucose-insulin system.

Source	Subject	Glucose entrance
Kraegen et al., [51]	Normal man	Oral glucose administration
Segre et al., [52]	Normal, diabetic, obese man	Constant glucose infusion
Ookhtens et al., [53]	Conscious dog	Constant glucose infusion
Bowden et al., [54]	Conscious dog	Constant glucose infusion
Simon et al., [55]	Normal man	Meals
Simon et al., [56]	Normal man	Continuous enteral nutrition
Polonsky et al., [57]	Normal & diabetic man	Meals
Sturis et al., [58]	Type 2 diabetic, obese, normal man	Fasting

Ultradian oscillation is the slower pulsatility of insulin, glucose and some other hormones with longer period. The periodic fluctuations of insulin and glucose concentration were observed in the arterial plasma of the conscious fasting dogs [53]. The measurement of glucose and insulin concentration was taken at frequent regular intervals. The observation period varied from 30 minutes to 10 hours and was divided into 64 even time sections. It was found that the sustained oscillations of insulin and glucose level were observable under constant intravenous glucose infusion.

A similar experiment was carried on conscious, intact dogs [54]. The oscillations of insulin and glucose in the plasma were observed with constant glucose infusion of 10 mg/kg/min. The glucose level went into regular oscillation after about 3 hours since the beginning of the glucose infusion until the end of it. The glucose and insulin concentration oscillated with frequencies of 0.54±0.03 cycles/h and 0.6±0.09 cycles/h respectively, which were quite close. A lead of glucose before insulin oscillation was

observed for 22±5 min. Peripheral glucose utilization was studied as well in this study. It proposed that the glucose fluctuation was due to the large fluctuation in peripheral glucose utilization; and glucose was the main factor for the hepatic glucose uptake during the glucose infusion and insulin for the peripheral glucose utilization.

Except the constant glucose infusion, meals and constant enteral glucose infusions can stimulate the oscillation of glucose and insulin in human body [55, 56]. Eight normal subjects were studied for the time profiles of glucose and insulin after three meals in [55]. The mean period of the synchronous oscillations of glucose and insulin was about 51-112 min. The amplitude of the oscillation reached peaks after meals, decreased with time and returned to its fasting levels after about 340 min. Rapid oscillations of glucose and insulin were observed to superimpose on the ultradian oscillation with different periods of 20-30 and 9-14 min. The influence of continuous enteral nutrition on the plasma glucose, insulin and C-peptide was studied in [56]. The period of the ultradian oscillation and the rapid oscillation for plasma glucose and insulin was 53-113 min and 8-14 min respectively. A rapid and small-amplitude insulin oscillation of 8-15 min was observed in experiments on animals and a slow and large-amplitude oscillation of insulin on human every 100-150 min [59].

The pulsatility of insulin in 24 hours was studied under 3 mixed meals on 14 normal subjects and 15 obese subjects [57]. By using a two-compartment kinetics model of peripheral C-peptide, insulin secretion rate was derived from the concentration of C-peptide in the plasma. In the normal subjects, about 11.1±0.5 pulses were observed during 24 hours. Obvious pulses of insulin were observable after three meals; and the insulin secretion pulsated in the fasting period overnight. For the normal and obese

subjects, the number and the time for the insulin secretion pulses was similar, with higher amplitudes for the obese subjects. The results suggested that pulse of glucose concentration was concomitant with those of insulin especially during postprandial period; and the concomitant rate during the fasting period was lower accordingly.

Sturis et al. investigated the ultradian oscillation of insulin secretion and glucose concentration under fasting condition on seven Type 2 diabetes patients, eight obese non-diabetic subjects and eight normal subjects [58]. Blood was sampled every 15 minutes to measure glucose, insulin and C-peptide on the diabetic and obese subjects. For the normal subjects, the fasting period was 8 hours. Insulin secretion rate was calculated in the same way with [57]. Ultradian oscillation of IS was reported to be evident during the fasting period for all the subjects. The rapid oscillation with period of 10-15 min was observed using short sampling every 2 minutes. The oscillation frequency was reported to be similar for the diabetic and non-diabetic subjects at 12-15 oscillations/24 h; and the concomitant rate for the two groups were approaching with mean value of 63%-65%. Compared with oscillation of insulin, a slowing of the glucose oscillation in the Type 2 diabetic subjects was observed.

3.2 Models of Ultradian Oscillation of Glucose-Insulin System

For better understanding of the endocrine regulatory system and shedding light on the oscillatory features of insulin and glucose, many models have been proposed. Some of the models exploring the oscillations of glucose and insulin are listed in Table 3.2.

Table 3.2. Models of investigating oscillations of glucose-insulin system.

Source	No. of explicit delays	No. of equations	No. of glucose compartment	No. of insulin compartment	Remark
Sturis et al. [44]	0	6	1	2	3 ODEs without physiological meaning.
Tolić et al. [17]	0	6	1	2	Express delay using Taylor expansion, simplify some functions.
Bennett and Gourley [60]	1 (HGP delay)	3	1	2	One equation for glucose dynamics and two for insulin.
Li et al. [15]	2	2	1	1	Analyzed 4 parameters' effect on the oscillatory behavior.
Chen and Tsai [18]	2	2	1	1	Two constants included to estimate the dysfunction due to diabetes.

A three-compartment model was proposed by Sturis et al. [44] to study ultradian oscillating behavior of glucose and insulin. The model structure is similar to Bergman minimal model: a single compartment was used to express glucose subsystem and insulin subsystem was modeled using plasma insulin and remote insulin compartment. The model of glucose-insulin system consisted of five metabolic functions and six nonlinear ODEs, three of which were auxiliary variables without biological meaning to introduce the delay of insulin effect on HGP. Tolic et al. [17] simplified the metabolic functions f_1-f_5 in Sturis' model, and two new functions were introduced into the model representing the effect of hyperglycemia on HGP and the splanchnic glucose uptake.

Engelborghs et al. [61] introduced the delay of HGP explicitly into the model to replace the three auxiliary variables based on the study [44], and one-compartment insulin model was used. There were only two differential equations instead of six. Another delay of glucose effect on IS was not considered in this model, which was proved to be unreasonable by Li et al [15]. In their work, they tried to model exogenous insulin infusion assuming that the form of exogenous insulin infusion was the same as the endogenous insulin secretion.

Bennett and Gourley [60] introduced the HGP delay explicitly into the model and kept the two insulin compartments to express indirectly the delay of IDGU without considering delay of IS. The model consisted of three differential equations and was analyzed for the sufficient conditions of global stability.

Li et al. [15] used one-compartment model of glucose and insulin, introduced delays of IS and HGP explicitly into the model, and suggested a model expressed by two differential equations. Their simulation results indicated that IS delay was important for sustaining oscillation of glucose and insulin. The time delay of IS was therefore suspected as one of the possibly causes of ultradian oscillation of glucose-insulin system.

Chen and Tsai [18] followed Li et al. study [15] and included a glucose submodel in the glucose-insulin system. There were two differential equations describing the glucose and insulin in the plasma compartment. Keeping the five algebraic equations f_1-f_5 unchanged, two functions were introduced to express the effect of hyperglycemia. Two constants α and β were included in the differential equations to estimate the dysfunction condition due to diabetes. There were other mathematical models with delays to express glucose-insulin regulatory system, and a review of these models can be found in [62].

The role for each delay or both was considered in different way. In [15, 44], the two delays were considered separately for their influence on the oscillation behavior of IS and HGP. While the two delays' effect was considered together by using the sum of the two delays in [63]. It was proposed that the combined effect of the two delays influenced the dynamics of the glucose-insulin feedback mechanism, but not each individual delay. Chuedoung et al [63] concluded that there was a critical composite delay of HGP delay and IS delay to affect the oscillatory behavior of the glucose-insulin system. Below this critical composite delay, stability can be expected. Li and Kuang [64] suggested that the sustained oscillation can occur in the unstable region divided by a curve. So far, there has not been any suitable method to conduct experiments to study and ascertain each delay's effect on the endocrine system. The credibility and applicability of the models remains largely debatable till further relevant research investigations and findings. In our work, the two delays are studied separately followed by combining them to investigate the effect on the glucose-insulin system.

Table 3.3. Range of time delays.

	HGP delay	IS delay
Sturis et al. [44]	25-50 min	N/A
Prager et al. [65]	0-23.5 min	0-23.5 min
Engelborghs et al. [61]	N/A	50 min(for simulation)
Li et al. [15]	6.75-40 min	5-15 min
Wang et al. [66]	15 min(for simulation)	N/A

In different studies on the oscillatory behavior of glucose-insulin system, the range of IS delay and HGP delay varied widely (Table 3.3). Delay can influence glucose

concentration and the lags of glucose and insulin between different compartments to a certain extent [66]. Definitions for the delays were not the same in different studies. HGP delay was defined as the time taken for the liver to release glucose responding to the plasma insulin change in [60, 67]. HGP delay was the time taken for "remote insulin" to stimulate HGP to a significant change (e.g. half-maximal) in [15]. IS delay was considered as the time from the elevated plasma glucose to the change point of IS in [63, 67]. In [15], IS delay was measured from the time plasma glucose concentration increases to the moment when newly synthesized insulin is transported to interstitial fluid and becomes the "remote insulin".

3.3 Modeling Glucose-Insulin System with Two Explicit Delays

3.3.1 Structure of Glucose-Insulin Model

The body tissues and organs were divided into two compartments by the different rates equilibrating with plasma compartment: slow-equilibrating with plasma and rapid-equilibrating with plasma compartment in [26, 31]. The organs with large blood flow relative to their interstitial volume have a rapid rate of equilibrating (e.g. heart, liver, gut and kidney); while other poorly perfused tissues have slow equilibrating rate (e.g. skin, muscle and adipose tissues).

After the insulin is secreted by pancreas and passes liver, it goes into plasma and circulates to various human organs. The insulin then transverses the capillary membrane and enters the interstitial fluid. Finally, insulin is bound to the cell receptors on the membrane of insulin-dependent tissue cells, and the cells 'open' to let the glucose in. IIGU mainly happens in brain and nerve cells. The permeability of the cells is so high that the cells can utilize glucose even without insulin [68]. IDGU often occurs in insulin-

dependent tissues, such as muscle and adipose tissues, where glucose in the ISF can be utilized under the aid of insulin in the ISF. The glucose uptake correlates closely with insulin in ISF rather than with plasma insulin [69]. For diabetic patients, due to insulin deficiency or insulin resistance, glucose level cannot be controlled within the normal range and complications are induced.

Glucose dynamic system was expressed as a one-compartment model and insulin dynamic system expressed as two-compartment model in [44]. In later studies, glucose and insulin dynamic systems were mostly expressed as a one-compartment model to study glucose-insulin oscillatory behaviors [15, 66, 67]. Optimal control of glucose level can be achieved by subcutaneous delivery of insulin after glucose measurement. It is crucial to investigate and understand the dynamics of glucose and insulin in the subcutaneous tissues for better regulation of blood glucose level. In order to investigate the oscillatory behavior of the glucose-insulin system and interactions between quick- and slow-equilibrating tissues and organs, we construct a two-compartment model of glucose and insulin with explicit introduction of two delays, and modify the functions of HGP [16], IS and IDGU. The model structure is shown in Figure 3.2, and the complete model is given by equation sets (3.1) and (3.2).

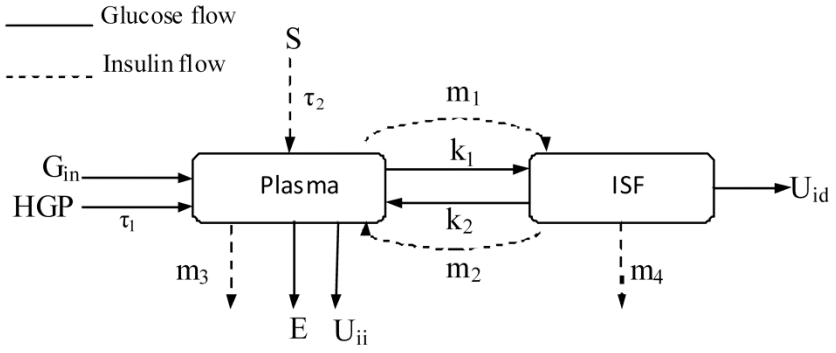

Figure 3.2. Diagram of two-compartment model. The solid and dashed arrows represent input, output, exchange of glucose and insulin, respectively.

$$
\begin{aligned}
&\dot{G}_p(t) = G_{in}(t) + HGP(I_p(t-\tau_1)) - U_{ii}(G_p(t)) - E(G_p(t)) - k_1 G_p(t) + k_2 G_i(t),\\
&\dot{G}_i(t) = k_1 G_p(t) - k_2 G_i(t) - U_{id}(G_p(t), I_i(t)),\\
&\dot{I}_p(t) = S(G_p(t-\tau_2)) - m_1 I_p(t) + m_2 I_i(t) - m_3 I_p(t),\\
&\dot{I}_i(t) = m_1 I_p(t) - m_2 I_i(t) - m_4 I_i(t).
\end{aligned}
\tag{3.1}
$$

$$
\begin{aligned}
&HGP(I_p) = 160/(1+\exp(0.29(I_p/V_{ip} - 7.5))),\\
&U_{ii}(G_p) = 72(1-\exp(-G_p/(144V_{gp}))),\\
&U_{id}(G_i, I_i) = f_3(G_i)\, f_4(I_i),\\
&f_3(G_i) = 0.01 G_i / V_{gi},\\
&f_4(I_i) = 4 + 90/(1+\exp(-1.772\log(I_i(1/V_{ii} + m_4/e)) + 7.76)),\\
&S(G_p) = 210/(1+\exp(5.21 - 0.003 G_p/V_{gp})),\\
&E(G_p) = \begin{cases} k_{e1}[G_p(t) - k_{e2} BW], & G_p > k_{e2} BW,\\ 0, & G_p \le k_{e2} BW. \end{cases}
\end{aligned}
\tag{3.2}
$$

The first compartment, plasma and rapidly equilibrating tissues, is expressed as plasma for short; the second compartment, slowly equilibrating tissues, which is also the remote compartment [31, 44], is expressed as ISF following the definition in [31]. The definition of all the variables and parameters in the model are listed in Table 3.4 and Table 3.5. HGP delay, defined in the same way in [60, 67], is the time from the insulin appearance in plasma to the moment HGP has significant changes. IS delay is expressed as the time difference for plasma glucose effect on IS by pancreas, following the definition in [63]. The IS delay is different from that in Li et al. [15] in that IS delay of Li et al. included the time lag of transporting plasma insulin to ISF compartment.

Table 3.4. Definition of state variables of the two-compartment model.

Variable	Definition	Unit
G_p	Glucose amount in plasma	mg
G_i	Glucose amount in ISF	mg
I_p	Insulin amount in plasma	μU
I_i	Insulin amount in ISF	μU
G_{in}	Glucose intake rate	mg/min
HGP	Hepatic glucose production	mg/min
U_{ii}	Insulin-independent glucose utilization	mg/min
E	Renal excretion	mg/min
U_{id}	Insulin-dependent glucose utilization	mg/min
S	Insulin secreted by the pancreas	mU/min

Table 3.5. Parameters definition and nominal value in the model.

Parameter	Definition	Nominal values
V_{gp}	Plasma glucose distribution volume	8.4 L
V_{gi}	ISF glucose distribution volume	7 L
V_{ip}	Plasma insulin distribution volume	3.15 L
V_{ii}	Insulin distribution volume in ISF	7 L
e	Exchange rate of insulin between plasma and ISF	0.1361 min^{-1}
k_{e1}	Glomerular filtration rate	0.0005 min^{-1} [31]
k_{e2}	Renal threshold of glucose	339 mg/kg [31]
k_1	Transfer rate from plasma to ISF of glucose	0.065 min^{-1} [31]
k_2	Transfer rate from ISF to plasma of glucose	0.079 min^{-1} [31]
m_1	Transfer rate from plasma to ISF of insulin	0.042 min^{-1} [26, 70]
m_2	Transfer rate from ISF to plasma of insulin	0.02 min^{-1} [26, 70]
m_3	Plasma insulin degradation rate	0.268 min^{-1} [26]
m_4	ISF insulin clearance rate	0.03 min^{-1} [26]
τ_1	HGP delay	20 min
τ_2	IS delay	10 min

Table 3.6. Distribution volumes for glucose and insulin in different compartments.

	Glucose space	Insulin in plasma	Insulin in ISF
Sherwin et al. [26]	N/A	45±3 mL/kg	95 ± 8 mL/kg
Cobelli et al. [70]	0.2 L/kg	0.045 L/kg	0.1 L/kg
Sturis et al. [44]	10 L (7-13 L)	3 L (2-4 L)	11 L (7-15 L)
Hovorka et al. [45]	0.16 L/kg	0.12 L/kg	
Dalla et al. [31]	0.188 L/kg (normal) 0.149 L/kg (Type 2)	0.05 L/kg (normal) 0.04 L/kg (Type 2)	N/A

Two state variables are considered in the glucose system: plasma glucose (G_p) and ISF glucose (G_i). The state variables in the insulin system are plasma insulin I_p and ISF insulin I_i. Their values are converted to mg/dL and μU/ml when we report the simulation results. The distribution volumes of glucose and insulin space in some studies are listed in Table 3.6. Using the estimation method for the distribution volumes of glucose and insulin in [70], V_{gp}, V_{gi}, V_{ip}, and V_{ii} are estimated respectively as 12%, 10%, 4.5% and 10% of bodyweight [14, 26, 31, 45, 70]. Bodyweight (BW) is assumed to be 70 kg in this chapter.

3.3.2 Glucose Dynamics of the Two-compartment Model

There are two glucose sources in the model: glucose intake G_{in} from gut and glucose production from the liver stimulated by the glucagon. Glucose intake rate is variable due to different glucose infusions. $G_{in}(t)$ can be considered to be constant when intravenous glucose infusion is applied. G_{in} increased toward a maximum value and then fell slowly to zero in [18]. More complex models for glucose intake from gut were proposed in [71, 72].

HGP increases with decreased plasma insulin concentration. HGP was suggested to depend on plasma glucose, liver insulin and plasma glucagon in [14]. Glucagon was suggested to be unimportant correlations with the oscillatory behavior of insulin and glucose in [44]. With a wide range of HGP delay, oscillations of glucose and insulin were observable with HGP delay changing from 4.5 to 36 min in [15]. A range of 0-50 min for HGP delay is applicable according to Table 3.3. HGP decreases with the increase of plasma insulin, shown in Figure 3.3.

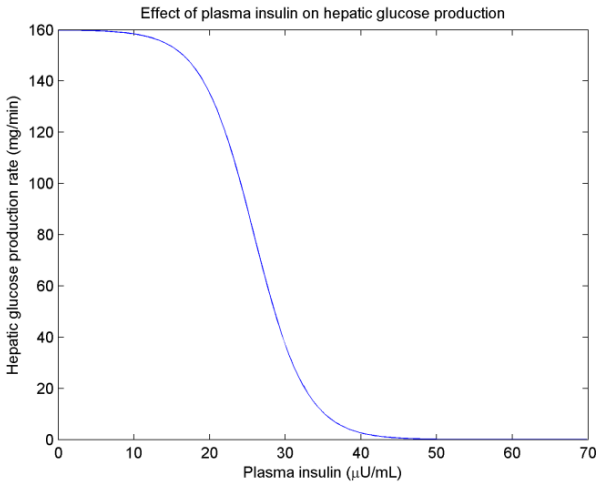

Figure 3.3. Change of HGP with plasma insulin level.

Glucose utilization was revealed to be dependent on plasma glucose and insulin concentration [14, 44]. It can be divided into insulin-dependent and insulin-independent utilization. There are different functions expressing IIGU. It followed Michaelis-Menten kinetics form in [73]. While IIGU was in the form of two hyperbolic-tangent functions' product in [14], relevant to plasma glucose and ISF insulin. In [44], IIGU relevant to plasma glucose climbed quickly to the constant value, as shown in Figure 3.4.

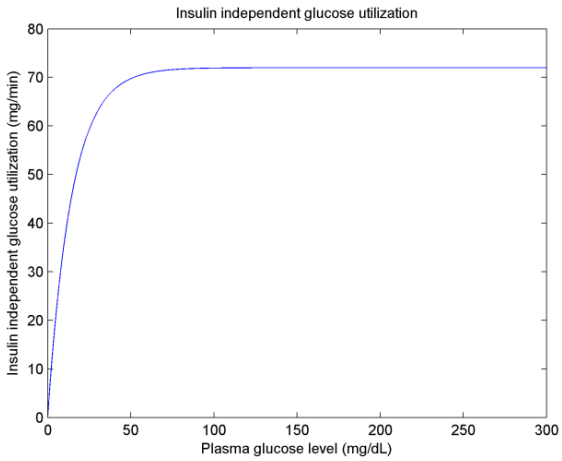

Figure 3.4. Effect of plasma glucose level on IIGU.

IDGU followed the Michaelis-Menten form in [31]. IDGU depended on the plasma glucose and ISF insulin suggested in [14, 16, 44], with the mathematical functions different. Glucose uptake by the peripheral tissues occurs in the ISF compartment, making IDGU a function of ISF glucose concentration [31]. We therefore modified IDGU to be a function relevant to glucose and insulin concentration in the ISF compartment. The relationship of glucose and insulin in the ISF compartment with IDGU was shown in Figure 3.5.

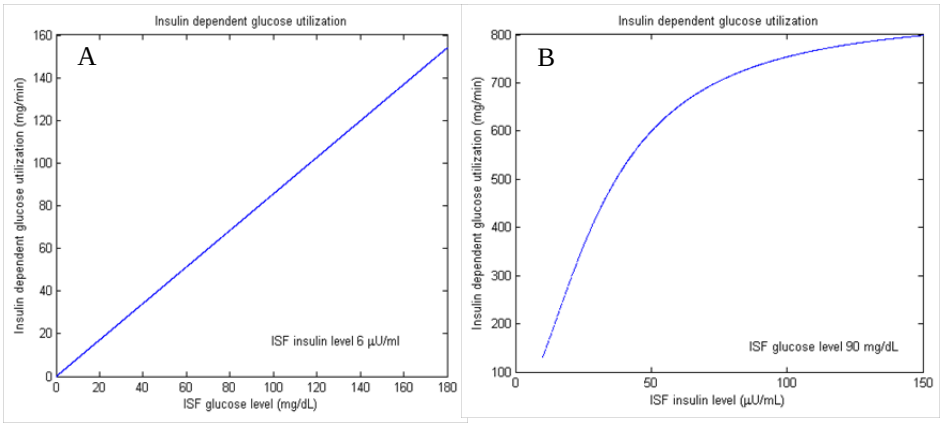

Figure 3.5. Change of IDGU with ISF glucose level when ISF insulin is constant at 6 µU/mL (A), and the relationship of IDGU with ISF insulin level when ISF glucose is constant at 90 mg/dL (B).

There was no glucose renal excretion in the model in [44, 60]. However, it is an important part in the regulatory system of glucose and insulin. The mathematical model of glucose renal excretion was adapted from [31]. Glucose eliminated by the kidney occurs when the plasma glucose level is higher than the threshold value and is assumed to be linear with plasma glucose. Threshold value of plasma glucose concentration is different for different subjects. Threshold value in [31] was therefore used in this chapter.

3.3.3 Insulin Dynamics of the Two-compartment Model

Basal plasma insulin was about 5-10 μU/ml after an overnight fasting in [74]. A mean value of 11.5 μU/ml was measured for the fasting arterial insulin level [26]. Insulin equilibration between plasma and ISF was governed by the insulin concentration difference in the two compartments [44].

Insulin is secreted by pancreatic beta-cells when stimulated by elevated plasma glucose concentration. Insulin has an inhibitory effect on the HGP and enhances glucose utilization by the tissue cells. In our work, the function of IS rate from [44] is modified following that in [16]. As shown in Figure 3.6, insulin secretion rate increased slowly first, followed by fast climbing from about 150 mg/dL and slowed down until reached a relatively stable value.

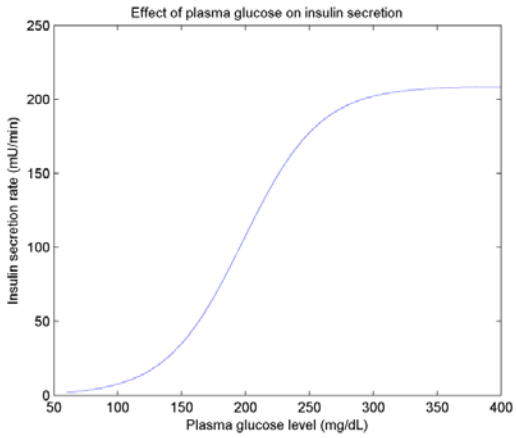

Figure 3.6. Change of insulin secretion rate with plasma glucose level.

There are three main clearance sites for insulin: kidney, liver and peripheral tissues. Portal insulin degradation happens mainly at liver, and peripheral insulin at kidney, with the insulin left to be removed by other tissues [15]. It was suggested that insulin clearance in plasma degrades in a single exponential form, and ISF in a linear form with its concentration [75, 76]. The process of newly secreted insulin passing liver would degrade insulin or recycle via hepatic artery. Insulin destruction by liver on first passage was estimated at 40%-55% [26]. In our work, it was assumed the secreted insulin enters directly plasma compartment after its first degradation passage through liver [26]. The insulin loss by the liver was considered with irreversible plasma insulin loss as a loss directly from plasma, which was expressed by the lumped parameter m_3.

