# MATHEMATICAL MODELING OF DIABETES

*A thesis submitted to*

**DELHI TECHNOLOGICAL UNIVERSITY**

*in partial fulfillment of the requirements of the award of the degree of*

**DOCTOR OF PHILOSOPHY**

*in*

**MATHEMATICS**

*by*

**SALONI RATHEE**

*under the supervision of*

**Dr. Nilam**


DEPARTMENT OF APPLIED MATHEMATICS

DELHI TECHNOLOGICAL UNIVERSITY

(Formerly Delhi College of Engineering)

BAWANA ROAD, DELHI-110 042, INDIA.

**January, 2017** **Enrollment No. : 2K11/Ph.D./AM/02**

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# DECLARATION

I declare that the research work reported in this thesis entitled "**Mathematical Modeling of Diabetes**" for the award of the degree of *Doctor of Philosophy in Mathematics* has been carried out by me under the supervision of *Dr. Nilam*, Department of Applied Mathematics, Delhi Technological University, Delhi, India.

The research work embodied in this thesis, except where otherwise indicated, is my original research. This thesis has not been submitted by me earlier in part or full to any other University or Institute for the award of any degree or diploma. This thesis does not contain other person's data, graphs or other information, unless specifically acknowledged.

**Date :** **(Saloni Rathee)**

# CERTIFICATE

This is to certify that the thesis entitled **"Mathematical Modeling of Diabetes"** submitted by **Ms. Saloni Rathee** in the Department of Applied Mathematics, Delhi Technological University, Delhi, India for the award of degree of *Doctor of Philosophy in Mathematics*, is a record of bonafide research work carried out by her under my supervision.

To the best of my knowledge the work reported in this thesis is original and has not been submitted to any other Institution or University in any form for the award of any degree or diploma.

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**Date :** **(Saloni Rathee)**

**Place : Delhi, India.**

**Dedicated to**

**My husband Dr. Sandeep Chaudhary**

**and**

**My son Shreyansh Chaudhary**

# Contents

# Abstract

In the present thesis, various aspects of glucose - insulin dynamics, its consequences and maintenance of glucose level in and around physiological range in diabetics have been discussed through mathematical model. We have analyzed different mathematical models which satisfies the physiology behind the mechanism involved in glucose - insulin dynamics of both type 1 diabetics and type 2 diabetics. We have investigated the facts and reasons behind the consistently raised glucose concentration level in the people suffering from diabetes. After analyzing several systems, various results obtained by dynamical analysis of the problems are discussed. All mathematical models have been analyzed for stability, positiveness and boundedness. Local linearization, Routh-Hurwitz stability criterion, Lyapunov function, Runge-Kutta method, Matlab 2012b (ode45, dde45) are the main tools applied for analysis and simulation of mathematical models.

We have studied two types of mathematical models : ordinary differential equations (ODE) model and delay differential equations (DDE) model. The delay occurred in the dynamics of different phenomena is responsible for the severity of the disease and hence in its treatment. Therefore, importance of DDE model can not be ignored in the development of artificial pancreas. DDE models have been developed for the better functioning of artificial pancreas.

Keywords : Glucose, Insulin, Insulin pump, Artificial pancreas, Vitamin D, Free Fatty Acids, Obesity, Liver, Kidney, Central nervous system (CNS), Delays, Intravenous glucose tolerance tests, Insulin analogues, Aspart, Lispro, Ordinary differential equations (ODE), Delay differential equations (DDE).

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# Chapter 1

# Introduction

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This chapter is introductory in nature which gives a short review of the work done in the field till now about the physiology of diabetes through important mathematical equations. In this chapter, literature survey has been made which describe the types of diabetes, its diagnosis, risk factors, symptoms and treatment of disease. The basic mathematical model is discussed in the chapter which explains the glucose - insulin dynamics precisely and clearly. The purpose of this chapter is to provide the motivation behind the work carried out in the thesis.

---

## 1.1 Introduction

Diabetes is a global problem with devastating human, social and economic impact. It is a growing epidemic threatening to overwhelm global health care services, especially in developing countries. The number of people with diabetes is increasing due to aging, urbanization, and increasing prevalence of obesity and physical inactivity. Diabetes is a highly prevalent disease in India where more than 35 million people suffer from diabetes. Diabetes is mostly a problem in the western countries today, but as more and more developing countries switch from manual to knowledge-based sedentary labor as their primary source of income, the number of people with diabetes in these countries is expected to soar. By the year 2030, total number of people in the world with diabetes will increase from 171 million in 2000 to 366 million [1]. India had 32 million diabetic subjects in the year 2000 and this number would increase to 80 million by the year 2030 as estimated by World Health Organisation (WHO) [1]. The International Diabetes Federation (IDF) also reported that the total number of diabetic subjects in India is 41 million in 2006 and this would rise to 70 million by the year 2025 [2]. International Diabetes Federation reported that 48.3 % of the total population have diabetes and the figures are expected to rise to 9.9 % by 2030 [2].