Exchange rate of insulin between plasma and ISF compartment e

The function of IDGU (U_{id}) in the proposed model is different from the original function in [44]. We define a parameter m_4 to express ISF insulin clearance rate. m_4 is used to replace $1/t_i$. The parameter e, which is the rate of exchange between plasma and ISF compartments, has a different value with that of the original function.

Since insulin exchange between plasma and ISF is proportional to the difference between the plasma and ISF compartment, the insulin exchange q in the original function was:

$$q = E * (x/V_1 - y/V_2), \tag{3.3}$$

where x and y are insulin masses in the plasma and ISF respectively, E is the rate constant for exchange of insulin between the two compartments, and V_1 and V_2 are the respective distribution volumes for the plasma insulin and remote insulin compartment as defined in [44]. In our model, the insulin exchange is:

$$q = m_1 I_p - m_2 I_i, \tag{3.4}$$

where I_p and I_i were masses of insulin in plasma and ISF compartment respectively, m_1 and m_2 were transfer rates of insulin mass between the two compartments. Assuming that the two insulin exchanges are equal, two values of E could be obtained, which is relevant with IDGU. The two values are averaged to obtain:

$$e = (m_1 V_1 + m_2 V_2)/2 = (m_1 V_{ip} + m_2 V_{ii})/2. \tag{3.5}$$

In our model, V_1 is expressed as V_{ip}, and V_2 is expressed as V_{ii}.

3.4 Physiological Analysis of the Model Parameters Effect on the Oscillatory Behavior of the System

Taking into account the variance of several parameters under different conditions and uncertainty of their effects on the oscillatory behavior, computer simulations were performed. Results were analyzed for parameters' impact on the oscillatory behavior of the system, and the physiological implication was discussed.

In our simulation, a parameter's value was altered with all the other parameters remained constant at their nominal values. The correlation of ISF glucose level with blood glucose level varied from 0.76 to 0.92 [77]. Blood glucose level within 80-120 mg/dL was suggested in existing studies as the target of glucose control [78] or normoglycemia range [79]. The optimal range of plasma glucose concentration (80 mg/dL-120 mg/dl) and glucose concentration difference (10%-25%) between the two compartments were therefore considered in deciding the optimal range for each parameter. For different subjects, the parameters' value should be different. Parameter range for different subjects was discussed based on physiological analysis of simulation results.

In order to investigate the oscillatory behavior of the glucose-insulin system and interactions between quick- and slow-equilibrating tissues and organs, we constructed a two-compartmental model of glucose and insulin with explicit introduction of two delays, and modified the functions of HGP, IS and IDGU. Based on the simulation results, the influence of parameters on the oscillatory behavior and their physiological implication was analyzed. From section 4.4.1 to 4.4.7, G_{in} was external glucose infusion rate constant at 108 mg/min.

3.4.1 Insulin Transfer Rate Constants m_1

The parameter m_1 is increased from 0 to 0.1. A range of m_1 is estimated at 0.02-0.08 to sustain the oscillation of the system (Figure 3.7.A). The lower and upper limits of plasma and ISF glucose are reduced because more insulin distributing to ISF increases glucose uptake by the tissues. This agrees with normal phenomenon. Plasma glucose level increases further with more insulin transferring to ISF in the range of 0.02-0.03 (Figure 3.7.B), which may be caused by insulin resistance in the subcutaneous tissues. It

is estimated that for Type 2 diabetes, m_1 may be in the range of 0.02-0.03. Difference between plasma and ISF glucose concentration widened with increasing m_1. Within one oscillation period, for a certain glucose level, level difference between plasma and ISF is different for rising and falling side [13, 80]. Therefore the glucose level difference in plasma and ISF changes like a closed curve (Figure 3.7.C). For m_1 greater than 0.06, glucose concentration difference is higher than 25% (Figure 3.7.C). This may indicate an inefficient glucose transfer from plasma to ISF caused by some illness.

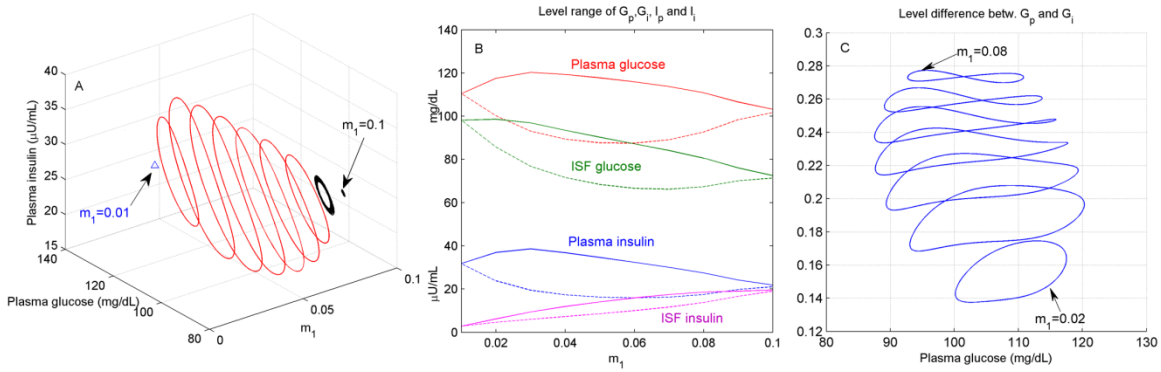

Figure 3.7. Phase plane of glucose and insulin in the plasma (A), glucose and insulin level distribution (B), and glucose level difference (C) when m_1 changes. The triangle indicates glucose and insulin in plasma go to a steady state when m_1=0.01. The level difference was calculated as 1-ISF glucose level/plasma glucose level.

3.4.2 Insulin Transfer Rate m_2

In Figure 3.8, m_2 is increased from 0 to 0.06. For m_2 out of the range of 0.01-0.04, oscillations of insulin and glucose are damped (Figure 3.8.A). An optimal range of m_2 is estimated at 0.02-0.04. By the simulation result, m_2 in the range of 0.01-0.02 may imply impaired function of glucose distribution in the body, which is shown by high difference of glucose concentration between the two compartments (Figure 3.8.B). For m_2 greater than 0.04, glucose-insulin system reached steady state quickly, and glucose concentrations in plasma and ISF vary in a narrow range.

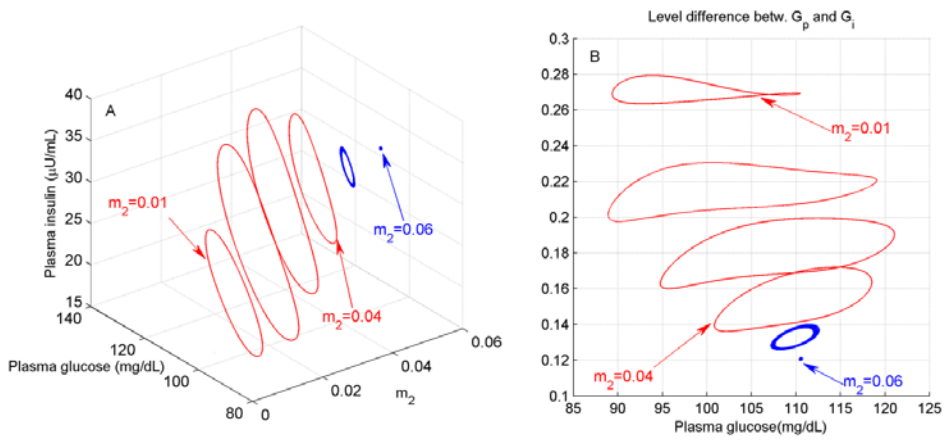

Figure 3.8. Phase plane of glucose and insulin in the plasma (A), and plasma and ISF glucose level difference (B) when m_2 changes.

3.4.3 Plasma Insulin Degradation Rate m_3

In our model, the loss of newly secreted insulin cleared by the liver was considered together with irreversible loss of plasma compartment as loss directly from the plasma compartment, expressed as a lumped parameter m_3. This degradation is named following the nomenclature in [44] as plasma insulin degradation. For the irreversible loss of plasma insulin and insulin degradation by the liver, they are assumed to be linear with plasma insulin mass with rate estimated at 0.125 and 0.268 respectively [14, 31].

When insulin degradation m_3 increases, glucose increases, and insulin decreases in both compartments. A range of m_3 is estimated at 0.1-0.6 for periodic solution of the dynamic system (Figure 3.9.A). The optimal range for m_3 may be within 0.2-0.3 (Figure 3.9.B and C). For m_3 less than 0.2, glucose concentrations in both compartments vary in wide range (Figure 3.9.B). This may be caused by inefficient glucose distribution. With m_3 increasing from 0.3 to 0.6, plasma glucose increases to almost 140 mg/dL and plasma insulin decreases to about 30 μU/mL. The high glucose and insulin level under low

glucose infusion may be induced by insulin resistance. m_3 in the range of 0.3-0.6 was thus estimated for Type 2 diabetics.

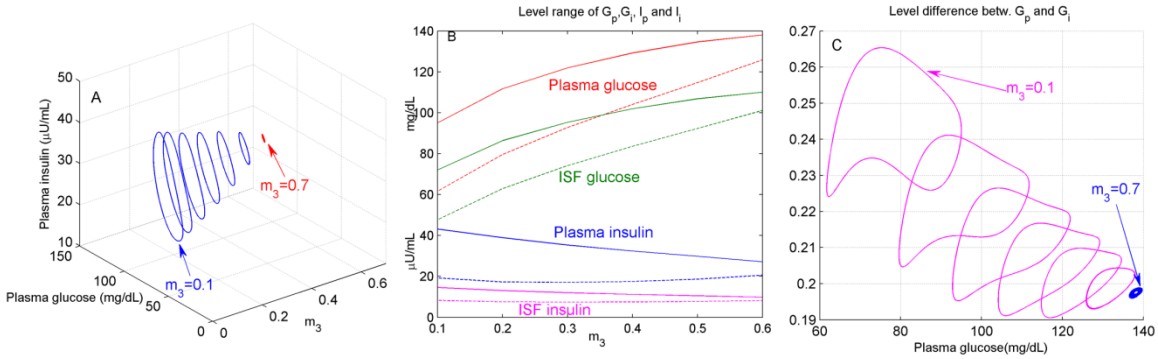

Figure 3.9. Phase plane of glucose and insulin in the plasma (A), glucose and insulin level distribution (B), and glucose level difference (C) when m_3 changes.

3.4.4 ISF Insulin Clearance Rate m_4

ISF insulin clearance rate is affected significantly by the subject's health conditions, exercises and other biological factors. A wide range of ISF insulin clearance rate exists, such as 0.001-0.07/min in [15], 0.01/ min in [44], 0.194/min for normal people and 0.269/min for Type 2 diabetic patients [31]. We observed that the oscillation of the dynamic system can be sustained in the range of 0-1. In agreement with existing studies, a range of m_4 is assumed to be 0-0.2.

From Figure 3.10.B, plasma glucose and glucose level difference are always within the optimal range. When m_4 increases from 0 to 0.02, insulin and glucose in plasma increase, and ISF insulin decreases rapidly. This may be caused by poor distribution of insulin from plasma to ISF due to disease. For sub-healthy people, the range of m_4 is likely to be 0-0.02. The optimal range of m_4 is estimated at 0.02-0.05. For m_4 greater than 0.05, ISF insulin level drops very low, while plasma insulin concentration hardly changes (Figure 3.10.A). Higher ISF insulin clearance results in wide glucose difference change,

and the pattern of glucose difference curves varies greatly with the increase of m_4 (Figure 3.10.B). ISF insulin clearance rate may be relevant with the sensitivity of subcutaneous tissues to insulin; thus the value of m_4 for Type 2 diabetics is likely to be higher than that for normal subjects.

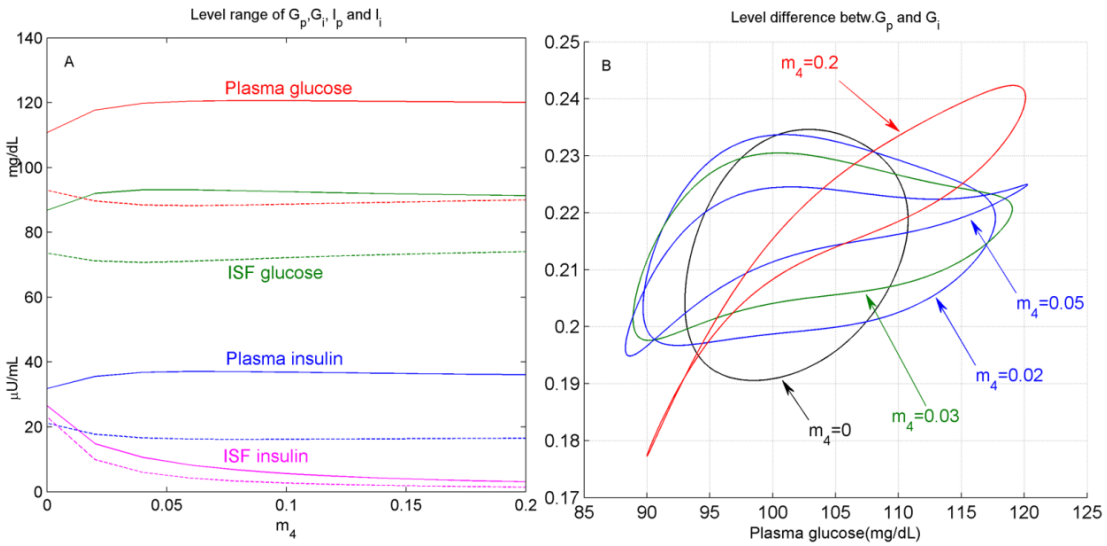

Figure 3.10. Plasma glucose and insulin level distribution (A), and plasma and ISF glucose level difference (B) when m_4 changes.

3.4.5 HGP Delay τ_1

Plasma insulin is relevant with HGP by transporting 'signal' to liver to stimulate or suppress the transformation between glycogen and glucose. During this process, a delay was reported to exist [65]. In Figure 3.11.A, HGP delay increases from 0 to 40 min. The oscillations can occur when τ_1 is greater than 14 min. When τ_1 increases, the amplitudes of the four state variables increases, and the range of the glucose concentration difference between compartments grows quickly (Figure 3.11.B). The observation indicates that glucose fluctuation become more significant with longer delay.

An optimal range of τ_1 is estimated at 14-22 min. For HGP delay longer than 22 min, glucose and insulin level are high by the simulation result, which could be due to insulin resistance. It is thus estimated HGP delay may be longer than 22 min for Type 2 diabetics. Besides, with τ_1 increasing, the lower limit of glucose decreases quickly, probably resulting in hypoglycemia. This is a potential danger for diabetics.

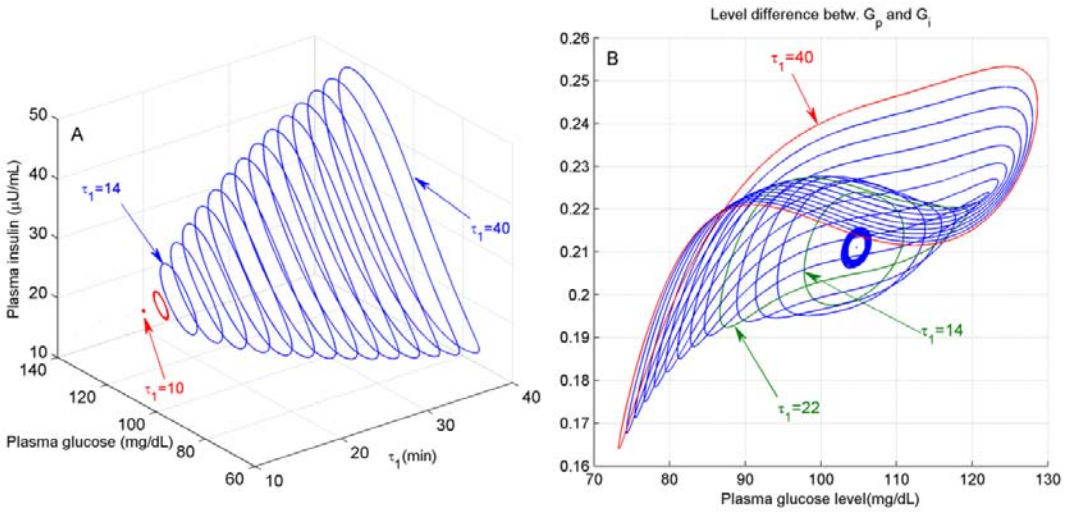

Figure 3.11. Phase plane of glucose and insulin in the plasma (A), and plasma and ISF glucose level difference (B) when τ_1 changes. Both glucose and insulin in plasma reach a steady state with $\tau_1 \leq 12$ min.

3.4.6 Insulin Secretion Delay τ_2

IS delay was reported to be in the range of 0-23.5 min [65]. An initial range of 0-20 min of τ_2 was assumed for the simulation.

When τ_2 increases, the ranges of glucose and insulin widen significantly. A critical value for τ_2 to sustain the oscillations is found to be about 4 min (Figure 3.12.A). For IS delay shorter than 4 min, the oscillations are damped quickly. For τ_2 within 4-12 min, glucose concentration is changing within the optimal range. With τ_2 increases from 12 min, glucose and insulin level are higher than normal, which may be caused by insulin

resistance. Therefore, the IS delay is estimated to be longer than 12 min for Type 2 diabetics. The possibility of occurrences of hyperglycemia at the peak is high with τ_2 longer than 12 min.

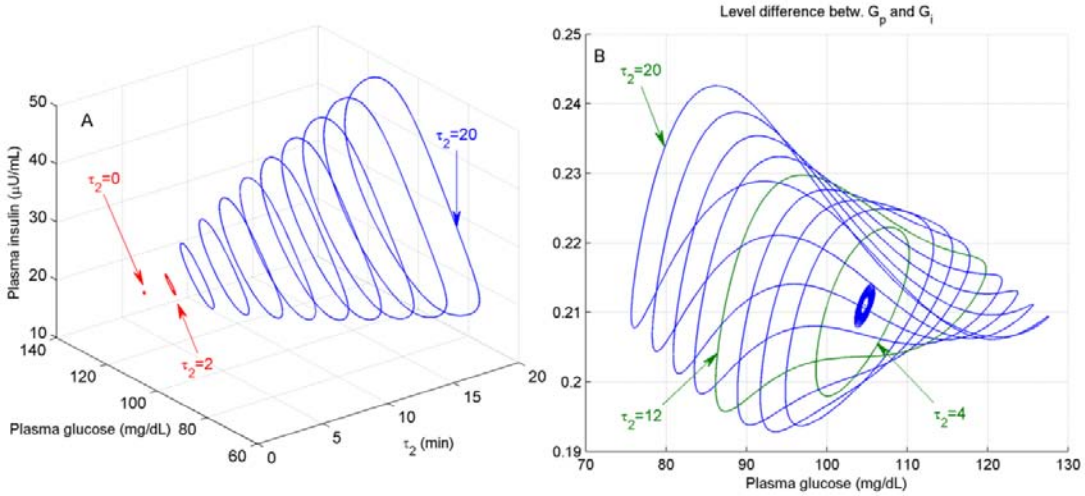

Figure 3.12. Phase plane of glucose and insulin in the plasma (A), and plasma and ISF glucose level difference (B) when τ_2 changes.

3.4.7 Combined Effect of the Two Delays

Based on the results in section 3.4.5 and section 3.4.6, the sums of τ_1 and τ_2 are equal to approximately 24 min. In subsequent simulation to investigate the influence of the two delays on the system, the sum of the delays is kept constant.

A critical value for the sum of the two delays is found to be about 24.6 min. When the sum of the two delays is greater than the threshold, the ultradian oscillation can be sustained. The critical sum of the two delays is quite close to the single delay within the range of 0-23.5 min suggested by [65]. Due to compartment split in our work, the time delay of glucose transporting and utilization always exists, which was included into IS delay in [15]. A critical value for HGP delay to stimulate oscillation was reported at

0.109223 [63]. In our simulation, due to the compartment split of insulin subsystem, when HGP delay is equal to 0, the oscillation is sustained (Figure 3.13.A).

When HGP delay increases from 0 to 24.6 min, glucose and insulin concentrations in two compartments change stably within the normal ranges, and glucose concentration difference between two glucose compartments is always within the optimal range (Figure 3.13.B). This indicates a good degree of stability of inter-regulation of glucose-insulin system.

The simulation result implies that the glucose-insulin regulatory system may reach the optimal situation with the constant sum of the two delays. A possible physiological explanation may lie on the negative feedback of human body. For normal subject, when one of the two delays becomes longer, in order to bring the body system back to stability quickly, the other delay may be accordingly decreased. For the diabetics, regardless of Type 1 or Type 2, the ability of adjusting one or both delays may be impaired, and therefore hypoglycemia or hyperglycemia may be induced.

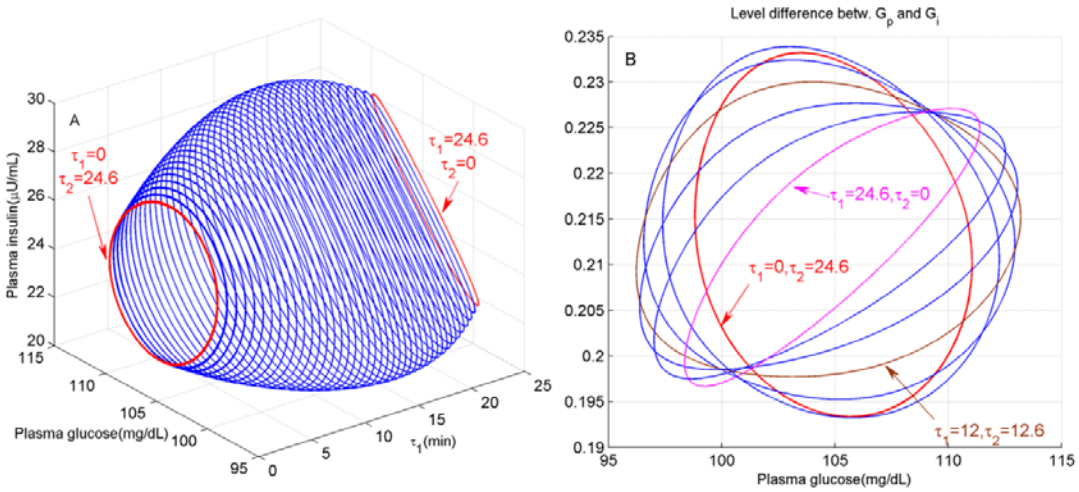

Figure 3.13. Phase plane of glucose and insulin in the plasma (A), and plasma and ISF glucose level difference (B) when the sum of the two delays is equal to 24.6 min.

3.4.8 Glucose Infusion Rate G_{in}

Ultradian oscillations of glucose and insulin are assumed to be caused by the instability of glucose-insulin regulatory system. Different glucose infusion rate is suggested to affect the critical delay time of stimulating ultradian oscillation. Glucose and insulin level are higher caused by higher glucose infusion rate (GIR). Ultradian oscillation was revealed by experiments during 3 meals daily, oral glucose intake, continuous enteral nutrition and constant glucose infusion (refer to Figure 1 in [44]). In this section, effect of varied glucose infusion rate on the oscillatory behavior of glucose-insulin system is investigated.

With GIR changing from 0 to 250 mg/min, glucose and insulin concentration in both compartments increase with growing GIR. Varying GIR has significant effect on the amplitudes of glucose and insulin concentration. Oscillations of glucose and insulin sustain for moderate GIR; and ultradian oscillation of glucose-insulin system damps under small and large GIR, which agrees with the result in [16]. A range of 60-190 mg/min for GIR is observed to sustain the oscillation (Figure 3.14.A). Oscillation damps out and the dynamic system goes for a steady-state for the infusion rate out of the range. An upper limit of GIR but without lower limit to stimulate the ultradian oscillations was reported in [15], which may be not reasonable in the sense of physiology. When glucose rise caused by low glucose intake is relatively small, glucose concentration would be reduced to normal level by insulin quickly, and regulation time is too short to induce oscillations of glucose and insulin.

When GIR is kept between 60-115 mg/min, plasma glucose level can be within the optimal range 90-120 mg/dL (Figure 3.14.B). The difference of glucose concentration in

the two compartments changes from 18% to 25% with growing GIR, and it increases with climbing plasma glucose level in each cycle (Figure 3.14.C).

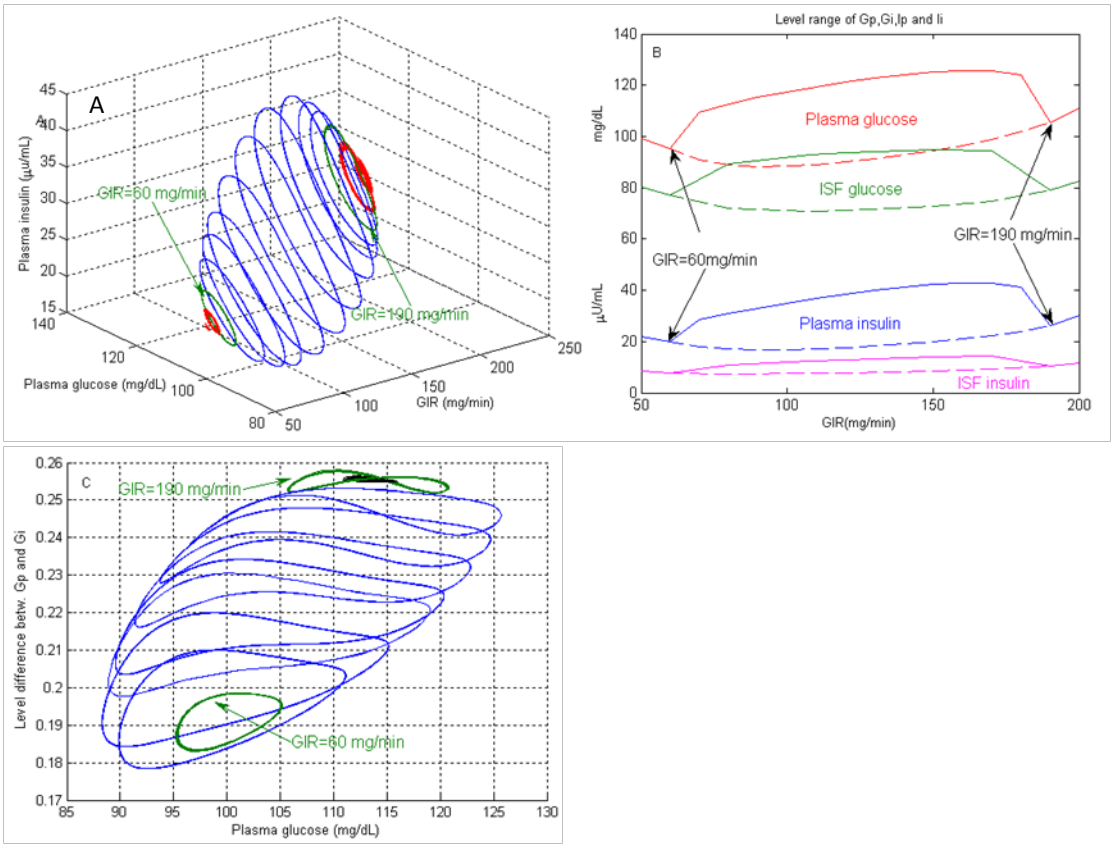

Figure 3.14. Phase plane of glucose and insulin in the plasma (A), range of plasma glucose and insulin (B), and plasma and ISF glucose level difference (C) when GIR changes.

3.4.9 Discussion

In existing studies on oscillatory behavior, the interaction between plasma glucose and ISF glucose was often ignored. The glucose measured by implantable glucose sensor in artificial pancreas is usually the ISF glucose concentration. It is necessary to study the dynamic relationship between plasma glucose and ISF glucose before an insulin therapy can be applied. The aim of this chapter is to investigate the oscillatory behavior of the regulatory system, and interaction between glucose and insulin in the two compartments.

Under constant glucose infusion rate, the values of the seven parameters are varied in our simulation study. The simulation results agrees with existing studies [15, 16, 44], and physiological effect relevant with the parameters is discussed.

When one of the six parameters: the four *m* parameters and the two delays varies, plasma and ISF glucose changes in the same direction with variable concentration difference. For insulin, when insulin transfer rate m_1, m_2 or ISF insulin clearance rate m_4 changes, insulin in the two compartments changes in the opposite direction and in the same direction when one of the other parameters is altered. This implies that m_1, m_2 and m_4 may have more significant effect on insulin distribution between the two compartments.

When each parameter is within the range sustaining the ultradian oscillations, ISF glucose concentration is 14% -28% lower than that in plasma compartment. Glucose level difference between plasma and ISF always changes, and is different for rising and falling side. For the parameters changing in the optimal range, the level difference curves changes clockwise, which indicates the plasma glucose changes faster than ISF glucose in the rising side. This agrees with the report from [13] that the change of ISF was less than that in plasma when glucose was increasing and was greater when glucose was decreasing. There are some situations where the glucose level difference changes in a different way. When m_4 is equal to 0.2 (Figure 3.8.B), with the closed curve changed anticlockwise, glucose level difference during falling was larger than that during rising. This may be due to the greater IDGU in subcutaneous tissues that could lower ISF glucose quickly.

Three lags have often been investigated in existing studies: lag between plasma and ISF glucose, lag between plasma glucose and plasma insulin, and lag between plasma and ISF insulin. The simulation results are shown in Figure 3.15 and Figure 3.16.

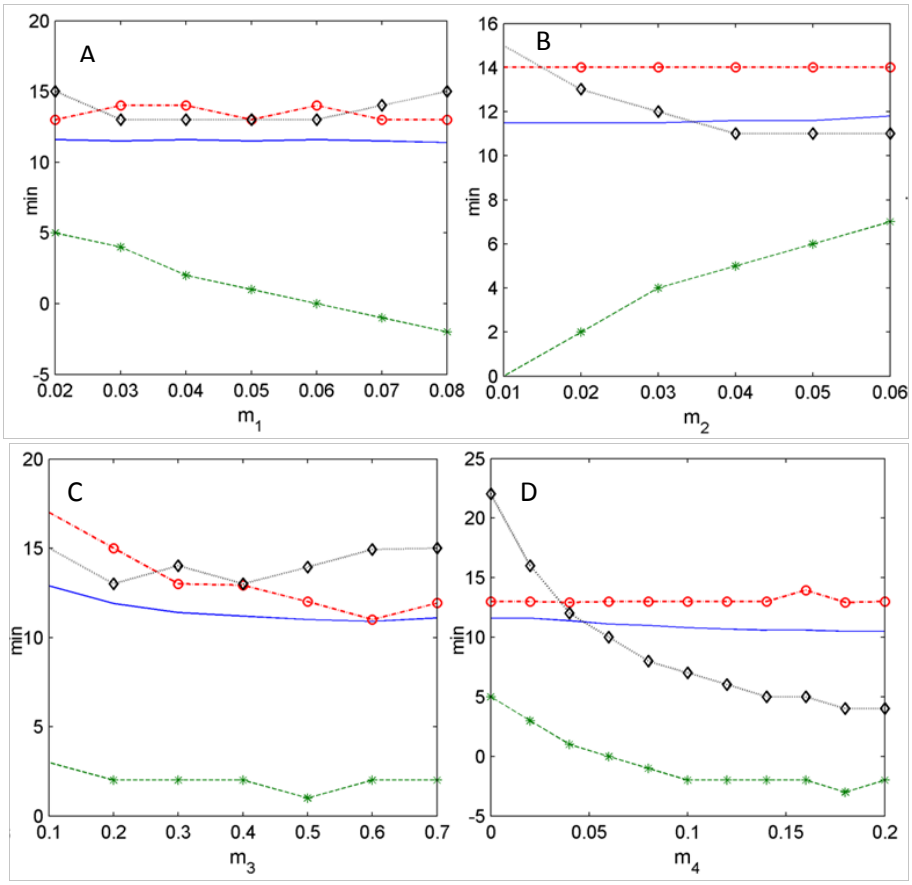

Figure 3.15. The effect of m_1, m_2, m_3, and m_4 on the change of lag and oscillation period. The oscillation period was divided by 10 in Figure 4.15 and Figure 4.16. In Figure 3.15 and Figure 3. 16, the definitions for the four lines in each panel are as following: green dash lines with star marker: lag of ISF glucose behind plasma glucose; blue solid lines: oscillation period; black dot lines with diamond marker: lag of ISF insulin behind plasma insulin; and red dash-dot lines with circle marker: lag of plasma insulin behind plasma glucose.

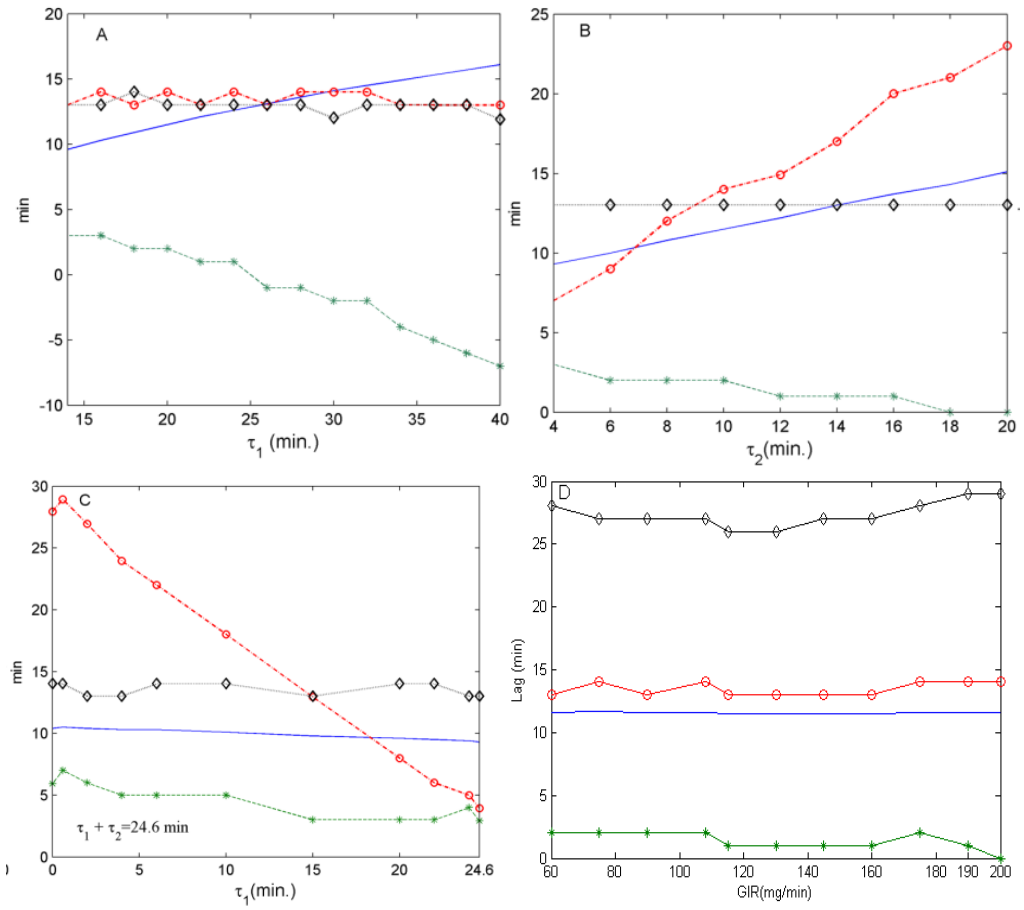

Figure 3.16. Effect of τ_1 (A), τ_2 (B), sum of two delays (C) and GIR (D) on the change of lag and oscillation period.

From the simulation, ISF glucose often lags behind plasma glucose for about 3-6 min (green dash lines with star marker in Figure 3.15 and Figure 3.16). It approaches the physiological lag of 5 min suggested by [13]. However, ISF glucose begins to lead plasma glucose with increasing insulin transfer rate from plasma to ISF m_1, ISF insulin clearance rate m_4 and HGP delay τ_1. Larger m_1 and m_4 can increase insulin transfer to ISF and glucose utilization respectively; and longer HGP delay would decrease the glucose production rate into plasma compartment. Thus ISF glucose begins to lead plasma glucose. It was also suggested that increased glucose clearance from ISF would decrease the lag [82].

In plasma compartment, glucose is observed to lead insulin to peak and fall for about 10-20 min (red dash-dot lines with circle marker in Figure 3.15 and Figure 3.16). This is significantly affected by plasma insulin degradation rate m_3 and IS delay τ_2. The lag becomes shorter when m_3 increases or τ_2 decreases. The reason might be that larger insulin degradation in plasma and shorter IS delay would stimulate or accelerate insulin secretion, and hence the lag is reduced.

Plasma insulin always leads ISF insulin for 10-15 min with significant change by altering ISF insulin clearance rate m_4 (black dot lines with diamond marker in Figure 3.15 and Figure 3.16). When m_4 increases, the lag decreases quickly. A possible explanation is that increased larger ISF insulin clearance rate would accelerate insulin distribution.

Longer HGP delay τ_1 or IS delay τ_2 would increase the oscillation period of the dynamic system and result in higher glucose concentration (blue lines in Figure 3.15 and Figure 3.16). Glucose fluctuation becomes more significant when one of the two delays increases. Large fluctuation of glucose should be avoided in glucose regulation. The two-delay bifurcation was also discussed in some studies [63, 64]. Keeping the sum of the two delays constant is considered in our simulation. Figure 3.13.A shows that as long as the sum threshold is greater than 24.6 min, the ultradian oscillation can be sustained with plasma glucose level always changing in the optimal range even if HGP delay τ_1 or IS delay τ_2 is equal to 0. The glucose-insulin system seems to have reached the optimal situation. Apart from the lag between plasma glucose and plasma insulin (red dash-dot lines with circle marker in Figure 3.16.C), the other two lags and oscillation period do not have significant change.

Although different GIR has significant influence on the amplitudes of insulin and glucose, it hardly affects the oscillation time and lag effect among the four state variables (Figure 3.16.D). The oscillation period of the regulatory system is almost constant at about 120 min, plasma insulin lags behind plasma glucose for 12-15 min, ISF insulin lags plasma glucose for about 27 min, and a lag of about 3 min exists between plasma glucose and ISF glucose. Investigation on varying GIR reveals that the effect of constant GIR on oscillatory behavior of the oscillatory glucose-insulin system is not important, which agrees with the result reported in [16].

In this chapter, the four *m* parameters of insulin dynamics, the two delays and GIR are analyzed for their influence on the glucose-insulin regulatory system, their ranges are estimated for sustaining the oscillation of glucose-insulin system, and ranges for different subjects are discussed. The estimated parameter range for different subjects is shown in Table 3.7. The seven parameters are related with the disease relevant to irregular blood glucose level. The resultant effect of these parameters on the lag between glucose and insulin in the two compartments provide an insight on the distribution and metabolism of glucose and insulin in quick- and slow-equilibrating organs and tissues.

Table 3.7. Ranges of model parameters for different subjects.

	m_1	m_2	m_3	m_4	τ_1	τ_2	GIR
Sustain oscillation	0.02-0.08	0.01-0.04	0.1-0.6	0-1	≥ 14	≥ 4	60-190
Optimal/Normal	0.03-0.06	0.02-0.04	0.2-0.3	0.02-0.05	14-22	4-12	60-115
Sub-healthy	0.06-0.08	0.01-0.02	0.1-0.2	0-0.02	/	/	/
Type 2 diabetics	0.02-0.03	/	0.3-0.6	>0.05	>22	>12	/
Nominal value	0.042	0.02	0.268	0.03	20	10	108

3.5 Summary

Glucose level measurement and insulin infusion are often implemented in the subcutaneous tissues in artificial pancreas. Understanding the dynamics of glucose and insulin in the subcutaneous tissues is important in the regulation of blood glucose level. We proposed a new two-compartmental model of glucose-insulin interaction with two explicit delays that can study the interaction of glucose in different organs and the oscillatory behavior of the glucose-insulin system.

In this chapter, glucose and insulin space are split into plasma compartment and ISF compartment respectively. The four *m* parameters of insulin dynamics, the two delays and GIR are analyzed for their influence on the glucose-insulin regulatory system. The ranges of the seven parameters are estimated for sustaining the oscillation of glucose and insulin, and ranges for different subjects are discussed based on simulation results. The effect of these parameters on the oscillatory system is related to diseases and irregular blood glucose level. The investigation of lag between glucose and insulin in the two compartments sheds light on the distribution and metabolism of glucose and insulin in quick- and slow-equilibrating organs and tissues. A model was studied in this chapter that can effectively deal with concentration of glucose and insulin in the ISF compartment. This is important for the research and development of a clinical viable artificial pancreas.

The characteristics of the model agree with most of the dynamic properties proposed up to now, and support the hypothesis that the ultradian oscillation of glucose and insulin in human body may originate from the interaction and negative feedback between glucose and insulin. This is consistent with our result that ultradian oscillations can still sustain with constant sum of HGP and IS delay, which may be a reflection of the

negative feedback between glucose and insulin. By removing insulin secretion from the model to simulate the situation of Type 1 diabetes, ultradian oscillation does not occur under constant external glucose infusion. This may indicate that insulin secretion function of the pancreas plays an important role of inducing ultradian oscillation of glucose and insulin.

4 Model of Glucose-Insulin System with Subcutaneously-Injected Insulin

4.1 Introduction

Reducing glucose fluctuation or duration of hyperglycemia and hypoglycemia can improve the morbidity of diabetics. Insulin delivery and glucose measurement via subcutaneous route has advantages over intravenous route: low incidence of infection, less pain and discomfort, and ease of administration. When insulin is administered intravenously, exogenous insulin enters vein directly. It is difficult to implement insulin delivery for ordinary people, and may cause infection due to improper operation. The development in subcutaneous administered insulin analogues makes the management of diabetes more effectively. The pharmacokinetic profile of the latest rapid and basal-acting analogues can mimic pancreatic insulin secretion better than previous insulin. When insulin is delivered subcutaneously, the delivery site is subcutaneous tissues. Insulin can be infused using an insulin pen or insulin pump by ordinary people. Subcutaneous delivery of insulin is safer and more convenient for daily use compared with intravenous delivery. Intravenous insulin delivery is sometimes applied in the intensive care unit so that it takes less time for insulin to take effect.

The most common therapy for diabetic patients is multiple insulin injections subcutaneously based on three or four glucose level measurements daily. Besides, in closed-loop glucose control system (artificial pancreas), glucose measurement and insulin administration are often implemented in the subcutis. The dynamics of glucose and insulin in the subcutis is thus important to achieve tight glucose control. With good

knowledge of the physiology of blood glucose regulation, an accurate glucose-insulin interaction model and an efficient glucose control algorithm could be developed.

The absorption of injected insulin is complex and can be affected by many factors (site and depth of injection, temperature [83], exercise [84], concentration and volume of injected insulin [85], species [86], etc.). The mechanism of how insulin absorption kinetics influenced by insulin dose size, concentration, insulin crystals etc. was explained in a recent study by quantitative description [87]. Poor absorption of insulin is apparent for patients with severely impaired endogenous IS. The mean absorption levels for different insulin were estimated in [88].

Published insulin absorption data was analyzed by non-compartmental analysis and pharmacokinetic methods. By this method, Friedberg et al. suggested the mean absorption level for different insulin (70% - 80% for regular and lispro, 30% or less for NPH, and 30% - 40% for lente insulin) [88]. Insulin remains in the subcutaneous fat layer for some time after the rapid injection. Possible reasons of delayed absorption at large injection volumes are: self-depression, saturable diffusion through the capillary membrane, and that the injected solution may create a separate space in subcutis, thus reducing contact with capillary system [89].

Polymerization and /or degradation may happen and result in decreased amount of insulin and slow rate of insulin diffusion from the injection site. The reduction of insulin amount due to polymerization and local degradation was represented by an effectiveness factor in [90]. Insulin degradation is relevant to insulin action, and is as important as that of insulin secretion.

The degradation of subcutaneously injected insulin has been found to occur in rat [91-93], pig [94] and human [93, 95, 96]. A considerable amount of insulin was degraded at the injection site in some studies [94]. About 40% of the injected insulin was reported to be degraded at the injection site of diabetic rats [93]. Local degradation of subcutaneously injected insulin was considered to be insignificant or relatively small [89]. In Type 1 diabetic patient, the SC degradation of infused insulin was reported to be insignificant and negligible [96]. In [97], total degradation of subcutaneous delivered insulin was reported to be less than 20% over 4 hours period based on the best-fitting parameters. Contrary to the view, a considerable amount of insulin was degraded at the injection site in some studies [94, 98, 99]. By studying both control subjects and in subjects who may have large SC degradation of insulin, a degradation rate of about 2% per milligram per minute was estimated in [100].

Due to the varying pharmacokinetics of injected insulin, glycemic control by insulin injection or continuous insulin infusion in the subcutis is challenging and meets significant practical difficulties to become a stable and consistent therapy. Qualitative and quantitative estimation of insulin kinetics after SC injection is useful for efficient dosing as well as reducing the fluctuation of glucose level.

Subcutaneous tissue is becoming the main measurement site of glucose sensor and administration sit of exogenous insulin in the future artificial pancreas. It is important to understand the kinetics interactions of glucose and insulin between plasma and subcutaneous tissues. Glucose dynamics was modeled using a one-compartment system in some models [15, 44], ignoring the dynamics of glucose in subcutis. Varying degradation and absorption of endogenous insulin for different diabetic patient changes

the effective dosage of insulin for glucose regulation. Hyperglycemia or hypoglycemia may be caused by insufficient or overdose of insulin subcutaneously-injected. The ignorance of the physiological changes (e.g., defective absorption or accelerated degradation of insulin [101, 102]) on the subcutaneously-injected insulin causes loose control of glucose concentration for diabetic patients.

In Chapter 3, a two-compartment model describing the oscillatory behavior of glucose – insulin system was proposed to investigate the influence of model parameters on the system and interactions between quick- and slow-equilibrating tissues and organs [103]. There was no exogenous insulin in this model. In this chapter, with exogenous insulin delivered subcutaneously, dynamics of both glucose in subcutis and subcutaneously-injected insulin [104] are considered for Type 1 and Type 2 diabetic patients. A submodel mimicking the kinetics of injected insulin in the subcutis is included. Two compartments expressing the plasma and subcutaneous tissues are used to express glucose subsystem, and insulin degradation in the subcutaneous tissues, two absorption channels for insulin are considered for the subcutaneously-administered insulin. The model of glucose – insulin system with insulin subcutaneously injected is evaluated using the clinical data of diabetic inpatients. This model considering the dynamics of subcutaneously-injected insulin simulates the situation of diabetic patient receiving subcutaneous insulin delivery, and helps derive control algorithms for treatment of diabetic patients.

4.2 Models of Subcutaneous Insulin

The kinetics of insulin injected subcutaneously has been investigated widely. Many models mimicking insulin kinetics differ essentially in the subcutaneous insulin

absorption, Plasma insulin, in most case, is modeled using a single compartment, except that by Hovorka et al. [105].

4.2.1 Compartmental Models

Kobayashi et al. used a one-compartment model with a delay to model the absorption of short-acting insulin injected or infused subcutaneously [106]. It was proposed that insulin absorption kinetics for the two modes: continuous infusion and bolus injection subcutaneously, did not have significant difference; and the insulin was degraded to the same extent using the two administration modes. The model diagram and equations were given by Figure 4.1 and Eq. (4.1), respectively.

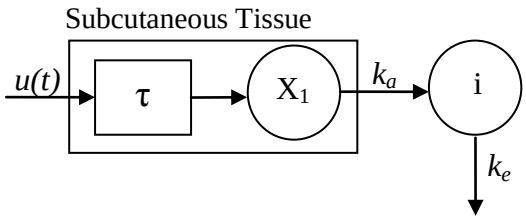

Figure 4.1. Diagram of SC insulin model proposed by Kobayashi et al..

$$\begin{aligned} \dot{x}_l(t) &= -k_a x_l(t) + u(t-\tau), \\ \dot{i}(t) &= -k_e i(t) + k_a / V_d x_l(t), \end{aligned} \tag{4.1}$$

where x_1 is the amount of insulin in the subcutaneous depot (μU), i is plasma insulin (μU/mL), k_a and k_e (min^{-1}) are the rate constants for absorption and elimination respectively, V_d (L/kg) is the distribution volume, τ (min) is the time lag and $u(t)$ (U/min) the rate of insulin administration.

Kraegen and Chisholm suggested a two-compartment model of subcutaneous insulin distribution: SC volume and plasma insulin volume [97]. Subcutaneous volume consisted of two connected pools. Insulin was modeled to move from a first to a second pool in the SC volume before delivered to the plasma volume. Insulin degradation was assumed from the two pools in the SC volume respectively, linear with the insulin amounts in the two pools (Figure 4.2). The model equations were given by Eq. (4.2).The insulin absorption delay was suggested to be important for clinical implications therein.

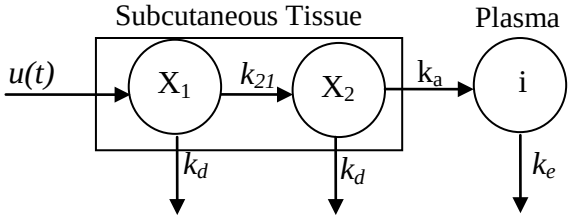

Figure 4.2. SC insulin model proposed by Kraegen and Chisholm.

$$\begin{aligned} \dot{x}_1(t) &= -(k_d + k_{21})x_1(t) + u(t), \\ \dot{x}_2(t) &= k_{21}x_1(t) - (k_d + k_a)x_2(t), \\ \dot{i}(t) &= k_a / V_d x_2(t) - k_e i(t), \end{aligned} \tag{4.2}$$

where x_1 and x_2 are the insulin masses in the subcutaneous compartments, $u(t)$ is the subcutaneous infusion rate, k_d is the rate constant of insulin degradation in subcutis, and k_{21} and k_a are the rate constants describing insulin transport within the subcutaneous space and from the subcutaneous depot to plasma, respectively; i is plasma insulin concentration, and k_e the elimination rate constant.

In [97], total degradation of SC delivered insulin was reported to be less than 20% over 4 hours period based on the best-fit parameters. In their later work [96], in Type 1 diabetic patient the subcutaneous degradation of infused insulin was proposed

insignificant and negligible, and local accumulation in SC space was considerable. The insulin absorption delay was suggested to be important for clinical implications.

A simple linear model was developed and identified using data of diabetic patients by Puckett and Lightfoot to predict plasma insulin and provide some insights on clinical issues (i.e., interpatient and intrapatient variation and insulin overlapping) [90]. The model structure was similar to that in [97]. The model was composed of three compartments: pocket insulin (formed by injected insulin solution), interstitium insulin and blood insulin (Figure 4.3). The model was described in Eq. (4.3).