Diabetes - a disease reorganised centuries ago has entered into an era of existing scientific research, discovery and controversy. Obesity and diabetes are the results of modern lifestyle adopted by human. It is also estimated that several million people have the diabetes but are unaware of it. Diabetes and the complications associated with it impose burden on the individuals, families, health system and on countries. WHO reported that diabetes will be the 7th leading cause of death by the year 2030 [3]. In 2012, an estimated 1.5 million deaths were directly caused by diabetes [4]. More than 80 % of diabetes deaths occur in low and middle income countries [4]. Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type 2 diabetes [5].

Due to large population of diabetes patients in the world and the big health expenses, many researchers are motivated to study the glucose-insulin endocrine metabolic regulatory system so that we can better understand the working of mechanism [6–12], what cause the dysfunction of the system [13].

Diabetic research is very young. It is reported that most of the path - breaking research

has been done in the late 80's and early 1990's. A total of 2,77,781 papers were published all over the world in the SCI (expanded) - indexed journals on diabetes during 1976 - 2006. Out of these, 3,068 research papers were contributed by India which was just 1.04 % [14].

Diabetes is epidemic ?

Increasing prevalence of the disease demands this description whether diabetes is epidemic or not. The declaring of diabetes as an epidemic also helps make clear that public health approaches must be brought to bear in its control. The strategies used to control the disease includes surveillance, risk identification, interventions, identification of affected individuals and monitoring of outcomes. Such approaches helps to control the communicable disease. In addition to surveillance and risk reduction, disease control also relies on "find them, treat them" approach. The diabetes epidemic is expected to increase at an alarming rate unless effective prevention and treatment measures are put in place.

## 1.2 History of diabetes

Diabetes was a well known disease by the 17th century. Apollonius of Memphis was the first physician to actually call "diabetes". In 20th century, if a patient was diagnosed with diabetes it was the same as a death sentence. During 1900's the first known treatment was starvation. In 1920's lack of insulin was considered as a symptom of diabetes. In 1944, an insulin syringe was developed in order to make diabetes more controllable. In 1990 external insulin pumps were created for own use. In 1993 doctors started use of glucose tablets [15].

## 1.3 What is diabetes?

Diabetes, commonly referred to as Diabetes Mellitus, means sweet urine. Long persistence of high blood sugar level in our bloodstream leads to a condition named as diabetes. In diabetes, the absence or insufficient production of insulin by the organ liver causes hyperglycemia. Diabetes is a syndrome characterized by chronic hyperglycemia resulting from absence or relative impairment in insulin secretion and/or insulin action. It can also

be referred to as a condition characterized by the disturbances of carbohydrate, protein and fat metabolism, the way our bodies use digested food for growth and energy [16].

### 1.3.1 Physiology of diabetes

When food is given to the body, it is broken down into smaller components - sugar and carbohydrates, which further broken down into glucose for the body to utilize it as an energy source. Glucose is also produced by liver. In normal body, the hormone insulin, which is secreted by the $\beta$ cells of the pancreas, helps the muscle and fat cells to utilize glucose. Glucagon is secreted by the $\alpha$ cells of the pancreas and increase the glucose level in body. Liver stores the glucagon into glycogen form, which further break down into glucose when the glucose level falls in the blood. When blood glucose level falls, during exercise for example, insulin level falls too. In diabetic condition, the glucose - insulin dynamics is disrupted and insufficient or no insulin is secreted from the $\beta$ cells due to $\beta$ cell defect which leads to high glucose level [17]. Also, the glucagon secretion from $\alpha$ cells is disturbed, resulting excess glucagon or insufficient glucagon release leads to high glucose level (hyperglycemia) or low glucose level (hypoglycemia).

### 1.3.2 Types of diabetes

Diabetes is of mainly three types : Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus and Gestational Diabetes.

#### 1. Type 1 diabetes mellitus (T1DM)

Type 1 diabetes also known as insulin - dependent diabetes mellitus (IDDM) or juvenile - onset diabetes. In this condition the immune system attacks and destroys the $\beta$ cells of pancreas, which will create insulin deficiency. Thus it is termed as an autoimmune disease where there are anti insulin or anti islet cell antibodies present in blood. These causes lymphocytic infiltration and destruction of the pancreas islets. The destruction may take time but the onset of the disease is rapid and may occur over a few days to weeks. Type 1 diabetes does not respond to insulin - stimulating oral drugs and hence always requires insulin therapy. About 5% to 10% of all diabetics are diagnosed with type 2 diabetes. Autoimmune, genetic, and environmental factors are the risk factors for type 1 diabetes.

**Symptoms of T1DM**

- Increased thirst
- Frequent urination
- Bedwetting in children
- Extreme hunger
- Weight loss
- Irritability
- Fatigue and weakness
- Blurred vision
- A vaginal yeast infection in females [18]

**Risk factors of T1DM**

- Family history
- Unhealthy food
- Overeating
- Diseases of pancreas

**2. Type 2 diabetes mellitus (T2DM)**

Type 2 diabetes also known as adult onset or non - insulin dependent diabetes mellitus (NIDDM). Type 2 diabetes is caused by a relative deficiency of insulin but not an absolute deficiency. The body is unable to produce sufficient amount of insulin to lower blood glucose level [19]. There is $\beta$ cell deficiency coupled with peripheral insulin resistance [20]. Peripheral insulin resistance means that inspite of high level of insulin, blood glucose level never lower down. The reason are may be the changes in insulin receptors that bring the actions of the insulin. Obesity is considered as the main cause of insulin resistance. Type 2 diabetes may account for 90% to 95% of all diagnosed with cases of diabetes. Type 2 diabetes is increasingly being diagnosed in children and adolescents [21].