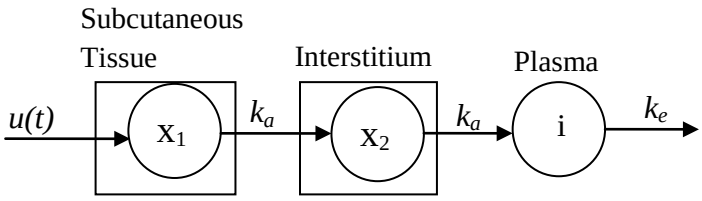

Figure 4.3. SC insulin model proposed by Puckett and Lightfoot.

$$\begin{aligned} \dot{x}_1(t) &= -k_a x_1(t) + u(t), x_1(0) = \alpha D / V_d, \\ \dot{x}_2(t) &= -k_a [x_1(t) - x_2(t)], x_2(0) = 0, \\ \dot{i}(t) &= k_a x_2(t) + k_e [i_b h(t) - i(t)], i(0) = i_b, \end{aligned} \tag{4.3}$$

where x_1 is the subcutaneous insulin mass per unit plasma distribution volume, x_2 is the interstitial fluid insulin mass per unit plasma distribution volume and i is plasma insulin concentration. D is the injected dose, a is the effectiveness factor accounting for insulin degradation at the injection site and V_d is the insulin distribution volume. k_a is the rate constant from subcutaneous depot to interstitial fluids and from interstitial fluids to blood, k_e is the rate constant of plasma insulin elimination. i_b is the constant plasma term describing the effect of ultralente insulin and $h(t)=1$ for $0<t<24$ h.

The pure time delay in [106] was replaced using the interstitium compartment. A component for long-acting ultralente insulin and representation of cumulative effect of multiple injections were considered.

A three-compartment linear model was proposed by Shimoda et al. to develop an insulin infusion algorithm used on a wearable artificial pancreas [107]. The SC insulin was modeled using two compartments: insulin at the injection site and insulin proximal to plasma, with exogenous insulin injected into the compartment representing injection site. The model was expressed using three differential equations (Eq. (4.4)). The insulin degradation in the SC tissues was more significant than that in [97].

$$\begin{aligned} \dot{x}_1(t) &= -k_{21}x_1(t) + u(t), \\ \dot{x}_2(t) &= k_{21}x_1(t) - (k_d + k_a)x_2(t), \\ \dot{i}(t) &= k_a / V_d x_2(t) - k_e i(t), \end{aligned} \tag{4.4}$$

where x_1 is the sc insulin mass where the injection takes place, x_2 is sc insulin mass proximal to plasma and i is plasma insulin concentration. The rates constants k_d and k_e are the degradation constants in the sc tissue and plasma respectively, V_d is plasma distribution volume.

A five-compartment model to describe the dynamics of insulin was presented by Hovorka et al. [105]. The model explored the insulin distribution in systemic plasma, hepatic plasma, interstitial fluid, and insulin bound to the liver and peripheral receptors. The receptor-mediated and non-receptor-mediated insulin degradation were taken into account in the model. Another linear absorption model of subcutaneously administered insulin Lispro was proposed and included into a glucoregulatory model to develop a model predictive controller in Type 1 diabetic subjects by Hovorka et al. [45]. The subcutaneous insulin absorption model was represented by a two-compartment chain, and

the plasma insulin was modeled using a single compartment (Figure 4.4). A long delay of over 90 min was observed between insulin SC delivery and its peak action. The delay may be relevant to the insulin absorption delay in SC depot and the insulin action duration.

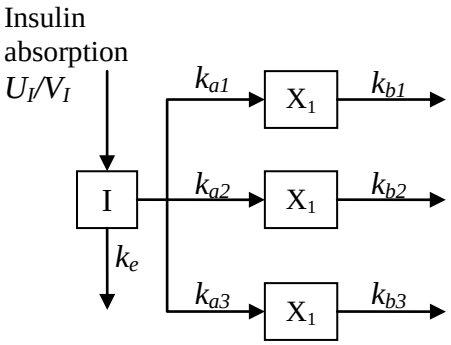

Figure 4.4. SC insulin model proposed by Hovorka et al..

$$\begin{aligned} \dot{S}_1(t) &= u(t) - S_1(t)/t_{\max,I}, \\ \dot{S}_2(t) &= [S_1(t) - S_2(t)]/t_{\max,I}, \end{aligned} \tag{4.5}$$

where S_1 and S_2 are a two-compartment chain representing absorption of subcutaneously administered short-acting (e.g. Lispro) insulin, u(t) represents administration (bolus and infusion) of insulin, and $t_{max,I}$ is the time-to-maximum insulin absorption. The insulin absorption rate (appearance of insulin in plasma) is obtained as $U_I = S_2(t)/t_{max,I}$.

The plasma insulin concentration $I(t)$ is described as

$$\dot{I}(t) = U_I(t)/V_I - k_e I(t). \tag{4.6}$$

k_e is the fractional elimination rate and V_I is the distribution volume. The model represents three actions of insulin on glucose kinetics:

$$\begin{aligned} \dot{X}_1(t) &= -k_{a1}X_1(t) + k_{b1}I(t), \\ \dot{X}_2(t) &= -k_{a2}X_2(t) + k_{b2}I(t), \\ \dot{X}_3(t) &= -k_{a3}X_3(t) + k_{b3}I(t). \end{aligned} \tag{4.7}$$

X_1, X_2 and X_3 represent the (remote) effects of insulin on glucose distribution, glucose disposal and HGP; k_{a1}, k_{a2} and k_{a3} represent deactivation rate constants, and k_{b1}, k_{b2} and k_{b3} represent activation rate constants.

Wilinska et al. proposed eleven alternative models of insulin Lispro kinetics under bolus and continuous delivery subcutaneously of Type 1 diabetes [104]. Insulin delivery mode, two channels of insulin absorption, effect of insulin dose on its clearance and absorption, insulin degradation at the injection site and insulin association state were assessed in the models. The models were validated using data from seven Type 1 diabetic patients based on the principle of parisimony and physiological plausibility. Two absorption channels and local insulin degradation of insulin were indicated in the four-compartment model (Figure 4.5) best representing the experimental data. Different with most insulin absorption models with linear insulin degradation, Michaelis – Menten dynamics was used to model the local insulin degradation. The insulin subsystem with injected insulin was described using four differential equations in Eq. (4.8).

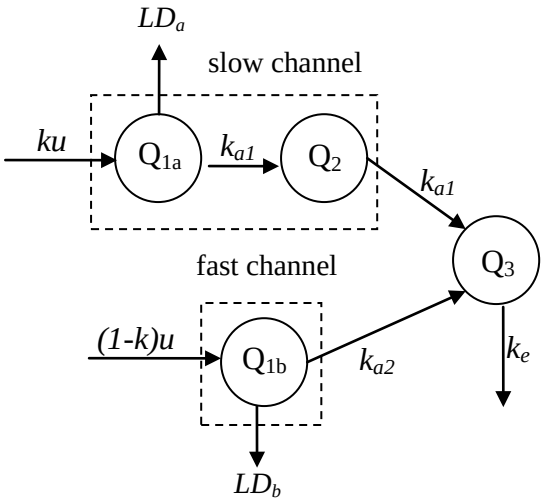

Figure 4.5. SC insulin model proposed by Wilinska et al..

$$\begin{aligned}
&\dot{Q}_{1a} = ku - k_{a1}Q_{1a} - LD_a, \quad \dot{Q}_{1b} = (1-k)u - k_{a2}Q_{1b} - LD_b, \\
&\dot{Q}_2 = k_{a1}Q_{1a} - k_{a1}Q_2, \qquad \dot{Q}_3 = k_{a1}Q_2 + k_{a2}Q_{1b} - k_eQ_3, \\
&LD_a = \frac{V_{\max_LD}Q_{1a}}{K_{m_LD} + Q_{1a}}, \qquad LD_b = \frac{V_{\max_LD}Q_{1b}}{K_{m_LD} + Q_{1b}},
\end{aligned} \tag{4.8}$$

where Q_{1a}, Q_{1b} and Q_2 are insulin masses in the channels, Q_3 is insulin mass in plasma compartment, k is the proportion of u, the insulin input, that passes through the slower channel, k_{a1} and k_{a2} are the transport rates between compartments, k_e is insulin clearance rate of from plasma by the liver and kidneys, and LD_a and LD_b are the Michaelis-Menten degradation in two channels, respectively.

4.2.2 Non-Compartmental Models

A pharmacokinetic model simulating the kinetics of subcutaneously-injected insulin, empirically derived from previous studies and included in the glucose – insulin model, was used to estimate the time course of plasma insulin for different combinations of preparations (regular, NPH, lente, and ultralente) [108]. The effect of changing insulin regimen, dose, or meals timing was investigated in the glucose control program to demonstrate the performance of glucose control in Type 1 diabetic patients. In this model, the percent of insulin amount absorbed from the subcutaneous space is given by:

$$A_{\%}(t) = 100A(t) = 100 - 100t^s / (T_{50}{}^s + t^s), \tag{4.9}$$

where s describes absorption rate of the various insulin preparations and T_{50} is the time interval to reach a 50% absorption of the injected insulin. T_{50} was described as:

$$T_{50} = aD + b, \tag{4.10}$$

where D is insulin dose, and a and b express different values for different insulin preparation. Insulin absorption velocity, the time derivative of $A(t)$ multiplied by the injected dose, is the insulin input flux into plasma. Thus plasma insulin concentration is:

$$\dot{i}(t) = -k_e i(t) + A(t)/V_d = -k_e i(t) + t^{s-1} s T_{50}{}^{s} D \Big/ V_d (T_{50}{}^{s} + t^{s})^2, \qquad (4.11)$$

where k_e is the rate constant for insulin degradation and V_d is the plasma insulin distribution volume.

Mosekilde et al. presented a model utilizing the chemical relationship between insulin oligomers to describe the absorption process of subcutaneously injected soluble insulin [89]. In this model, insulin was presumed to be present in three forms: a low molecular weight form (dimeric insulin), a high molecular weight form (hexameric insulin) and an immobile form where molecules were bound to the tissue (bound insulin). Three compartments were used to express the insulin present in three forms: hexameric insulin, dimeric insulin and bound insulin in the subcutaneous depot. By presuming that mainly dimeric insulin penetrated the capillary wall, the dimeric insulin compartment was connected with plasma insulin, and controlled the absorption rate. Effective diffusion constant for insulin in subcutis, absorption rate of dimeric insulin, equilibrium constant between hexameric and dimeric insulin, binding capacity for insulin in the tissues, and the average life time for insulin in its bound state can be determined using this model. Only the dimeric state can be absorbed into plasma. Solving the non-linear coupled differential equations is computationally burdensome when dose, volume and concentration are considered. Due to the number of parameters, model parameters are *a priori* identified from literature. The model is theoretically unidentifiable and computationally burdensome to implement.

The model by Mosekilda et al. [89] was simplified by Trajanoski et al. for ease of parameter estimation [109]. The insulin binding in the subcutaneous space was assumed to be negligible at therapeutic concentrations. The model was further extended to describe the absorption of both soluble insulin and monomeric insulin analogues. The influence on the absorption of various injection volumes, concentration, and injection depth was investigated for soluble and monomeric insulin. The mechanism of how insulin absorption kinetics influenced by insulin dose size, concentration, insulin crystals etc. was explained in a recent study by quantitative description [87]. The model of Trajanoski et al. was further extended to include the long-acting basal insulin Glargine [110].

The non-compartmental models capture published insulin absorption kinetics well and are more accurate physiologically than the compartmental models. However, computational cost is prohibitive compared to compartmental models, especially if it is used for a real-time diabetes decision system or an *in silico* simulation tool. These six model [90, 97, 106-109] were reviewed critically and discussed by Nucci and Cobelli [111]. Other reviews were also available to present insulin absorption kinetics in subcutis [62, 112].

Subcutaneous tissue is to become the main measurement site of glucose sensor and administration sit of exogenous insulin in the future artificial pancreas. It is important to understand the kinetics interactions of glucose and insulin between plasma and subcutaneous tissues. Glucose dynamics was modeled using a one-compartment system in some models [15, 44], ignoring the dynamics of glucose in subcutis. Different degradation and absorption of endogenous insulin for different people changes the actual dosage of insulin effecting on glucose regulation. Hyperglycemia or hypoglycemia may

be thus caused by insufficient or overdose of insulin subcutaneously-injected. For diabetic patients, loose control of glucose concentration may arise from the ignorance of the physiological changes on the subcutaneously-administered insulin.

In this chapter, the dynamics of both glucose in subcutis and subcutaneously-injected insulin [104] are considered. A variant of the glucose-insulin model in [103] with meals and insulin subcutaneously-administered is proposed for diabetic patient. Two compartments expressing the plasma and subcutaneous tissues are used to express glucose subsystem, and insulin degradation in the subcutaneous tissues, two absorption channels for insulin are considered for the subcutaneously-administered insulin. This model considering the dynamics of subcutaneously-injected insulin simulates the situation of diabetic patient receiving subcutaneous insulin delivery, and helps derive control algorithms for treatment of diabetic patients.

4.3 Modeling Glucose-Insulin System with Subcutaneously-Injected Insulin

Oscillatory behavior of glucose-insulin system in human body has been observed during in vivo and in vitro experiments [51-54, 57]. In the recent models studying the ultradian oscillations of glucose and insulin, glucose is often modeled as a one-compartment system [15, 18, 44, 60], which ignores the dynamics of glucose in subcutis. In this model, dynamics of both glucose in subcutis and subcutaneously injected insulin [104] are considered. Following the model proposed previously in [103], a model for diabetic patient with meal inputs and insulin injection was proposed.

4.3.1 Model of Glucose and Insulin Subsystems

The organs with large blood flow relative to their interstitial volume may have a rapid rate of equilibrium (e.g., liver, heart, kidney, etc.), while other poorly perfused tissues have a slow equilibrating rate (e.g., muscle and adipose tissues). The first compartment, plasma and rapidly-equilibrating organs, is named plasma for short; and the slowly-equilibrating tissues is expressed as subcutaneous tissues compartment (SC compartment for short). The model structure was shown in Figure 4.6, and the complete model was described in Eq. (4.12) and (4.13).

$$
\begin{aligned}
&\dot{G}_p(t) = G_{in}(t) + HGP(I_p(t-\tau_1)) - U_{ii}(G_p(t)) - E(G_p(t)) - k_1 G_p(t) + k_2 G_i(t),\\
&\dot{G}_i(t) = k_1 G_p(t) - k_2 G_i(t) - U_{id}(G_p(t), Q_{1a}(t), Q_{1b}(t), Q_2(t)),\\
&\dot{Q}_{1a}(t) = p\ (t) - LD_a(Q_{1a}(t)) - k_{a1} Q_{1a}(t),\\
&\dot{Q}_{1b}(t) = (1-p)u(t) - LD_b(Q_{1b}(t)) - k_{a2} Q_{1b}(t),\\
&\dot{Q}_2(t) = k_{a1} Q_{1a}(t) - k_{a1} Q_2(t),\\
&\dot{I}_p(t) = a \times S(G_p(t-\tau_2)) + k_{a1} Q_2(t) + k_{a2} Q_{1b}(t) - k_e I_p(t).
\end{aligned}
\tag{4.12}
$$

$$
\begin{aligned}
&U_{id}(G_i, Q_{1a}, Q_{1b}, Q_2) = \beta \times f_3(G_i) \times f_4(Q_{1a}, Q_{1b}, Q_2),\\
&f_3(G_i) = 0.01 G_i / V_{gi},\\
&f_4(Q_{1a}, Q_{1b}, Q_2) = 4 +\\
&90/\{1 + \exp(-1.772 \log[(Q_{1a} + Q_{1b} + Q_2) \times (1/V_{ii} + 0.03/e)] + 7.76)\},\\
&S(G_p) = 210 / (1 + \exp(5.21 - 0.003 G_p / V_{gp})),\\
&E(G_p) = \begin{cases} 0.0005 \times [G_p(t) - 339 \times BW] & \text{if } G_p > 339 \times BW \\ 0 & \text{if } G_p \le 339 \times BW \end{cases},\\
&LD_a(Q_{1a}) = V_{\max\_LD} \times Q_{1a} / (K_{m\_LD} + Q_{1a}),\\
&LD_b(Q_{1b}) = V_{\max\_LD} \times Q_{1b} / (K_{m\_LD} + Q_{1b}).
\end{aligned}
\tag{4.13}
$$

In the insulin subsystem, the state variables in the insulin subsystem are plasma insulin I_p (mU), Q_{1a}, Q_{1b} and Q_2 (mU) in the SC compartment. SC insulin I_i (mU) is assumed to be the sum of the three states in the SC compartment. After exogenous insulin

(u: mU/min) is administered subcutaneously, local insulin degradation (LD_a, LD_b: mU/min) occurs at the injection site in the two pathways of insulin absorption. Injected insulin moves from a first (Q_{1a}: mU) to a second (Q_2: mU) pool in the slow channel before reaching plasma. V_{max_LD} (mU/min) is the saturation rate for continuous infusion and bolus; and K_{m_LD} (mU) is the insulin mass at which insulin degradation is equal to its half maximal value. p (unitless) is the proportion of insulin flux passing the slow channel. k_{a1} and k_{a2} are transfer rates (min^{-1}) in the two channels accordingly. Insulin clearance in plasma compartment is represented by the rate parameter k_e (min^{-1}).

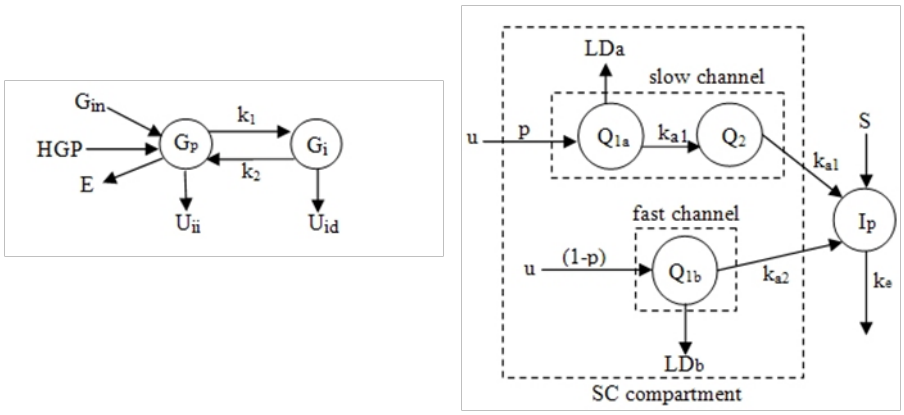

Figure 4.6. Model of glucose-insulin system with subcutaneously-injected insulin.

For the glucose subsystem, two state variables were considered: plasma glucose G_p (mg) and SC glucose G_i (mg). The concentration of SC glucose was measurable during experiments. The state variables in the insulin subsystem were plasma insulin I_p (mU), Q_{1a}, Q_{1b} and Q_2 (mU) in the SC compartment. V_{gp}, V_{gi}, V_{ip}, and V_{ii} were the distribution volumes of plasma glucose, SC glucose, plasma insulin and SC insulin accordingly, which was estimated respectively as 12%, 10%, 4.5% and 10% of body weight [14, 31, 45, 81]. τ_1 and τ_2 are HGP and IS, respectively. BW is the bodyweight of the subject.

In the insulin subsystem, after exogenous insulin (u: mU/min) is administered subcutaneously, local insulin degradation (LD_a, LD_b:mU/min) occurs at the injection site in the two pathways of insulin absorption. Injected insulin moves from a first (Q_{1a}: mU) to a second (Q_2: mU) pool in the slow channel before reaching plasma. V_{max_LD} (mU/min) is the saturation rate for continuous infusion and bolus; and K_{m_LD} (mU) is the insulin mass at which insulin degradation is equal to its half maximal value. p (unitless) is the proportion of insulin flux passing the slow and fast channel. k_{a1} and k_{a2} are transfer rates (min^{-1}) in the two channels accordingly. Insulin clearance in plasma compartment is represented by the rate parameter k_e (min^{-1}).

IDGU in this model was different with that in [103]. The process of IDGU was presented as a function of the sum of insulin mass in the SC compartment. The value of insulin exchange rate between SC and plasma compartment e followed that in [44]. The effect of diabetes on insulin secretion and IDGU in diabetic patients was estimated by α and β [18]. Smaller α and β implies less insulin secretion from pancreas and increasing insulin resistance in the diabetic patients, respectively. For the definitions of other parameters, refer to previous chapter.

4.3.2 Models of Meal

When a healthy patient eats a meal, the carbohydrates are broken down into glucose, galactose and fructose, with galactose and fructose transformed quickly into glucose. Fats are converted to phospholipids, triglycerides, and cholesterol; and proteins are converted to amino acids. During this period insulin level increases naturally to stimulate glucose uptake.

Insulin increase results in increased glucose uptake by liver and peripheral tissues, keeping plasma glucose level within normal range. Glucose level of a healthy patient rarely goes over 140 mg/dL, even during a meal.

For a diabetic patient, insulin effect on glucose regulation strongly depends on the quality of insulin therapy, depending on the insulin amount administered and the time of administration. If insulin level is very low, insulin is not enough for glucose uptake by liver and peripheral cells; and low insulin level results in relatively high glucagon level, which actually causes higher glucose level in the blood. The time of insulin administration plays a major role in maintaining normoglycemic conditions. Early administration would cause hypoglycemia before the meal is absorbed and hyperglycemia at the end of meal, because insulin is not sufficient for glucose utilization from the end of the meals. Late insulin administration would result in hyperglycemia at the beginning of the meal and hypoglycemia at the end of the meal or shortly after.

Glucose from gut absorption is assumed to enter plasma directly into the accessible compartment with clearance by first pass splanchnic degradation. Glucose appearance rate in plasma was described with a mono-compartment model by Fisher [113], as given in Eq.(4.14). b represents the absorption rate of the meal, A is meal size and t_{meal} represents the beginning time of meal digestion.

$$D(t) = A\exp(-b(t - t_{meal})). \tag{4.14}$$

Plasma described by two compartments, an accessible and non-accessible compartment, was suggested by Hovorka et al. [45]. A two-compartment chain with identical transfer rates was used to describe digestion, gastric emptying, and the gut absorption rate directly into plasma, as shown in Eq. (4.15). A_{meal} represents the percent

availability of the meal consumed, M_{meal} is the size of meals, and t_{max} represents the time from the beginning of the meal consumption to reach the maximum of absorption rate.

$$D(t) = \frac{M_{meal} A_{meal} t \exp(-t / t_{\max})}{t_{\max}^{\ 2}}. \tag{4.15}$$

In the study by Dalla Man et al. [114], model was evaluated against a linear and non-linear three-compartment model. This model in Eq. (4.16) consists of dual stomach compartments with a non-linear gastric emptying rate. Gastric emptying k_{empt} is a constant in the linear model; and in the non-linear model gastric emptying is described by a hyperbolic tangent function, as shown in Eq. (4.17).

$$\begin{aligned} \dot{q}_{sto1}(t) &= -k_{21} q_{sto1}(t) + D\delta(t), \\ \dot{q}_{sto2}(t) &= -k_{empt} q_{sto2}(t) + k_{21} q_{sto1}(t), \\ \dot{q}_{gut}(t) &= -k_{abs} q_{gut}(t) + k_{empt} q_{sto2}(t), \\ Ra(t) &= f k_{abs} q_{gut}(t). \end{aligned} \tag{4.16}$$

$$\begin{aligned} k_{empt}(q_{sto}) &= k_{\min} + (k_{\max} - k_{\min}) / 2 \cdot \{\tanh[\alpha(q_{sto} - bD)] \\ &\quad - \tanh[\beta(q_{sto} - cD)] + 2\}, \\ \alpha &= 5 / [2D(1-b)], \beta = 5 / (2Dc), \end{aligned} \tag{4.17}$$

where

$q_{sto1}(t)$	Amount of glucose in the stomach (solid phase),
$q_{sto2}(t)$	Amount of glucose in the stomach (liquid phase),
$\delta(t)$	Impulse function,
D	Amount of ingested glucose,
$q_{gut}(t)$	Glucose mass in the intestine,
k_{21}	Rate of grinding,
k_{empt}	Rate of gastric emptying,
k_{abs}	Rate of intestinal absorption,
f	Fraction of intestinal absorption appearing in plasma,
k_{min}	Minimum gastric emptying rate,

k_{max} Maximum gastric emptying rate.

The glucose absorption model, relevant to the size of carbohydrate (CHO) in the meal, followed that in [18, 115] with k and b as listed in Table 4.1. The value of k for 15 g and 7.5 g carbohydrate (CHO) was estimated by fitting the curve of k and meal size (Figure 4.7). For each meal began at time t_m, the glucose intake rate $G_m(t)$ was shown in Eq. (4.18). $u(t-t_m)$ was the unit step function with unity value only when $t \geq t_m$. $G_{in}(t)$ was calculated by integrating each meal intake G_m. This model of meal absorption was used in the following simulation for its simplicity.

$$G_m(t_m, k, b) = kt \exp(-(t - t_m)^2 / 2b^2) / b^2 \times u(t - t_m). \quad (4.18)$$

Table 4.1. Parameters value for the glucose absorption model.

	7.5 g CHO	10 g CHO	15 g CHO	30 g CHO	60 g CHO	75 g CHO
b	80					
k	1115	1500	2157	3400	4300	5100

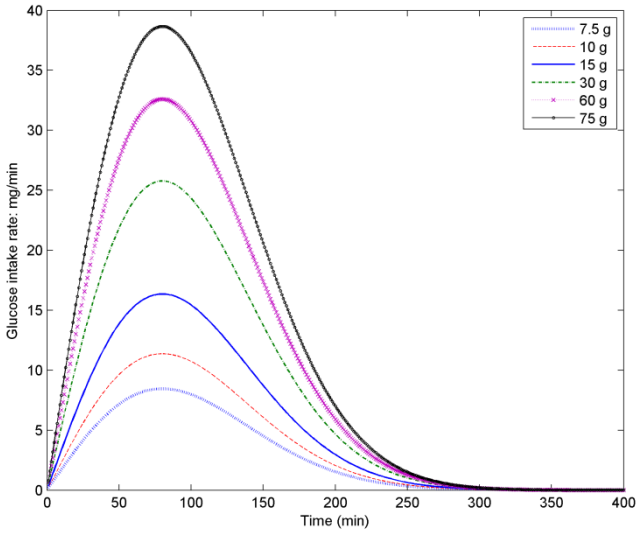

Figure 4.7. The glucose profiles with various carbohydrate uptake.

4.4 Clinical Evaluation of Model with Subcutaneously-Injected Insulin

4.4.1 Material

Model cannot give meaningful prediction unless its parameters are accurately determined. Average parameter values in literature are often used for modeling, such as the organ volumes and blood flow rates of dogs in [116] or humans was used by Sorensen [20]. Patient parameters is identified by fitting the model to patient data and selecting reasonable parameter values which give the closest fit to the data.

Twenty five cases (three Type 1 and twenty-two Type 2) with subcutaneously-injected insulin were studied. Information of gender, age, bodyweight, glucose concentration, insulin injections and meals were recorded for each subject. The glucose was measured regularly by finger prick before meals. Three meals (60 g, 30 g or 15 g CHO contained) and snacks (15 g or 10 g CHO contained) were offered for the subjects. Mixtard 30 or short-acting insulin of individually dosage was injected 3-15 min before meals. Each insulin injection lasted for about 1 minute.

In this model, rate parameters in insulin subsystem (k_{a1}, k_{a2}), two delays (τ_1 and τ_2), and two parameters (α and β) expressing the dysfunction of the diabetic patients are adjustable. Model constants of the model are listed in Table 4.2. Since blood glucose level was measured by finger prick, modeled glucose level in SC compartment was used to match that of the clinical glucose data. The first glucose data in each case was set as the initial glucose concentration. The initial values of the model parameters were determined by adjusting the simulated glucose level with the measured glucose level manually and then refining the parameters with successive iterations.

Table 4. 2. Model constants of our model.

Parameter	Value	Unit
k_1	0.032	min^{-1}
k_2	0.02	min^{-1}
k_e	0.37	min^{-1}
p	0.55	unitless
V_{max_LD}	235	mU/min
K_{m_LD}	65	mU
e	0.2	min^{-1}

4.4.2 Methods

Model-based and sliding scale protocols have been clinically tested for glucose regulation. Model-based methods can be accurate, but require identifying patient specific parameters and capturing all of the observed dynamics. Currently, most common parameter identification methods are non-linear, and sometimes computationally intense for real-time use. An accurate identification method is important for refining and testing a model. For non-linear methods, fitting or prediction error can be caused by the dynamics not captured or not finding the global minima. Using different starting points may find a better optimal solution, with increased computational time.

The most commonly used method for fitting parameters in compartment models is non-linear recursive least squares (NRLS) [19, 117, 118]. This method requires a range of initial values to produce optimal result. NRLS is computationally intensive as well [19], particularly with longer periods of data. Iterative, Bayesian and gradient descent based methods have been used in many different forms [39, 119, 120]. These methods are computationally intensive and not necessarily robust to noise in the data, and are not necessarily generalizable to broader situations. Overall, traditional methods, such as

NRLS, generate results with some potential limitations which is dependent on the specific problems. These methods require repeated simulations resulting in significantly added computation.

The integral method integrates the differential equations of the model and converts the problem to match areas under curves [121]. Using numerical integration and measured data, the problem can be converted into a least squares problem. The numerical integration can further filter the data and make it robust to noise. Finally, significant computation effort can be saved because it does not require gradients or re-simulation of the model. The integral method has been used in may glycemic control studies [121-123] and in other biomedical models [124].

In this section, the model parameters are estimated using least square method which fits a set of observations with the proposed model by estimating the values of a subset of the unknown parameters. Our objective is to adjust the parameters to best fit the clinical data comprising glucose level, insulin injection dosage and meals of anonymous diabetes inpatients. Each data set consists of N data pairs (t_j, G_j). The least squares method finds its optimum when the sum of the squares

$$S = \sum_{j=1}^{N} r_j^{\,2} \tag{4.19}$$

is minimum where the residuals (errors) r_j are given by

$$r_j = G_j - G_M(t_j, \theta), \tag{4.20}$$

where θ=[k_{a1}, k_{a2}, τ_1, τ_2, α, β] is a parameter vector to be estimated. G_j and $G_M(t_j, \theta)$ are the measured glucose level and modeled glucose level at time t_j, respectively. The minimum value of S occurs when the gradient for each parameter

$$\frac{\partial S}{\partial \theta_i} = 2\sum_j r_j \frac{\partial r_j}{\partial \theta_i} = 0 \quad (i = 1,...m) \tag{4.21}$$

is zero.

In nonlinear system the derivatives of *S* do not have closed solution. With initial value of the parameters given, the parameters can be estimated by iterative approximation:

$$\theta_i \approx \theta_i^{k+1} = \theta_i^k + \Delta\theta_i. \tag{4.22}$$

k is the iteration number and $\Delta\theta$ is the shift vector. At each iteration, the model can be linearized by approximation using Taylor series expansion at θ^k:

$$\begin{aligned} G_M(t_j,\theta) &\approx G_M(t_j,\theta^k) + \sum_i \frac{\partial G_M(t_j,\theta^k)}{\partial \theta_i}(\theta_i - \theta_i^k) \\ &\approx G_M(t_j,\theta^k) + \sum_i J_{ji}\Delta\theta_i. \end{aligned} \tag{4.23}$$

J is the Jacobian matrix. The residuals is given by

$$\begin{aligned} r_j &= \Delta y_j - \sum_{s=1}^{m} J_{is}\Delta\theta_s; \\ \Delta y_j &= G_j - G_M(t_j,\theta^k). \end{aligned} \tag{4.24}$$

Substituting into the gradient equation, we obtain

$$-2\sum_{j=1}^{N} J_{ji}(\Delta y_j - \sum_{s=1}^{m} J_{js}\Delta\theta_s) = 0. \tag{4.25}$$

The nonlinear problem of matching the clinical data with the proposed model is approximated as a linear least square problem which can be solved using Gauss-Newton algorithm.

To the best of our knowledge, there has not been any glucose-insulin model including the sub-model of subcutaneously-injected insulin for Type 2 diabetic patients. Type 2 diabetes is more prevalent than Type 1 diabetes, and the metabolism of glucose-insulin system and automatic glucose control is more complex for Type 2 diabetes.

Developing a model to simulate the metabolism of glucose-insulin system including subcutaneously-delivered insulin for Type 2 diabetes is especially important for the derivation of control algorithm of closed-loop insulin delivery system.

Most of them modeled external insulin to be infused directly into the plasma compartment such as the Minimal model [36]. This is not applicable for closed-loop glucose regulation system applying subcutaneous glucose monitoring and subcutaneous insulin delivery. In order to evaluate the performance of modeling the dynamics of glucose and insulin, our model was compared with Hovorka model [45]. Since the Hovorka model was proposed only for Type 1 diabetic patient, clinical data of the three Type 1 cases were fitted using Hovorka model for comparison.

In Hovorka model, glucose subsystem was represented by two compartments: glucose in accessible and non-accessible compartments. Six differential equations were used to describe insulin absorption and action system. Six parameters in the model (glucose transfer rate k_{12}, insulin elimination in plasma compartment k_e, endogenous glucose production EGP extrapolated to zero insulin level EGP_0, insulin sensitivity of distribution, disposal and EGP: S_{IT}, S_{ID}, S_{IE}) were adjusted to fit the clinical data of three Type 1 subjects. With the values of other model parameters remained the same as that of [45], initial values of the six model parameters were determined by adjusting the simulated glucose level with the measured glucose level manually.

4.4.3 Results and Discussion

The accuracy is determined by normalizing the sum of the square error (SSE) with the number of glucose measurement of each case. Figure 4.8 shows the normalized SSE of the 25 cases using our model and SSE of the three Type 1 cases using Hovorka model.

With the initial values of glucose and insulin level determined explicitly, our model was compared with Hovorka model [45] using clinical data of three Type 1 cases (Case 1, 11, and 17), as shown in Figure 4.9; and Case 20 and Case 3 of Type 2 patients with respectively smallest and largest normalized SSE values are presented in Figure 4.10 to illustrate the curve fitting results of Type 2 cases. The information of the five diabetic subjects is shown in Table 4.3; and the size and time of glucose intake and insulin injection are shown in Table 4.4.

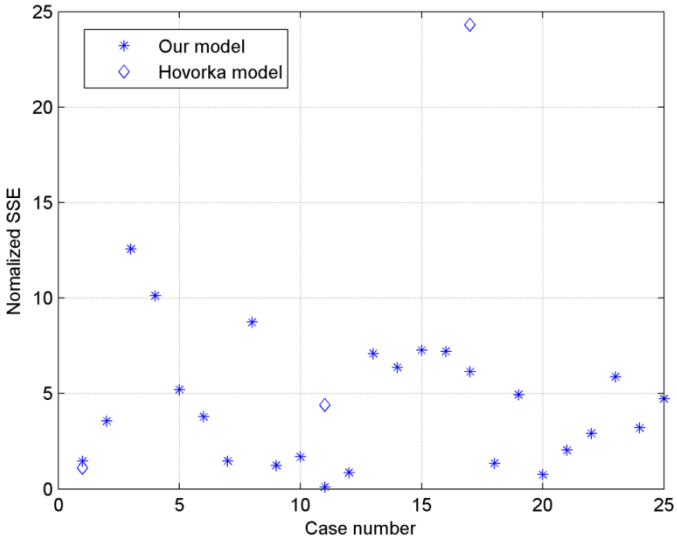

Figure 4.8. The normalized SSE of the 25 cases of our model and that of the three Type 1 cases of Hovorka model.

Table 4.3. Information of the five diabetic subjects.

	Case 1	Case 3	Case 11	Case 17	Case 20
Diabetes Type	Type 1	Type 2	Type 1	Type 1	Type 2
Age	22	46	32	39	70
BW (KG)	58	40.9	82	66.6	52.7
Gender	Male	Male	Male	Male	Male
HbA1c	/	16.8%	10.9%	/	12.2%
Mean Glucose Level (mmol/L)	11.5	13.5	11.2	13.0	10.3

Table 4.4. Time and size of meal intake and insulin injections of the five subjects.

Case	Glucose		Insulin	
	Time (min)	Size (g)	Time (min)	Dose (U)
Case 1	540, 660, 750, 900, 1020, 1320	60, 15, 60, 15, 60, 15	600, 660, 720, 785,840, 930, 1660, 1730, 1767, 1830, 1895, 900, 1050, 1115, 1180, 1240, 1300, 1360, 1420, 1480, 1540, 1660	5, 2.5,1, 1, 1, 1, 1, 1, 1, 1, 1, 1.5, 1.5, 1.5, 1.5, 1.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5
Case 3	0, 1440, 1980, 2880, 3120, 4320, 240, 540, 1680, 3420, 420, 840, 1860, 3300	60, 60, 60, 60, 60, 60, 30, 30, 30, 30, 15, 15, 15, 15	0, 540, 1980, 3420, 1440, 2880, 4320	16, 6, 6, 6, 14, 14, 14
Case 11	0, 2645, 720, 2195, 2715, 3645	45, 45, 15, 15, 15, 15	0, 240, 1215, 1455, 1695, 1935, 2715, 3435, 480, 720, 960, 2485, 2955, 3195	4, 4, 4, 4, 4, 4, 4, 4, 2, 2, 2, 2, 2, 2, 2
Case 17	10, 370, 1450, 1810, 180, 1620	60, 60, 60, 60, 60, 15	1205,1795, [365-400], [735-900], [2255-2800]	20, 0.20, 0.23, 0.2, 0.17
Case 20	10, 1090, 2530, 850, 2290, 3730, 4030, 1450, 2890, 4330, 960, 1260, 2700, 3070, 4140, 4510	30, 30, 30, 60, 60, 60, 60, 60, 60, 60, 15, 15, 15, 15, 15, 15	5, 845, 1085, 4025, 3725, 2525, 2285, 3255, 4325	6, 8, 8, 8, 28, 12, 12, 15, 18

The proposed model can mimic the change patterns of the observed glucose level, and demonstrate ultradian oscillations in Figure 4.9 and Figure 4.10. Although the same model structure for short and intermediate acting insulin was applied, our model was demonstrated to be adequate for simulating human glucose – insulin system. The value of parameters of our model and Hovorka model of the Type 1 cases is listed in Table 4.5. The parameter ranges of twenty two Type 2 patients are listed in Table 4.6.

Table 4.5. Parameters value of our model and Hovorka model of three Type 1 cases.

	Our model	Hovorka model
Case 1	k_{a1}=0.34, k_{a2}=0.19, τ_1=38, β=0.95	EGP_0=0.016, k_e=0.238, k_{12}=0.116, S_{IT} =0.00392, S_{ID}=0.00062, S_{IE}=0.029
Case 11	k_{a1}=0.24, k_{a2}=0.13, τ_1=31, β =0.88	EGP_0=0.0145, k_e=0.14, k_{12}=0.095, S_{IT} =0.0031, S_{ID}=0.00034, S_{IE}=0.033
Case 17	k_{a1}=0.13, k_{a2}=0.16, τ_1=29, β =0.61	EGP_0=0.017, k_e=0.21, k_{12}=0.105, S_{IT} =0.0019, S_{ID}=0.00021, S_{IE}=0.013

Table 4.6. Parameters range of our model for the twenty-two Type 2 subjects.

Parameter	Range	Parameter	Range
k_{a1}	0.095—0.29	τ_1	30—49
k_{a2}	0.085—0.22	τ_2	31—51
α	0.21—0.97	β	0.23—0.75

In Figure 4.9, simulated glucose concentration of our model agreed well with that of the clinical data. Insulin dosage injected is much less than that of Type 2 cases in Figure 4.10 although there is no insulin secreted by the pancreas. It agrees with the large β in Table 4.5, implying lower insulin resistance in Type 1 subjects. The sharp change of glucose concentration in Type 1 cases, which is significantly different from the disrupted oscillations of other Type 2 cases, indicates that the insulin secretion plays an important role of stimulating the ultradian oscillations of glucose and insulin. The Hovorka model is demonstrated to be able to agree with the clinical data of the three Type 1 cases. Glucose level changed more gradually compared with that of our model in Figure 4.9 (A) with multiple small-dosage insulin injections. With the reduced sampling of glucose measurement in Figure 4.9(B) and (C), simulation results of Hovorka model have higher glucose peak levels than ours, which should be avoided for diabetic subjects. There are

less sharp changes in the estimated glucose levels with our model under sparse glucose measurement in the three Type 1 cases. With more frequent glucose sampling, our model could better simulate glucose change, and explain the interactions between glucose and insulin in the terms of physiology and pathology of diabetes.

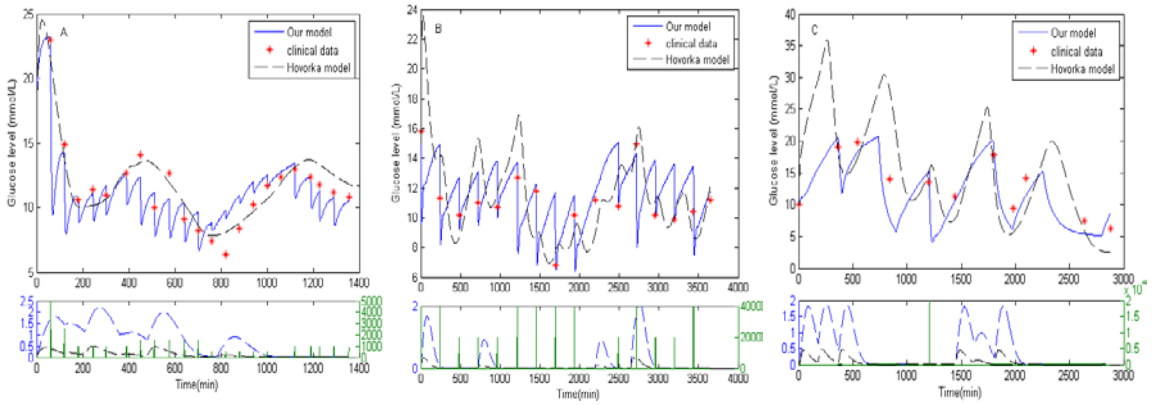

Figure 4.9. The comparison result of our model with Hovorka model (Case 1: A, Case 11: B, Case 17: C). Modeled glucose level and clinical data were shown in the top panel. In the bottom panel the blue solid and black dash curves represented glucose intake rate using our model and Hovorka model, respectively (mmol/min); and the green solid line represented insulin injection dosage (mU). IS was not considered for Type 1 subjects, insulin secretion delay τ_2 and α were not estimated.

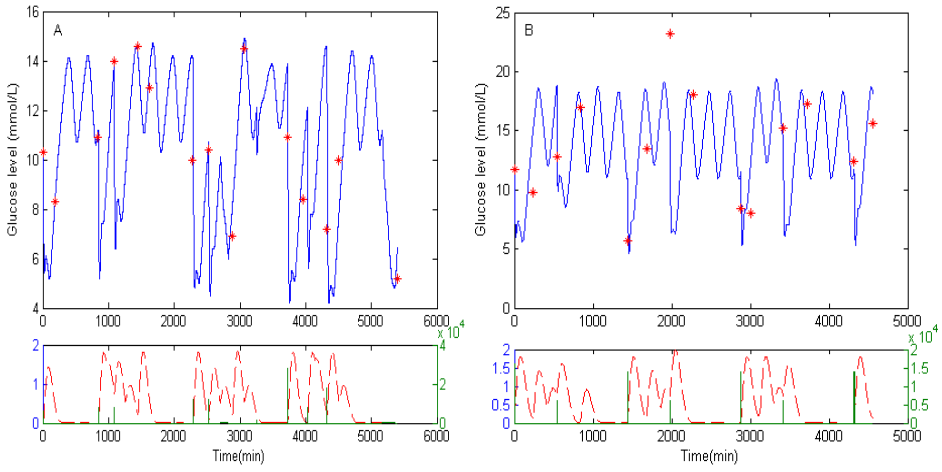

Figure 4.10. The fitting result of measured glucose with estimated glucose level using our model for the Type 2 cases with the smallest (A: Case 20) and highest (B: Case 3) normalized SSE. In the bottom panel, the red dash curve and the blue lines represented glucose intake rate (mmol/min) and insulin injection dosage (mU), respectively. In the left figure, the parameters were estimated: k_{a1}=0.14, k_{a2}=0.13, τ_1=37, τ_2=45, α=0.42, β=0.52. In the right figure, the parameters were estimated: k_{a1}=0.22, k_{a2}=0.17, τ_1=34, τ_2=48, α=0.35, β=0.32.

In Figure 4.10 (A), most data points can be simulated using our model. Measured glucose level is significantly decreased after insulin injections, agreeing well with the simulated glucose change pattern using our model. Subcutaneous glucose level oscillates mostly between 10-14 mmol/L. However, glucose level decreases sharply immediately after insulin injection which is due to the fact that subcutaneous tissue is one of the main glucose utilization locations. Glucose oscillations between two successive insulin injections are mostly stimulated by endogenous insulin secretion. The subject in Case 20 is a 70 years old male Type 2 patient with weight 52.7 kg. HbA1c (Glycated hemoglobin) measured before 4-day glucose monitoring in hospital was 12.2%. Although this subject is older than the one in Case 3 (Figure 4.10 B), average glucose level is much lower than Case 3. The situation of this subject is better than Case 3 with lower HbA1c. Larger α and β than Case 3 demonstrates more insulin secretion and less insulin resistance of this subject. The insulin transport rates and the two delays are all in the reasonable ranges.

In Figure 4.10 (B), although the sparse glucose measurement resulted in missing information of glucose change, our model has been demonstrated to be robust in modeling the change in glucose level. This Type 2 case has the largest normalized SSE, and the subject is a 46 years old male patient with weight 40.9 kg. HbA1c measured before 3-day glucose monitoring was 16.8%. HbA1c for normal is often below 6%, which implies that glucose control for this subject is not good in the past several months. High glucose level of this Type 2 subject may be caused by severely impaired function of pancreas and increased insulin resistance. This agrees with the small values of α and β estimated using the clinical data of this subject. High insulin transport rate between the SC and plasma compartment from two absorption channels k_{a1} and k_{a2} in Figure 4.10 (B)

implies quick transfer of insulin, which was reasonable for a thin male. Delay of insulin secretion τ_2 was quite long, slowing secretion of endogenous insulin; and small α and β demonstrated weak ability of insulin secretion and high insulin resistance in the insulin sensitive tissues. The above factors may explain the extremely high HbA1c. Extended period of high glucose level would result in malfunction of many organs and further aggravate the symptoms of diabetes. There is a significant mismatch of modeled glucose level with the measured glucose at 2040 min. It is much higher than the glucose levels measured at the same time on the previous day (600 min) and the following day (3480 min) with similar size of insulin dosage in each day. The considerable differences between the theoretical estimation and measurement might be caused by other disturbances or large change of the subject's condition. Glucose-insulin system may be disrupted by severe diabetes, which changes the parameter values and makes the estimation of glucose level using mathematical models more complicated. Frequent change of model parameters is surmised to be affected by the severity of diabetes, which may cause proposed glucose-insulin unable to predict glucose level for severe diabetic patients. This may explain the simulation result in Figure 4.10 that fitting with clinical data in Case 20 is better than that of Case 3.

The large interpatient variation on the model parameters indicates the necessity of identifying individual parameters. Regular recalibration is therefore necessary for patients using commercial continuous glucose monitoring system (CGMS) with automatic insulin delivery. The curve fitting between model simulation and clinical data is limited by low sampling frequency, measurement noise, and lack of measurement of pertinent variables in the clinical data. These factors introduce a considerable uncertainty on the exact

parameter value. When the model was used to predict glucose change, this can be improved by glucose controller calculating optimal dosage of injected insulin under more frequent glucose sampling. Glucose level could be regulated back to normal range and reduced the fast change of glucose level.

The rate parameter in the SC insulin compartment k_{a1} and k_{a2} is relevant to the diffusion of injected insulin from SC to plasma through slow and fast channels, respectively. More insulin can be delivered to the plasma with larger value of rate parameters. In the peripheral tissue where insulin is administered, insulin resistance is significantly high which slows down insulin transport via capillary wall [125]. Smaller value of k_{a1} and k_{a2} implies high insulin resistance in the subcutis. The diffusion and action of insulin could also be protracted by thick adipocytes in the subcutis [69].

HGP delay is relevant to the plasma insulin's effect on glucose production by liver; and IS delay is dependent on the action time of insulin secretion stimulated by the plasma glucose. The estimated range of τ_1 in this work approximates the value of 25-50 min reported in [44]. Insulin secretion delay τ_2 was proposed in the range of 0-23.5 min [65]; however the experimental results on normal subject is probably different from that of diabetic patients. A value of 50 min of τ_2 was used in numerical simulation [61], which was within the our proposed range. HGP and IS delay are related to the action of glucose production by liver and insulin secretion by pancreas, which is significantly affected by the situation of the subjects. For younger and healthier subjects, liver and pancreas takes faster action to the change of insulin and glucose level, respectively. Long HGP delay would probably induce hypoglycemia when external glucose input is not given in time,

and hyperglycemia is possible to be caused by long IS delay, especially after meals intake which makes glucose level increase fast.

The parameters α and β indicated the ability of insulin secretion and glucose utilization in diabetic patient respectively. α was set to be 0 for Type 1 cases. This was different from the situation in [18] that Type 1 subjects had endogenous insulin secretion. Decrease in insulin secretion was reported in the elder patients [126], which agrees with our result that smaller value of α often occurred in the older subjects. The values of β for Type 2 cases are smaller than Type 1 cases. The impairment of IDGU is more significant in Type 2 diabetic patient due to insulin resistance in the subcutis. Moderate-to-severe muscle insulin resistance may happen in lean Type 2 subjects, while there is no further defect in insulin action in obese Type 2 subjects [127].

Possible mechanisms contributing to insulin resistance included variable capillary density [128], large local degradation of insulin [95], and alternations of the receptor-mediated transendothelial insulin transport [125]. These factors may affect transport of glucose and insulin between blood and subcutis and subsequent glucose utilization by insulin-sensitive cells, and play an important role of diffusing insulin from injection site to other parts of the body and altering of postprandial glucose metabolism.

Obesity and aging may deteriorate the situation of diabetic patients. In an obese subject, thick fat layer delays the diffusion of injected insulin followed by larger local degradation of insulin; reduced number and impaired function of glucose transporter slows glucose transport from plasma to insulin-sensitive cells; and impaired IS and sensitivity would reduce glucose uptake in the periphery and cause hyperglycemia. Obese rat hearts was reported to have decreased total glucose transporter number [129]. Insulin

resistance is a common for obese individuals, where the pancreatic β-cell is less sensitive to increment of plasma glucose level is compared with subjects with normal insulin sensitivity.

Changes in anthropometric characteristics with increasing age (e.g., increase of fat mass and visceral fat) may cause insulin resistance in humans [130]. The decline in insulin action has been demonstrated to be relevant to the increasing age under euglycemic-hyperinsulinemic clamp conditions [131]. Glucose stimulated insulin secretion was reported to be functionally impaired in aging rats [126]. It is obvious that functions of body organs (e.g., pancreas, liver, kidney, blood vessels, etc.) are retrograded due to aging. The metabolism of glucose and insulin is disrupted and diabetes would be further aggravated.

4.5 Summary

Subcutaneous tissue is to become the main measurement site of glucose sensor and administration sit of exogenous insulin in the future artificial pancreas, in any case, it is important to understand the kinetics interactions of glucose and insulin between plasma and subcutaneous tissues. Subcutaneous tissues cause significant degradation for injected insulin, and absorption of endogenous insulin is different for different people, which changes the actual dose of insulin taking effect on glucose regulation. Hyperglycemia or hypoglycemia is to be caused by insufficient or overdose of insulin subcutaneously-injected. A model including the dynamics of glucose in the subcutaneous tissues and the dynamics of subcutaneously-administered insulin is thus proposed.

The number of patients with Type 2 diabetes is more than that of Type 1 diabetes, and the metabolism of glucose and insulin, and glucose regulation is more complex for Type 2 diabetes. There has not been a glucose-insulin model including the dynamics of subcutaneously-injected insulin for Type 2 diabetic patients up to now. therefore, developing a model to simulate the metabolism of glucose-insulin system including subcutaneously-delivered insulin for Type 2 diabetes is especially important for the derivation of control algorithm of closed-loop insulin delivery system. Our study could be a possible solution for glucose control of Type 2 diabetes.

In this chapter, a model of glucose – insulin system was developed to simulate the dynamics of glucose and insulin in diabetic patients receiving insulin injection. Quantitative estimation of insulin absorption and transport is useful for efficient dosing as well as reducing the fluctuations of glucose level. The slowly-equilibrating compartment (SC compartment) of insulin was divided into three compartments to simulate the local degradation and different absorption rate of subcutaneously-injected insulin. The effect of concentration, volume, etc. of injected insulin was not considered in our proposed model.

The glucose-insulin model including subcutaneous insulin was fit to clinical data of diabetic patients. The simulated glucose level agrees well with the measured glucose level. The fitting result using our model was compared with that of existing model using Type 1 cases, and our model obtains smaller SSE, especially when the glucose measurements are sparse. Six model parameters were estimated and analyzed physiologically and pathologically.

Irregular oscillation of glucose level and influence of meals and insulin injections are observed in Type 2 cases. The glucose – insulin model is able to mimic the dynamics

of glucose and insulin based on long term clinical monitoring of the diabetic subjects. The estimated kinetic parameters are physiologically meaningful, and could be related to the subject's dysfunction due to diabetes and the pathology of diabetes.

Obesity and aging have significant effect on the situation of diabetic patients. In an obese diabetic subject, thick fat layer delays the diffusion of injected insulin followed by larger local degradation of insulin, related to the model parameters k_{a1} and k_{a2}. Impaired IS and insulin sensitivity would reduce glucose uptake in the periphery and cause hyperglycemia. This agrees with smaller α and smaller β for obese subjects implying less insulin secretion and less glucose utilization due to high insulin resistance. Insulin resistance is a common for obese individuals, where the pancreatic β-cell is less sensitive to increment of plasma glucose level compared with subjects with normal insulin sensitivity. In addition, reduced number and impaired function of glucose transporter for obese subjects slows glucose transport from plasma to insulin-sensitive cells.

The decline in insulin action and glucose stimulated IS has been demonstrated to be relevant to the increasing age. Changes of anthropometric characteristics with increasing age (e.g., increase of fat mass and visceral fat) may cause insulin resistance in humans. Liver and pancreas takes faster action for younger and healthier subjects. For diabetic patient, long HGP delay τ_1 would probably induce hypoglycemia when external glucose input is not given in time. Hyperglycemia is possible to be caused by long IS delay τ_2, especially after meals intake which makes glucose level increase fast.

Severe diabetes disrupts functions of some organs, which changes model parameters values from time to time, and complicates the modeling glucose-insulin

dynamic system. Glucose measurement and insulin delivery in subcutaneous tissues are important in the development of artificial pancreas. The proposed model incorporating subcutaneous glucose and subcutaneously-injected insulin, and its validation with patient data provides an insight on diabetes therapy via artificial pancreas.

5 Glucose Control Using Model Predictive Controller

5.1 Model Predictive Control

The most common therapy for diabetic patient is multiple insulin injections subcutaneously based on three or four glucose level measurements daily. It is the so-called ‘open-loop control’. This method is not only painful and inconvenient, but may result in hyperglycemia and hypoglycemia. Keeping glucose within the narrow normoglycemia range 70-120 mg/dl or 4-7 mmol/L (different ranges were reported: 70-120 mg/dl [132, 133], 80-110 mg/dl [134, 135] or 70-110 mg/dl [136, 137]) is difficult for a diabetic patient using the ‘open-loop control’. Closed-loop glucose control methods have been studied to replace the existing therapies due to its convenience and safety [134, 138-140].

The study of human physiology and pharmacokinetics makes MPC suitable for glucose control. MPC has some advantages over conventional control methods such as PID control to regulate blood glucose level. The anticipatory ability of MPC can reduce the fluctuations of blood glucose by controlling insulin delivery carefully, compensate for dead time existing in glucose-insulin system [141], and handle the constraints problem and patient variability considering hardware specifications of insulin pump [142]. Due to its robustness and stability, MPC has been applied widely in the development of artificial pancreas [45, 143-145].

In MPC, future system output is predicted based on a model simulating the dynamic system subject to the change of system disturbance. Future control action to the system is calculated using control history and current system measurements by optimizing an objective function and considering the tracking error and constraints of system.

The MPC control strategy uses current measured output and past input to predict the future input within the control horizon and future output trajectory within the prediction horizon (Figure 5.1) by solving a finite horizon optimal control problem. The cost function (Eq. 5.1) is minimized with respect to the inputs under the system model's state dynamics and constraints of states and inputs. After we obtain the solution of the FHOCP, a feedback control law can be obtained by applying the first part of the solution to the system, as shown by the diagram of overall control process in Figure 5.2.

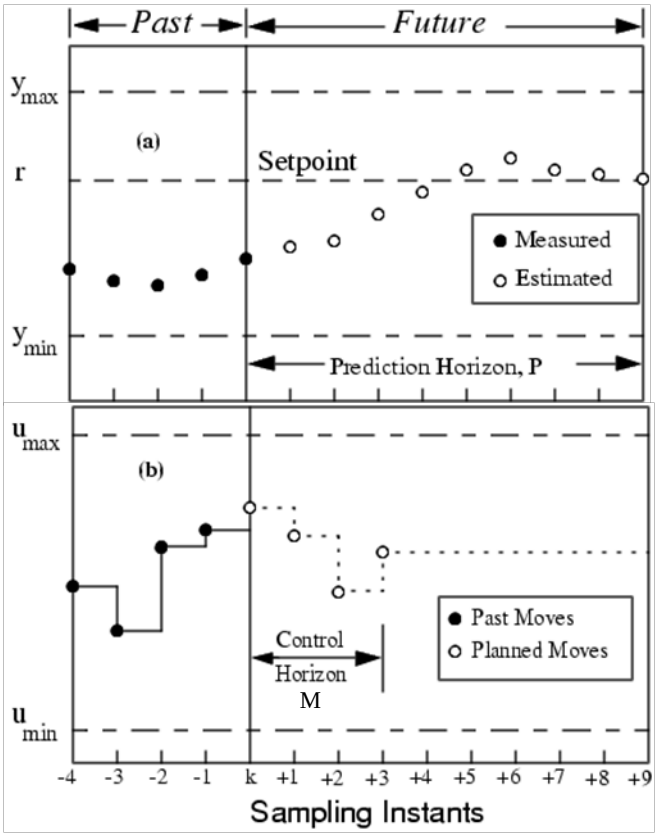

Figure 5.1. MPC strategy (Adapted from the Model Predictive Control Toolbox of Matlab).

As shown in Figure 5.1, the future outputs for the prediction horizon *P* are predicted at each instant *k* using the process model. The predicted output depends on the known values up to instant *k* (past inputs and outputs) and on the future control signals *u*.

The future control signals *u* are calculated by optimizing a determined criterion to keep the process close to the determined reference trajectory *r*. The criterion is often a quadratic function of the errors between predicted output and the determined reference trajectory.

Applying MPC in blood glucose control, the predicted glucose level is calculated *P* sample times into future. The aim is to minimize the square of the difference between the predicted glucose level and the desired setpoint trajectory by adjusting *M* future insulin infusion rates. In each step, only the first in the *M* future insulin infusion rate is implemented. At the next sampling instant, the procedure would be repeated with a new control move. Control moves are included in the objective function:

$$J = \sum_{i=1}^{P} (r_{k+i} - \hat{y}_{k+i})^2 + \lambda \sum_{i=1}^{M} \Delta u^2{}_{k+i-1}, k \geq 0, \tag{5.1}$$

where λ is the weighting on manipulated input increment Δu, *r* is the desired glucose level setpoint, $\hat{y}$ is the predicted glucose level, and *k* is the sample time index. MPC can enforce the system constraints explicitly. This is important for a glucose control system with physiological constraints.

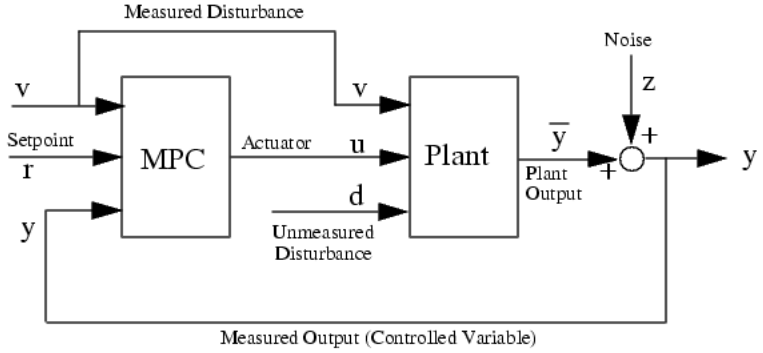

Figure 5.2. Diagram of overall control process (Adapted from the Model Predictive Control Toolbox of Matlab).

The objective of designing a controller based on MPC is to mimic a healthy pancreas to regulate the glucose concentration for the diabetic patients. The controller should be able to keep glucose level within the normal range under different situations such as after meal intake, during fasting condition and during exercise as well. Therefore, as shown in Figure 5.2, measured disturbance *v* and unmeasured disturbance *d* are sent to the system together with the control input *u*; and the measured output including predicted output by the model and noise signal *z* is sent to the model predictive controller.

5.2 Glucose Control using Two-compartment Model and Minimal Model

To study the effectiveness of using MPC to regulate glucose level, the two-compartment model in Chapter 3 is used to design a model predictive controller. The result of glucose regulation using our model is compared with that of Bergman's minimal model with the same glucose disturbance. The ability of the two controllers to regulate glucose level in response to meal disturbance and unnoticed disturbance in plasma glucose compartment is investigated by analyzing the glucose response and the insulin infusion profile. The minimal model and two-compartment model are shown in Figure 5.3 and Figure 5.4, respectively. There is no external insulin input in the two-compartment model in Chapter 3. In agreement with minimal model that external insulin is input into plasma compartment, external insulin is added to the plasma insulin compartment in the two-compartment model. The nominal value of the two-compartment model parameters is adapted from Table 3.5; and the parameter value of minimal model is shown in Table 5.1 (adapted from [146]).

Table 5.1. Parameter value of minimal model.

Parameter	Value
p_1	0.0316
p_2	0.0107
p_3	0.0000053
n	0.264
h	80.26
γ	0.0042
G_b	70
I_b	7

The imposed constraints for insulin infusion rate and plasma glucose level of the two models in simulation are as follows [147]:

$$\begin{aligned} &0 \le u \le 80\ mU/\min, \\ &\left|\Delta u\right| \le 16.7\ mU/\min\ per\ sample\ time, \\ &4\ mmol/L \le y \le 7\ mmol/L, \end{aligned} \tag{5.2}$$

where u is external insulin input, Δu is the change rate of u and y is measured plasma glucose level. The constraint on u maintain insulin level below 80 mU/L. Hard constraint on Δu ensure that insulin infusion rate change is within the capability of the pump, and gentle glucose reduction is more beneficial and safe for the patient. Constraint on y ensures glucose level is within the safe range by avoiding hypoglycemia. The normoglycemia range of 4-7 mmol/L is chosen.

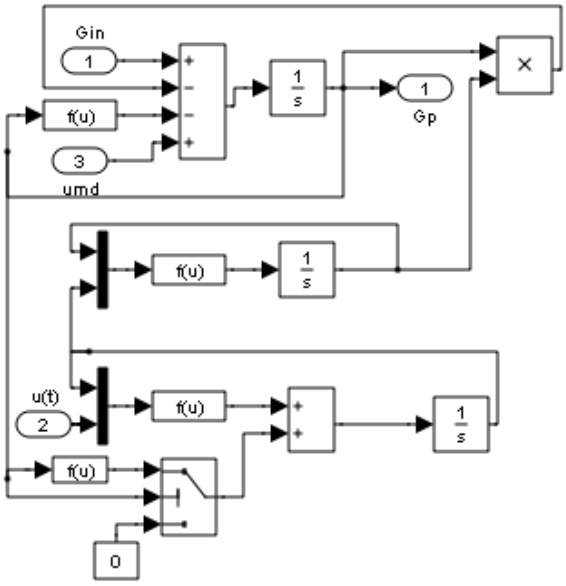

Figure 5.3. Diagram of the Bergman minimal model in Simulink.

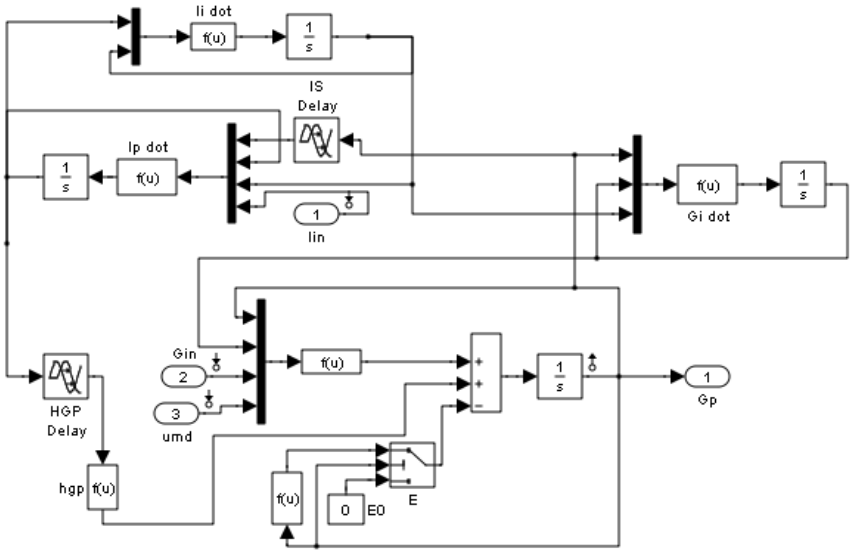

Figure 5.4. Diagram of the two-compartment model in Simulink.

In order to compare the performance of the two models in controlling glucose level, four different forms of meal intake were used: constant glucose infusion for 10 minutes for 3 times, constant glucose infusion, impulse glucose injection and exponentially decreasing glucose infusion. In the simulations in this chapter, it was assumed the models

can match the virtual glucose-insulin system in the human. The unnoticed glucose disturbance was set to happen randomly with positive or negative value in plasma glucose compartment to simulate unnoticed meal intake or unexpected exercise. This disturbance was set to take place less than 15 times during the simulation and last for 5 minutes each time, and the value of this disturbance was taken to be within -500 ~ 500 mg/min.

Three times of constant glucose infusion for ten minutes is added to the plasma compartment. 10 g glucose was infused within ten minutes for the first and third time and 20 g glucose for the second time. The simulation results are shown in Figure 5.5 and Figure 5.6.

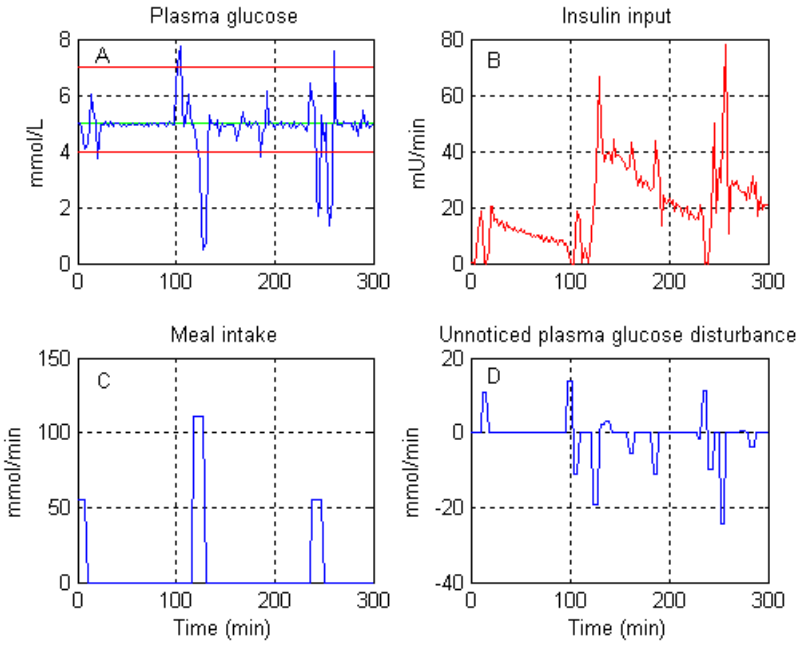

Figure 5.5. Simulation result using minimal model with three constant glucose infusions. From Figure 5.5 to Figure 5.12, A: Plasma glucose concentration (blue), upper and lower limit of normoglycemia range (red), and desired glucose level (green). In the simulations of this chapter, the prediction horizon and control horizon is set to be 10 and 5, respectively. The sampling time is 2 minutes. The weight of manipulated variable and output is 0.1 and 0.9, respectively.

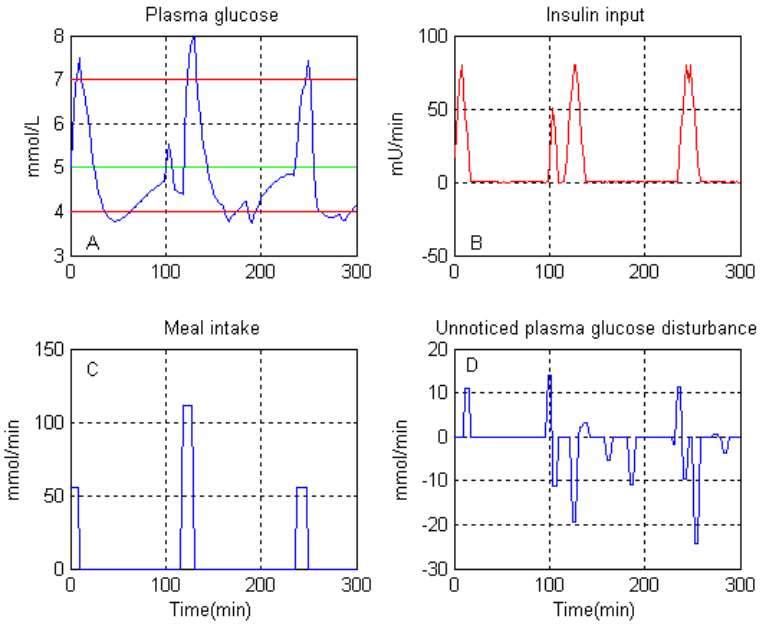

Figure 5.6. Simulation result using two-compartment model with three constant glucose infusions.

In Figure 5.5.A, glucose level changes within the normoglycemic range most of the time. Slight hyperglycemia and serious hypoglycemia happen for several times for minimal model. The time of hypo- and hyperglycemia agrees with that of unnoticed glucose disturbance. The hyperglycemia and hypoglycemia is caused by large unnoticed disturbance in plasma glucose compartment. Noticed meal intakes and small unexpected glucose disturbances do not cause large change of glucose level under the regulation of MPC controller. In Figure 5.6.A, slight hyperglycemia happens with each meal intake. Glucose oscillates slowly with the meal intake and external insulin infusions as well. Unnoticed glucose disturbances do not cause any hyperglycemia or hypoglycemia. The effect of unnoticed disturbance is negligible for the two-compartment model, which is better than the minimal model. During the period without glucose input, external insulin input for minimal model is more than that of the two-compartment model. Less insulin is needed for the two-compartment model during the whole simulation. It is harmful for

patients with plasma glucose level lower than 60 mg/dL (3.3 mmol/L), and avoiding hypoglycemia is more important than avoiding hyperglycemia. The two-compartment model performs better than minimal model under this situation.

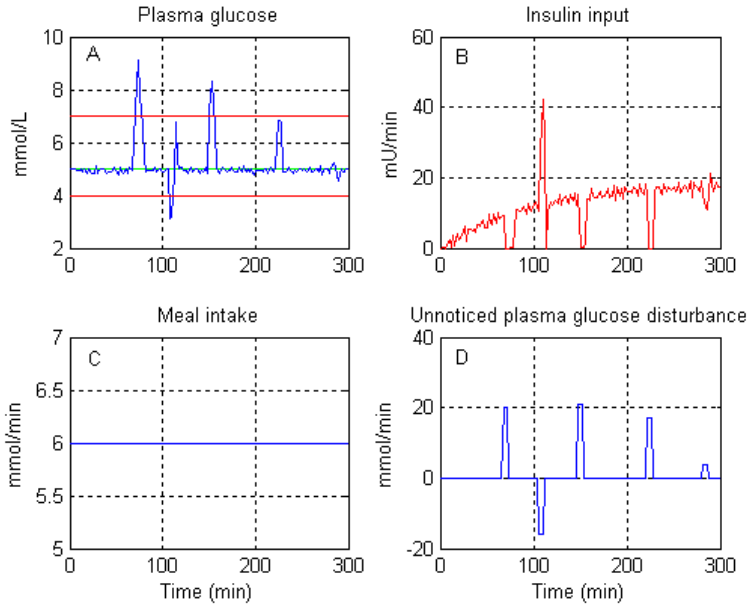

Figure 5.7. Simulation result using minimal model with constant glucose infusion.

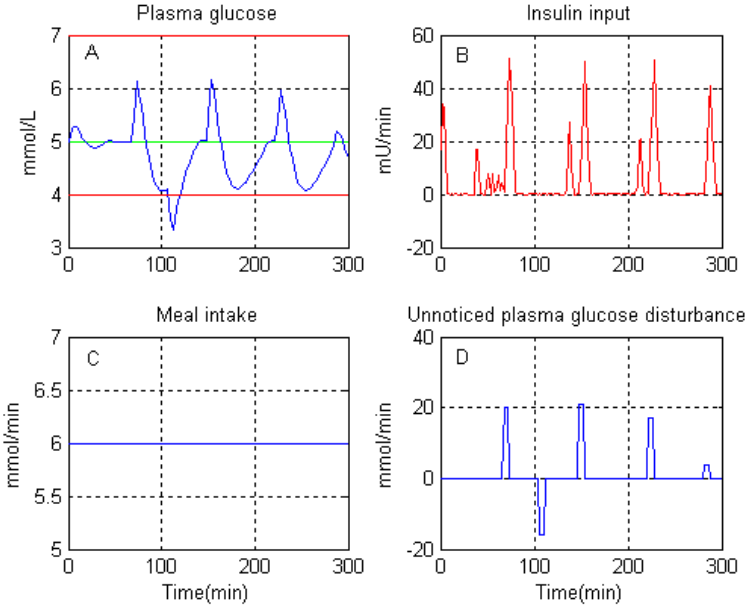

Figure 5.8. Simulation result using two-compartment model with constant glucose infusion.

In Figure 5.7.A, when glucose is infused constantly, glucose level oscillates around the desired glucose level except when unnoticed glucose disturbances happen, and insulin infusion rate keeps increasing with the time. When large unnoticed glucose disturbance increases glucose input, hyperglycemia occurs for minimal model. The increase of glucose level caused by small glucose disturbance can be regulated by the MPC controller. When negative glucose disturbance occurs at around 100 min, there is a sharp increase of insulin infusion (Figure 5.7.B), and slight hypoglycemia occurs. The unreasonable result happens as well to the four times of positive glucose disturbances which cause fast decrease of insulin infusion. Insulin infusion rate should increases when more glucose enters plasma compartment due to unnoticed glucose disturbance. The unreasonable simulation result caused by the glucose disturbance may be the inability of minimal model to regulate glucose level caused by unnoticed disturbances, which may be improved by parameter tuning.

Glucose level is regulated within normoglycemia for the two-compartment model except the single instance of slight hypoglycemia caused by the unnoticed decrease glucose level, as shown in Figure 5.8.A. Glucose oscillates within 4~6 mmol/L around the desired glucose level with a oscillation period 90~100 min. The oscillation period agrees with the simulation result in Chapter 3 for the two-compartment model with the same glucose infusion rate of 108 mg/dL. According to the time of insulin infusion and unnoticed disturbance, it is estimated that insulin infusion with amplitude larger than 40 mU/min is caused by the large unnoticed disturbance. Insulin infusions with smaller amplitude regulate glucose level within the normal range under constant glucose intake.

With the constant glucose intake and same unnoticed glucose disturbance, the two-compartment model is better for glucose control compared with minimal model.

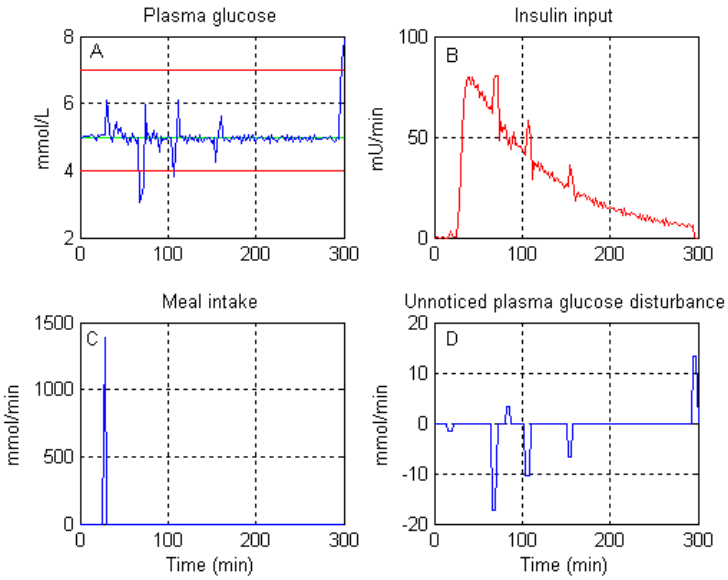

Figure 5.9. Simulation result using minimal model with impulse glucose injection.

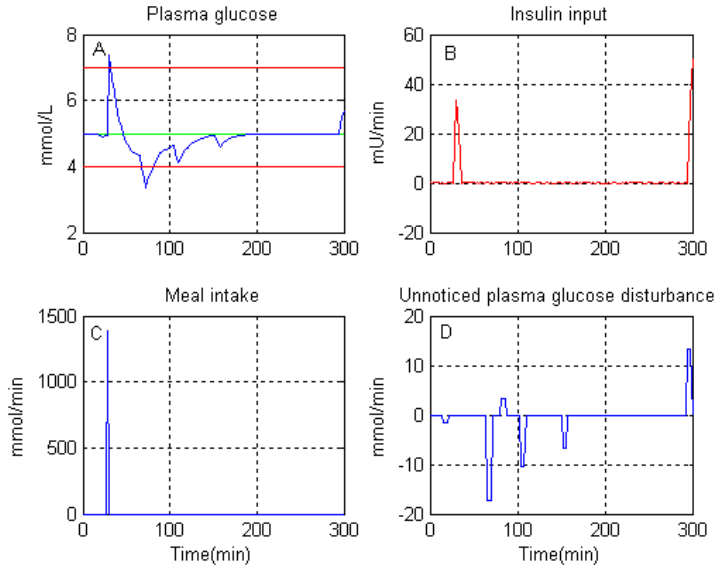

Figure 5.10. Simulation result using two-compartment model with impulse glucose injection.

After 25 g glucose is infused quickly, glucose level increases slightly under the effect of increasing infused insulin for minimal model in Figure 5.9. After the insulin infusion rate increases to its maximal value, it decreases slowly. Some small change of insulin infusion rate occurs on the time of unnoticed glucose disturbance. Hyperglycemia and hypoglycemia happen around the time of large glucose disturbance, the reason of which is similar to that of Figure 5.7. Glucose level of the two-compartment model increases sharply and slight hyperglycemia occurs after fast glucose intake in Figure 5.10.A. Under the combined effect of increased insulin infusion and unexpected negative glucose disturbance with large amplitude, slight hypoglycemia occurs as well. The simulation result is similar to that of some diabetic patients that hyperglycemia occurs first after meal intake when the action time of insulin injected before the meal is too long; and hypoglycemia follows hyperglycemia after injected insulin takes effect to regulate glucose and overdose insulin is injected. As shown in Figure 5.10.A, glucose level keeps within the normal glucose range except some obvious change of glucose level caused by unnoticed glucose disturbance. Glucose level reaches the steady state quickly after the glucose disturbances, and insulin amount infused for the two-compartment model is much less than that of minimal model.

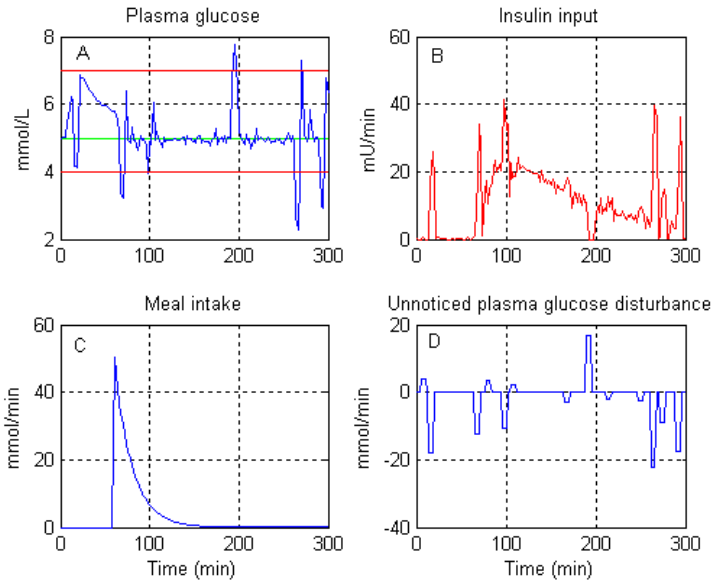

Figure 5.11. Simulation result using minimal model with glucose infusion decreasing exponentially.

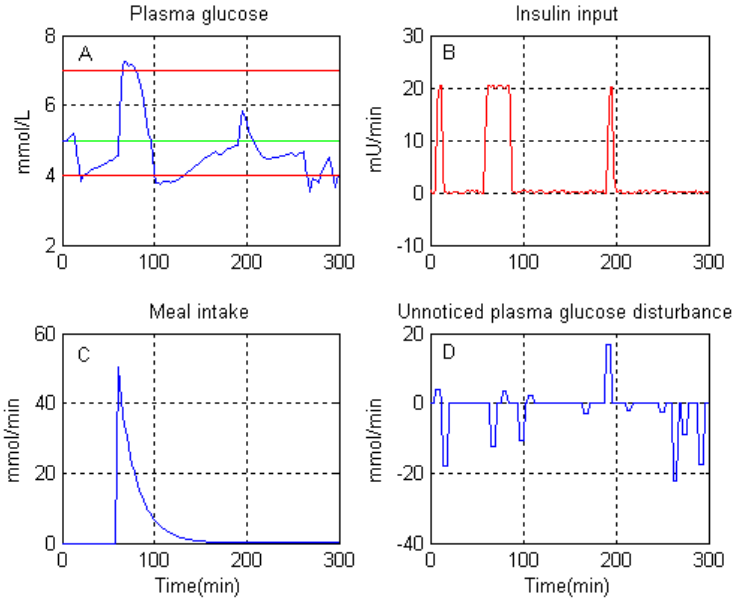

Figure 5.12. Simulation result using two-compartment model with glucose infusion decreasing exponentially.

When glucose intake rate is set to be decreased exponentially from 50 mmol/L from 60 min to 180 min and unnoticed glucose disturbances are included in the minimal model,

glucose level can be kept in the desired range most of the time (Figure 5.11.A). However, slight hyperglycemia and severe hypoglycemia take place around the time of some large glucose disturbances. During the period without disturbance, glucose level is close to the desired glucose level. With the effect of disturbance on insulin infusion ignored, insulin infusion rate increases to the maximal value and decreases slowly with the decreased glucose intake rate. The decrease rate is much slower than that of the two-compartment model in Figure 5.12.B. For the two-compartment model, insulin infusion caused by the exponentially decreased glucose intake stops before 100 min (Figure 5.12.B), and glucose level reaches the lower limit of normoglycemia at around 100 min (Figure 5.12.A), which avoids hypoglycemia in time and shows the good performance of MPC controller. Glucose level almost changes within the normoglycemia with some negligible glucose levels out of this range.

For the four forms of glucose infusion rate, the MPC controller using the two-compartment model shows some advantages over that of using minimal model: it causes less hypoglycemia and hyperglycemia, less insulin is used and glucose change caused by unnoticed glucose disturbance is better controlled. The two-compartment model proposed in the thesis is possible to be applied in the future closed-loop insulin delivery system.

5.3 Glucose Control with Injected Insulin

The glucose-insulin model with subcutaneously-injected insulin in Chapter 4 and the Hovorka model [45] were used to design a model predictive controller. With the same glucose disturbance, the results of glucose regulation using the two models are compared to study the effectiveness of using the two MPC controllers to regulate glucose level. The diagrams of the two models in Simulink are shown in Figure 5.13 and Figure 5.14.

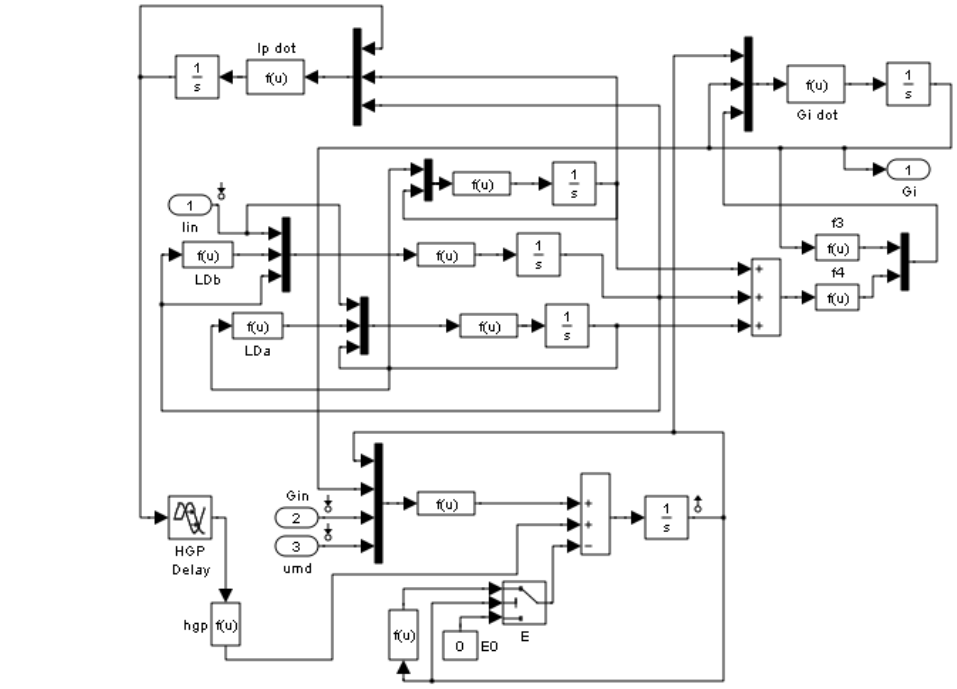

Figure 5.13. Diagram of our model with subcutaneous insulin dynamics for Type 1 cases in Simulink.

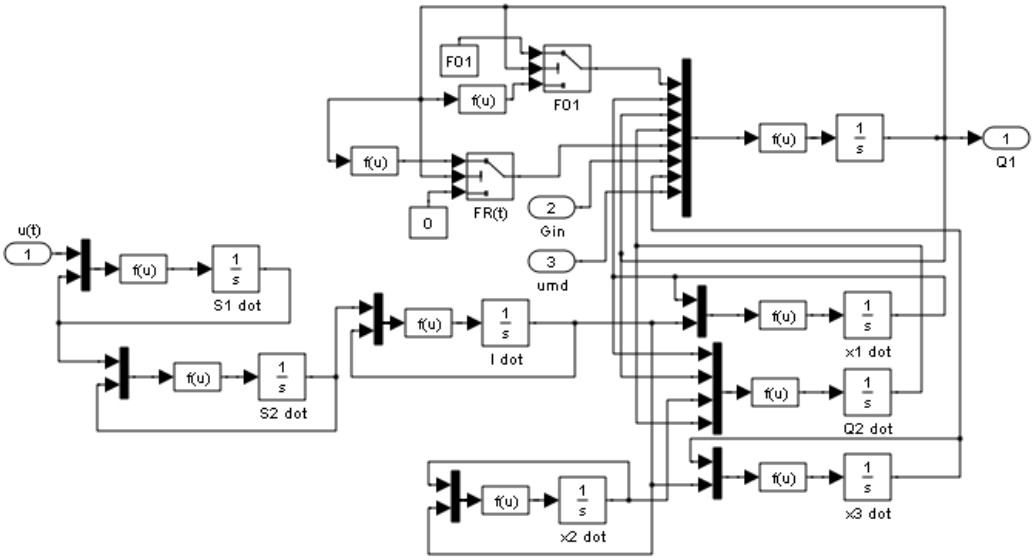

Figure 5.14. Diagram of the Hovorka model for Type 1 diabetic patients in Simulink.

The model parameters of the three Type 1 cases were estimated in Chapter 4 using our model and Hovorka model. In this section, the model parameters estimated, the same

initial values of the model states and meal intakes of the two models are used in the MPC controllers; and glucose level using the two MPC controllers is to be compared with that controlled by manually insulin injections. For the five diabetic subjects, two situations for the two MPC controllers were proposed: noticed meal intake is the only glucose input, and besides noticed meal intake, unnoticed glucose disturbances in the plasma compartment occur at random time.

In the five diabetic cases, case 1, case 11 and case 17 are Type 1 cases; and case 20 and case 3 are Type 2 cases with the best and worst fitting result in Chapter 4. The simulation results of the Type 1 cases under the two situations are shown from Figure 5.15 to Figure 5.20; and that of the Type 2 cases are shown in Figure 5.22 and Figure 5.23.

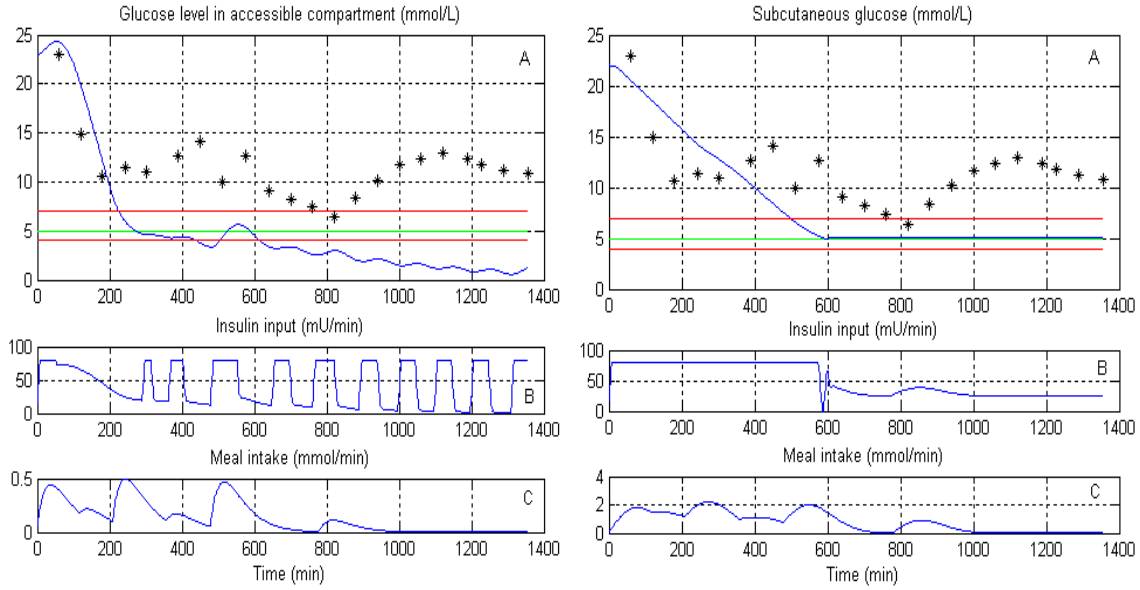

Figure 5.15. Simulation result of MPC controller using Hovorka model (left) and our model (right) to regulate glucose level of Type 1 diabetic patient (case 1). From Figure 5.15 to Figure 5.20, Figure 5.22 and Figure 5.23, black stars represent the measured glucose level, red lines represent upper and lower limit of normal glucose range, and green line represents the ideal glucose level.

When there is no glucose disturbance in the system (Figure 5.15), glucose level controlled by Hovorka model controller reduces fast from initial hyperglycemia and reach normal glucose level around 200 min, which is faster than that of using our model (450 min). However, severe hypoglycemia happens from 600 min using Hovorka model controller while glucose level controller using our model reaches the ideal level after 600 min. Glucose level regulated by the controller using our model is higher than measured glucose level before 400 min, which is caused by the limited insulin infusion rate of insulin pump. Hovorka controller fails to control glucose level for case 1, while the controller using our model is able to regulate glucose level well.

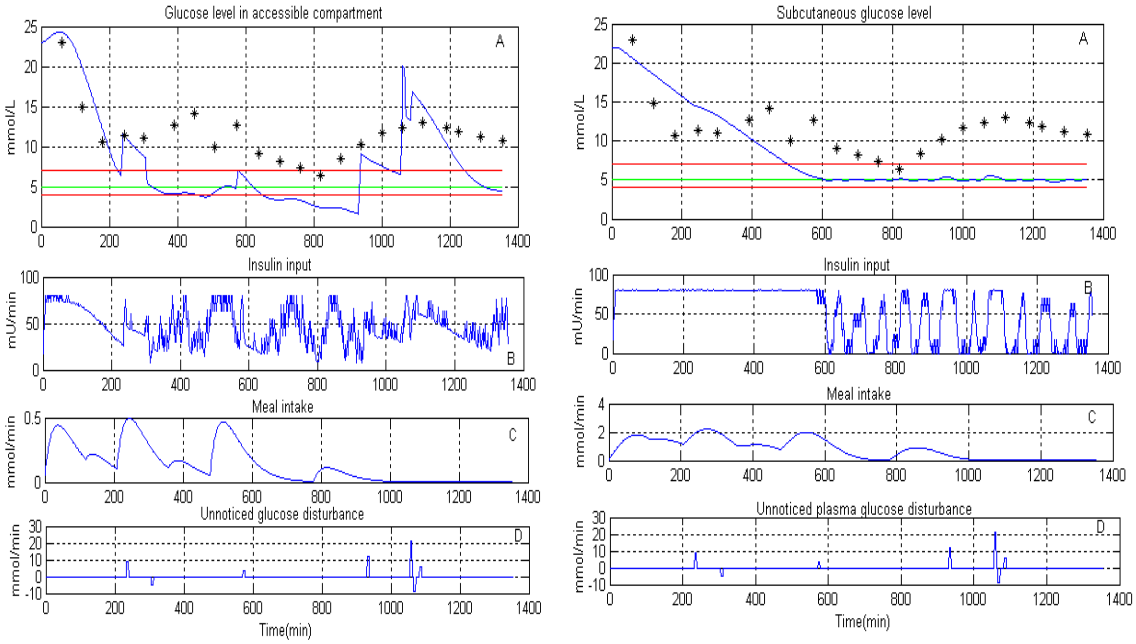

Figure 5.16. Simulation result of MPC controller using Hovorka model (left) and our model (right) to regulate glucose level of Type 1 diabetic patient (case 1) with unnoticed plasma glucose disturbance.

When unnoticed glucose disturbances are added to the system (Figure 5.16), compared with simulation results in Figure 5.15, glucose level changes significantly using Hovorka model, however glucose level controlled by our controller almost remains

unchanged with some negligible changes. Severe hypoglycemia and hyperglycemia happen as well to the system using Hovorka model. Hyperglycemia after 200 min is stimulated by glucose disturbance and hypoglycemia is improved by glucose input from glucose disturbances.

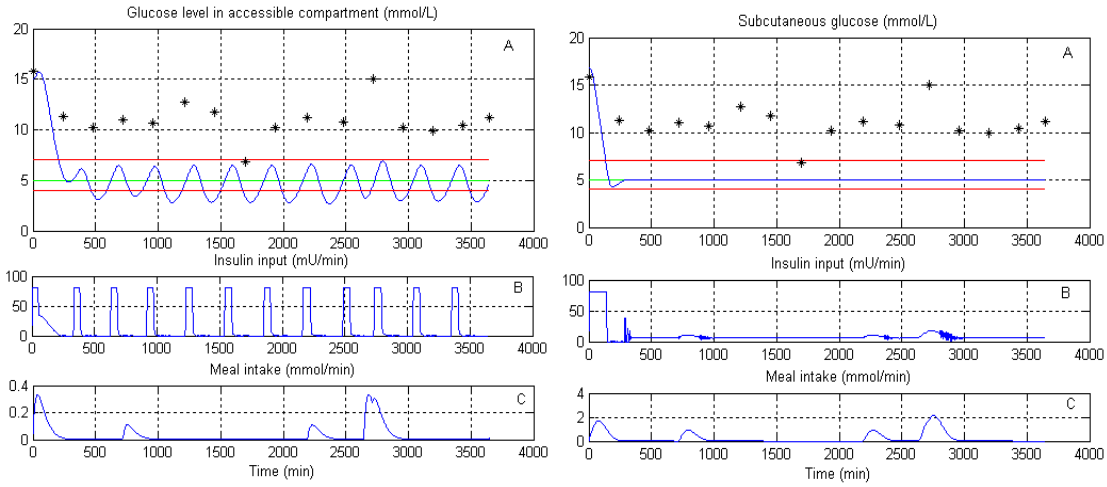

Figure 5.17. Simulation result of MPC controller using Hovorka model (left) and our model (right) to regulate glucose level of Type 1 diabetic patient (case 11).

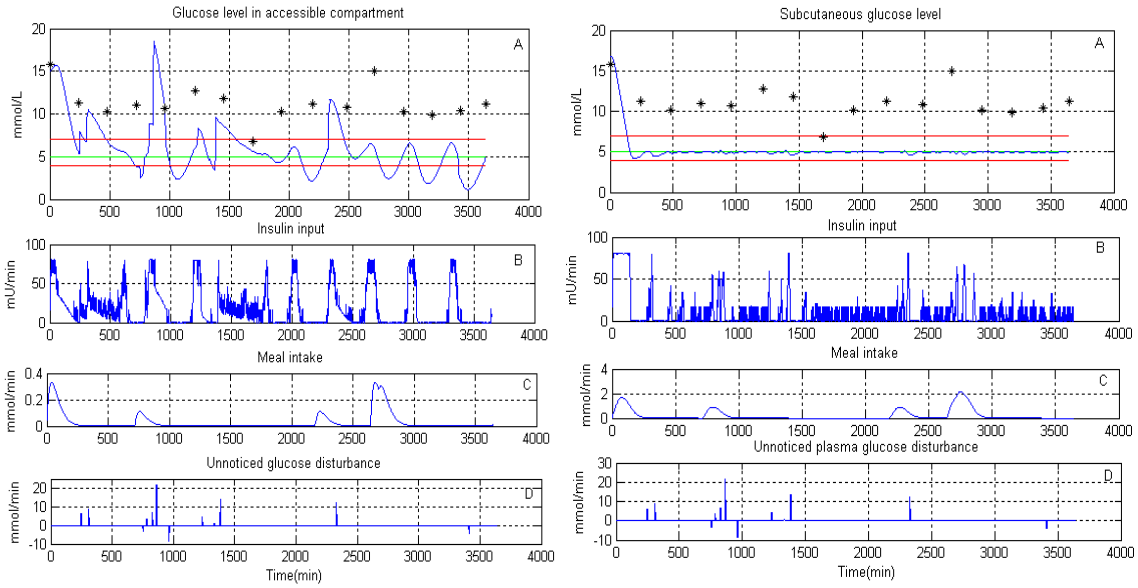

Figure 5.18. Simulation result of MPC controller using Hovorka model (left) and our model (right) to regulate glucose level of Type 1 diabetic patient (case 11) with unnoticed plasma glucose disturbance.

For glucose regulation of case 11, hypoglycemia often happens using Hovorka controller when there is no glucose disturbance (Left subplot of Figure 5.17). Glucose level oscillates around normoglycemia range stimulated by oscillating insulin infusion with period about 250 minutes. When glucose disturbance is included, due to glucose disturbance, the oscillation of glucose level is disrupted, severe hyperglycemia occurs several times, and hypoglycemia is improved in the length of time for Hovorka model (Left subplot of Figure 5.18). Hovorka model controller cannot eliminate the effect of unnoticed disturbance on glucose level. Glucose level regulated by our controller is much lower that measured glucose level, and our controller is shown to be able to regulate glucose level well under these two situations. Glucose reaches normal level fast and remains around the ideal glucose using our controller. Glucose disturbances result in negligible change to glucose level under the regulation of our controller. The MPC controller using our model is demonstrated to be better than Hovorka model controller for glucose regulation.

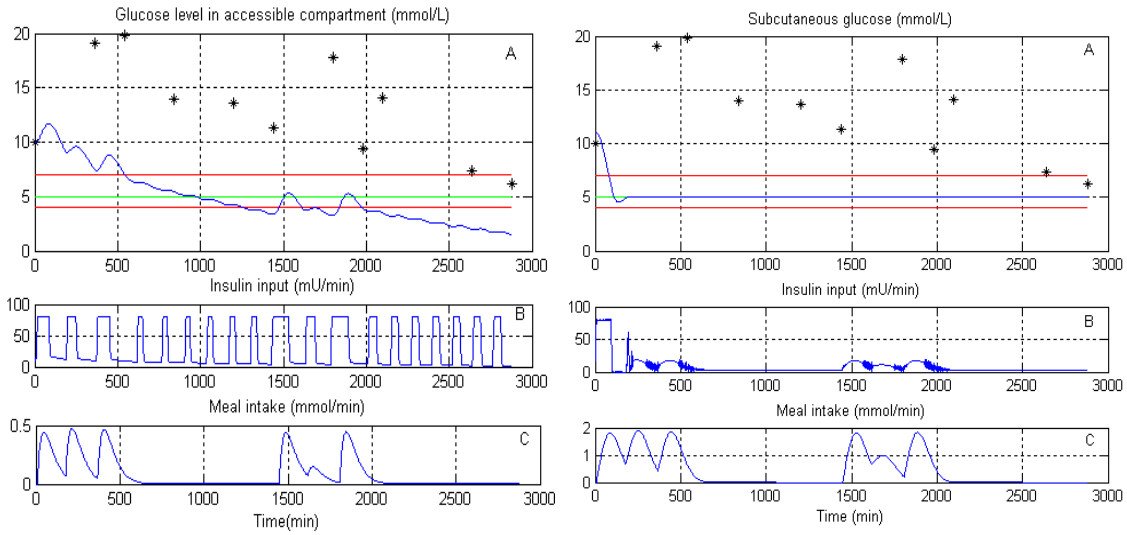

Figure 5.19. Simulation result of MPC controller using Hovorka model (left) and our model (right) to regulate glucose level of Type 1 diabetic patient (case 17).

When there is no glucose disturbance for case 17 (Figure 5.19), glucose level controlled by Hovorka model decreases slowly, reaches normal glucose range at 500 min, and hypoglycemia takes place from 2000 min. Insulin keeps infusing after glucose lower than 4 mmol/L, which is unreasonable and may be explained by the inability of Hovorka model controller to regulate glucose level for case 17. However, glucose level is well regulated by our controller. Glucose level decreases to normal level at around 100 min, and it remains close to the ideal level (Right subplot of Figure 5.19). Except the period 0~100 min, insulin infusion dosage by our controller is small compared with that of Hovorka model controller.

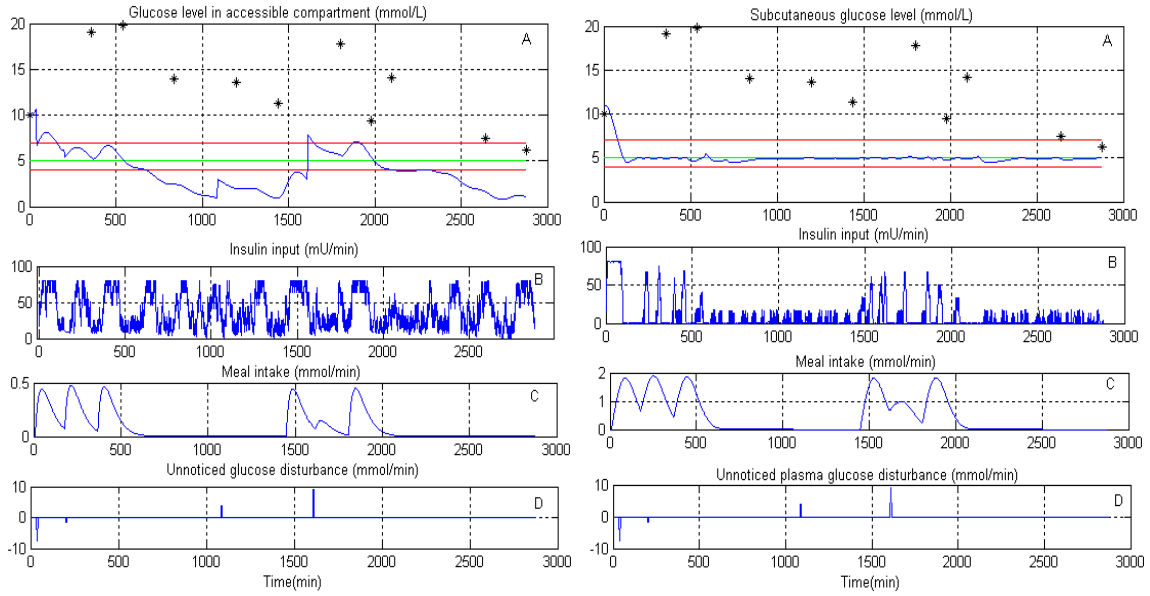

Figure 5.20. Simulation result of MPC controller using Hovorka model (left) and our model (right) to regulate glucose level of Type 1 diabetic patient (case 17) with unnoticed glucose disturbance.

With glucose disturbance introduced into the system, the time of hypoglycemia increase for glucose level regulated by Hovorka model controller (Left subplot of Figure 5.20). Hypoglycemia takes place when the meal intake is zero. Insulin keeps infusion

during the period of hypoglycemia, which is similar to the simulation result when there is no glucose disturbance. As shown in the right subplot of Figure 5.20, glucose level is well regulated within the normoglycemia range. Insulin infusion rate during the periods without meal intake is small to facilitate glucose utilization for the Type 1 diabetic subject. Under the effect of glucose disturbance and infused insulin, glucose always changes around the ideal level. The parameters' value of Hovorka model was estimated using sparse glucose level measurements for case 17, which may cause the failure of glucose control using Hovorka model controller. Glucose is better regulated for case 17 using our controller, which is able to avoid hyperglycemia and hypoglycemia, cost less insulin, and regulate glucose close to the ideal level.

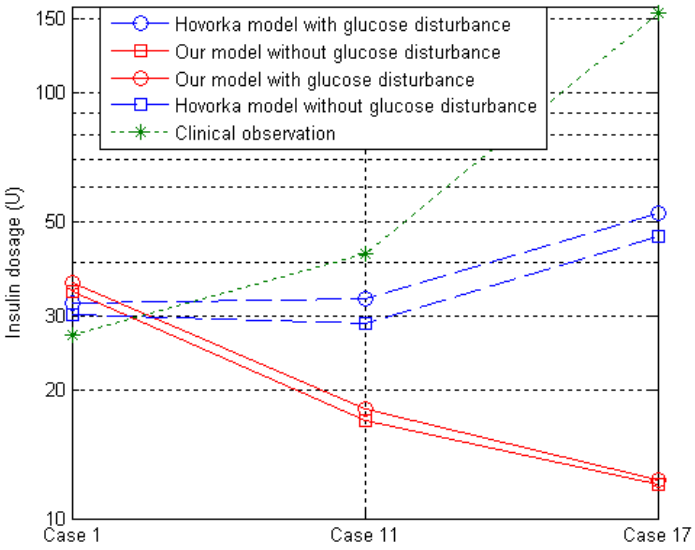

Figure 5.21. Insulin dosage used in the simulations of glucose control using Hovorka model (Blue squares and circles represent insulin cost without and with glucose disturbance, respectively), our model (Red squares and circles represent insulin cost without and with glucose disturbance, respectively.), and in clinical experiment for the three Type 1 cases (Green stars represent insulin dosage injected in the clinical experiment). The y axes is displayed in log form.

Total insulin dosage infused by the two controllers for the three Type 1 cases under the two situations were calculated, as shown in Figure 5.21. Insulin cost using the two

controllers is less than that of manual insulin injections during clinical observation. Insulin infused by Hovorka model controller is more than that of using our model. Insulin used to control glucose by our controller is close regardless of the inclusion of glucose disturbance, while large difference of insulin dosage infused exists under the two situations using Hovorka model controller. Insulin used for case 1 in clinical observation was less than that in simulation. However, glucose level regulated by our controller is much lower than measured glucose level (Right subplot of Figure 5.15), and glucose remains close to the ideal level under the regulation effect of MPC controller.

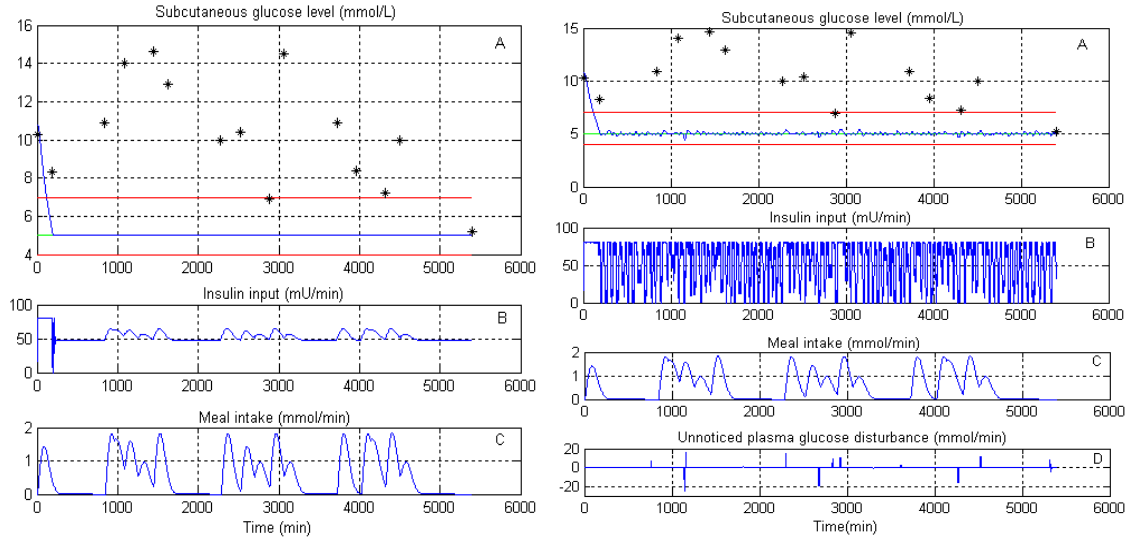

Figure 5.22. Simulation result of MPC controller using our model to regulate glucose level of Type 2 diabetic patient (case 20) without glucose disturbance (left) and with glucose disturbance (right). The total insulin dosages for the two situations are 57.6 U (left) and 57.4 U (right), respectively.

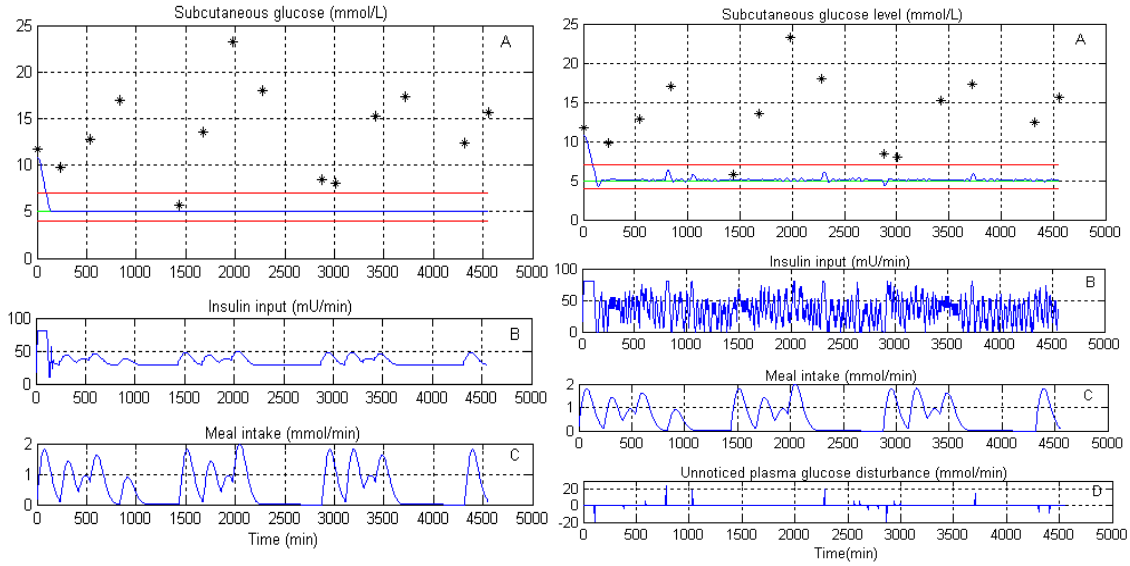

Figure 5.23. Simulation result of MPC controller using our model to regulate glucose level of Type 2 diabetic patient (case 3) without glucose disturbance (left) and with glucose disturbance (right). The total insulin dosages for the two situations are 32.1 U (left) and 32.5 U (right), respectively.

Glucose of the two Type 2 cases regulated by our controller decreases quickly to the ideal level with insulin infused in the maximal rate during this period (Figure 5.22 and Figure 5.23). After glucose reaches the ideal level, glucose level remains almost unchanged with the stimulation effect of infused insulin on glucose utilization. Glucose level under the regulation of our controller is much lower than measured glucose level. Severe hyperglycemia often takes place using manual insulin injections, as shown by clinical data of glucose level in the figures. When glucose disturbance is included in the system, glucose has some small changes around the ideal level; and insulin infusion is significantly different from that of the situation when there is no glucose disturbance.

When there is no glucose disturbance introduced into the system, insulin dosage infused by the controller for case 20 and case 3 was 57.6 U and 32.1 U. It is much lower than the insulin dosage used in clinical observation, which is 115 U and 76 U for case 20 and case 3, respectively. Due to the combined effect of positive and negative glucose

disturbance, the total insulin cost under the two situations for the two Type 2 cases are very close. Although glucose disturbance is not frequent, insulin infusion rate changes frequently.

5.4 Summary

Intravenous glucose sensing and insulin delivery may be applied in closed-loop insulin delivery system for diabetic patients in intensive care unit. Intravenous glucose sensing providing glucose level in the bloodstream facilitates the controller to calculate more accurate insulin dosage and achieves tight glucose control. Intravenous insulin delivery shortens the time of insulin taking effect to stimulate glucose utilization. The intravenous-intravenous form of closed-loop insulin delivery can be simulated using the two-compartment model, which sets plasma glucose to be system output, and insulin infusion into plasma compartment to be system input.

In Section 5.2, the two-compartment model proposed in Section 3.3 was used to design a controller, and the simulation results of glucose control were compared with that of a MPC controller using the Bergman minimal model. Four forms of glucose infusion: constant glucose infusion for 10 minutes for 3 times, constant glucose infusion, impulse glucose injection and exponentially decreasing glucose infusion, were included in the plasma compartment to compare the two models' performance of regulating glucose level. It was demonstrated that the MPC controller using the two-compartment model shows some advantages over that of using minimal model: it causes less hypoglycemia and hyperglycemia, less insulin is used and glucose change caused by unnoticed glucose disturbance is better controlled.

Glucose measurement and insulin delivery in subcutaneous tissues is safe and convenient to be implemented in future artificial pancreas. A MPC controller using our model proposed in Section 4.3, which included the dynamics of glucose and insulin in subcutaneous tissues, was designed for glucose control, and the results are compared with that using Hovorka model for the three Type 1 cases. The initial conditions, value of model parameters and meal intake remained the same as that in Chapter 4. The two controllers were investigated for the performance of glucose regulation without and with unnoticed glucose disturbance in Section 5.3.

Hyperglycemia and hypoglycemia often occurred to the system using Hovorka model controller, and insulin infusions calculated by the controller sometimes were unreasonable. The parameters' value of Hovorka model was estimated with sparse glucose level measurements, which may cause the failure of glucose control using Hovorka model controller. Regardless of the inclusion of glucose disturbance, glucose regulated by the controller using our model proposed in Section 4.3 decreased from initial hyperglycemia fast and approached the ideal glucose level quickly, with negligible change around the ideal glucose level when glucose disturbance was introduced. Although the parameter value of model with subcutaneous insulin was estimated using the same clinical data with Hovorka model, the performance of glucose control using this model is good. Glucose control of the two Type 2 cases using this controller was studied following that of Type 1 cases. Glucose level was shown to be well regulated by the controller and insulin dosage calculated by the controller is much smaller than that used in the clinical observation.

Overall, the two-compartment model and the model with subcutaneous insulin proposed in this thesis were investigated for the performance of glucose control. Compared with the simulation results of glucose regulation of Bergman minimal model and Hovorka model, our models were demonstrated to be able to control glucose level well.

6 Conclusion and Future Work

6.1 Conclusion

Closed-loop insulin delivery system (also known as an artificial pancreas) could potentially be the ultimate solution for blood glucose control in diabetic patients, which is comprised of a glucose sensor for measuring glucose concentration, control algorithm for regulating insulin infusion, and an insulin infusion device for delivering insulin to the human body. MPC has been widely applied in glucose control. By developing an accurate glucose-insulin model, an efficient glucose control algorithm could be developed.

Glucose measurement and insulin delivery in subcutaneous tissues has been applied to design artificial pancreas. A mathematical model of glucose-insulin system incorporating the dynamics of glucose and insulin in the subcutis is crucial for the investigation of glucose metabolism and MPC controller design. Based on existing studies on ultradian oscillations of glucose and insulin, a two-compartment model with two explicit delays on hepatic glucose production and insulin secretion was proposed in Chapter 3 to explore the oscillatory behavior of glucose-insulin system without external insulin delivery. Four model parameters in insulin subsystem, the two delays and glucose infusion rate were analyzed for their influence on the oscillations of glucose-insulin system. The irregular glucose level caused by different value of the model parameters was analyzed physiologically and related to diseases. Range of the model parameters were estimated for different cases: sustaining the oscillations of glucose and insulin level, Type 1 diabetes, Type 2 diabetes, and normal people. Three lags existing in the glucose-insulin model were firstly investigated for the change with model parameters and related to the distribution and metabolism of glucose and insulin in different compartments. The

effect of the sum of the two delays was explored. It was proposed that delay-adjusting ability for normal people may regulate glucose level back to normal range quickly. However the delay-adjusting ability of delays may be impaired for diabetic patient to cause hypoglycemia or hyperglycemia. The characteristics of the model agree with most of the dynamic properties reported in literature, and support the hypothesis that the ultradian oscillation of glucose and insulin in human body may originate from the interaction and negative feedback between glucose and insulin.

Type 2 diabetes is more prevalent and complex than Type 1 diabetes. There has not been a model of glucose-insulin system including the dynamics of subcutaneously-injected insulin for Type 2 diabetic patients up to now. Therefore, developing a model to simulate the metabolism of glucose-insulin system including subcutaneously-delivered insulin for Type 2 diabetes is important for the derivation of control algorithm for automatic glucose regulation. Local degradation and time delay of transportation and absorption should be considered in the insulin module of the glucose-insulin system if exogenous insulin is injected in the subcutaneous tissues. Based on the two-compartment model, a modified model which includes two absorption channels and local insulin degradation was proposed to simulate the glucose-insulin system with external insulin injections in Chapter 4. The two rate parameters expressing insulin transportation from subcutis to plasma compartment, the two time delays and two parameters expressing the dysfunction of the diabetic patients were estimated using nonlinear least squares method. The clinical data of anonymous diabetes inpatients was collected, which comprised glucose level, insulin injection dosage and meals. Comparing the fitting results with that of Hovorka model, the proposed model was demonstrated to be able to mimic the

dynamics of glucose-insulin system based on long term clinical monitoring of diabetic subjects. The estimated model parameters were physiologically discussed. The discussion provided insights on the subject's dysfunction caused by diabetes. Irregular oscillation of glucose level and influence of meals and insulin injections were observed in Type 2 cases. The effect of obesity and aging on the parameter value was investigated physiologically as well as based on the simulation result of the model. Due to obesity and aging, diffusion of injected insulin and glucose transport is slowed, insulin secreted by pancreas may be reduced, and insulin resistance becomes stronger resulting in lower glucose utilization.

The aim of developing a mathematical model of glucose-insulin system is to study the physiological behaviors of the feedback system, as well as explore the approaches of controlling glucose level using the glucose-insulin dynamic model. MPC has been used in glucose level regulation. Insulin dosage calculated by the MPC controller is the input to the plant (i.e., human body). Glucose level was output and fed to MPC controller to calculate the next input iteratively. Glucose control using the two-compartment model proposed in Section 3.3 was used to mimic closed-loop insulin delivery with glucose measurement and insulin infusion intravenously, and compared with the simulation result of Bergman minimal model using different meal intakes. The model with subcutaneous insulin proposed in Section 4.3 was used to design a MPC controller, which simulated the closed-loop glucose control using glucose measurement and insulin delivery in the subcutaneous tissues. Simulation results of using this model were compared with that of Hovorka model. Comparing the simulation results using our proposed models with that of the two existing models, glucose level was demonstrated to be regulated within the desired glucose range using the two proposed models. The glucose curves and insulin

dosages of using these models to design MPC controller were compared to evaluate the performance of glucose control. It was shown that MPC controllers using our models are more advantageous for glucose regulation: fewer occurrences of hypoglycemia and hyperglycemia, less insulin cost and it can better deal with glucose changes caused by glucose disturbances. Simulation results demonstrated that the issues and challenges of using MPC on glucose control can be addressed adequately. The two-compartment model in Chapter 3 and the model with subcutaneous insulin in Chapter 4 proposed in the thesis could be applied in closed-loop insulin delivery system in future.

6.2 Future Work

6.2.1 Model Improvement

In order to improve the controller performance, the model can be further explored. Other physiological and physical factor may be incorporated into the virtual patient model to better describe the metabolism of glucose of diabetic patients.

FFA has been studied and modeled to make the virtual patient model closer to the human body. Oxidation of free fatty acids can be increased by increased rate of lipolysis in the adipose tissue during overnight fasting, starvation and exercise. The contribution of free fatty acids on the metabolism in the body and its interactions with glucose-insulin system is often ignored in the mathematical models which are mainly glucocentric. The dynamics of FFA was included in the Bergman minimal model, and its interaction with the dynamics of glucose and insulin was investigated for Type 1 diabetes in [42]. The plasma FFA, effect of remote FFA on glucose uptake, and effect of remote insulin on plasma FFA level were described by differential equations in this model.

Glucagon, secreted by α cells of pancreas, is another hormone important for glucose regulation. Glucagon is released to raise glucose level when glucose level is low by converting glycogen stored in the liver into glucose and delivered to the bloodstream. Both insulin and glucagon play an important role of maintaining stable glucose level. Present control studies focus on glucose and insulin as output and input respectively. Glucagon has been studied and incorporated into the mathematical models in some studies [14, 148, 149]. Glucagon may be utilized as another input in future controller design for its effect of preventing hypoglycemia.

Exercise has significant influence on epinephrine. The metabolism of most tissue cells increases significantly with increasing epinephrine. Glucose production can be increased with increasing epinephrine level to provide energy during exercise, and glucose uptake into liver is decreased simultaneously. Two exercise models were proposed in [150, 151] respectively. Both models described increase of metabolic rates as a function of exercise level. The minimal model was extended to include the effect of exercise on plasma insulin clearance, elevation of glucose uptake and HGP rate in [150]. Mild and moderate intensity exercise was incorporated into an existing model for glucose metabolism in [151]. Increase in metabolic rates in both models was described by current oxygen consumption level as a percentage of maximum oxygen consumption level. In order to investigate the influence of exercise on glucose regulation, three parameters were introduced into minimal model to express the effect of exercise in accelerating glucose utilization by tissues, increasing insulin utilization and increasing sensibility of muscular and liver to the insulin action in [152] .

Further research on the effect of stress, sickness, exercise, etc. can provide more information about the interaction of these factors and pathology of diabetes. The incorporation of other hormones or physiological/physical states can increase the accuracy and applicability of the virtual patient model.

6.2.2 Abnormalities of Ultradian Oscillations

Many physiological and pathological factors can modulate or affect the ultradian oscillation of the glucose-insulin system. For non-diabetic people, the frequency of ultradian oscillation may be driven or affected by the exogenous disturbance such as oscillating glucose infusion [153]. The entrainment of ultradian oscillation and rapid oscillation was regarded as a feature of ultradian pulsatility; however, this feature is not for Type 2 diabetic patients [154, 155]. In this thesis, only constant glucose infusion was investigated for its effect on the ultradian oscillation. The investigation of ultradian oscillation of glucose and insulin focused on the influence of model parameters. Different forms of glucose infusion (e.g., oscillating, random glucose infusions, etc.) can be further explored for its effect on the ultradian oscillation.

Ultradian oscillations of the non-diabetic obese people was proposed to have higher amplitude of oscillations without affecting the oscillation frequency, which was due to the impaired response of peripheral tissues to insulin [156]. For long-standing Type 2 diabetes with the function of insulin secretion and action impaired, ultradian oscillation may be disrupted greatly, which showed irregular amplitude, frequency or concomitance of insulin and glucose [58]. Besides, oscillation of plasma glucose in Type 2 diabetes was observed to be broader and more sluggish, without sharp peaks. The reason may be the failure of insulin to suppress HGP and/or the insulin resistance in the periphery, which

results in diminished glucose utilization [58]. Further investigation based on Chapter 3 and Chapter 4 can give insights on the effect of diabetes on ultradian oscillations. Loss of oscillation inducement for diabetic patients without exogenous insulin delivery may be a symptom of abnormality of the glucose-insulin system, and investigating ultradian oscillation and its entrainment using the two-compartment model may find some abnormalities of the glucose-insulin system.

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