**Symptoms of T2DM**

- Increased thrust and frequent urination
- Increased hunger
- Weight loss
- Fatigue
- Blurred vision
- Frequent infection
- Areas of darkened skin [22]

**Risk factors of T2DM**

- Family history of diabetes
- Overeating
- Unhealthy diet
- Physical inactivity
- Increasing age
- High blood pressure
- History of gestational diabetes
- Poor nutrition during pregnancy
- Insulin resistance
- Low level of High Density Lipoprotein (HDL) cholesterol and high level of triglycerides (TG)
- Sedentary lifestyle
- Polycystic ovary syndrome

**3. Gestational diabetes**

Gestational diabetes is among pregnant women who have never had diabetes before but having high blood glucose levels during pregnancy. It is caused when there are excessive counter insulin hormones of pregnancy and leads to a state of insulin resistance and high blood sugar. According to 2014 analysis by the centers for diabetes control and prevention, the prevalence of gestational diabetes is as high as 9.2 % [23].

**Risk factors of gestational diabetes**

- Age greater than 25 : When older than 25 age, they are more likely to develop gestational diabetes
- Family history
- Over weight
- Women who are black Hispanic, American Indian or Asian are more likely to develop gestational diabetes, while the reason is not clear.

## 1.4 Glucose - insulin endocrine metabolic regulatory system

Normal range of the glucose concentration level is considered as 70 - 110 $mg/dl$ and the person is said to have glucose problem if the glucose concentration crossed the normal physiological range. Glucagon and insulin are the pancreatic endocrine hormones which plays an important role in regulating the glucose - insulin metabolic system. When plasma glucose concentration level is high in the body, then following process will occur :

- Raised plasma glucose concentration triggered the pancreas to release insulin from $\beta$ cells.
- Insulin binds to the cells insulin receptors.
- Insulin receptors holding the insulin cause the glucose transporters (GLUT4) to transport glucose into cells (muscles and adipose cells).
- Glucose is consumed by cells and later converted into energy.

When plasma glucose concentration level is low, the following dynamics will occur :

- Low glucose concentration level triggered the $\alpha$ cells of pancreas to secrete glucagon.
- Secreted glucagon is transported to liver.
- Liver convert the glucagon into glucose.

The process increase the glucose concentration level in the plasma and unused glucose is stored in liver which further convert into glucose if the glucose concentration lower down in the plasma. Exogenous glucose infusion (meal ingestion, oral glucose uptake, continuous eternal nutrition) increase the glucose concentration. Liver plays an important role in maintaining the glucose concentration in the normal physiological range.

## 1.5 Some basic definitions and terms

- Glucose : is the most widely used aldohexose in living organisms. It is the main source of energy for human body. Glucose is stored as a polymer, in plants as starch and in animals as glycogen [24].
- Glycogen : is a multi branched polysaccharide of glucose that serves as a form of energy. Glycogen is stored in the cells of liver and muscles hydrated with three or four parts of water. Glycogen is found in the form of granules in the cytoplasm of cells and pays an important role in the glucose cycle [25].
- Glucagon : is a peptide hormone, produced by $\alpha$ cells of the pancreas. It raises the glucose concentration in the bloodstream and works just opposite to hormone insulin which lowers glucose level. When the glucose concentration falls low in the blood, then pancreas secrete glucagon [26].
- Endocrine system : is made up of glands that secrete chemical called "hormones" into bloodstream or surrounding tissues. The system includes pituitary gland, thyroid gland, parathyroid gland, adrenal gland, pancreas, testes and ovaries [27].
- $\alpha$ cells : are endocrine cells in the pancreatic islets of the pancreas and secrete the peptide hormone glucagon [28].
- $\beta$ cells : are found in the pancreatic islets of the pancreas and make upto 65-80 % of cells in the islets. The primary function of $\beta$ cells is to store and release insulin [29].

- GLUT4 : Glucose transporter type 4, is a protein encoded in human, by the GLUT4 gene and is insulin - regulated glucose transporter found primarily in adipose tissues and muscles [30].

- Peptide hormone : is synthesized in cells from amino acids and having short amino acid chain length than protein hormones [31].

- Pancreas : is an endocrine gland producing several important hormones like insulin, glucagon, somatostatin etc. which circulate in the blood and performed different functions. Pancreas also secrete several pancreatic juice containing digestive enzymes that helps in digestion and absorption of nutrients in small intestine [32].

- Insulin : Insulin is a peptide hormone produced by $\beta$ cells of the pancreas. It absorb glucose from blood to skeletal muscles and fat tissue to regulate the metabolism of carbohydrates and fats. Insulin also inhibits the production of glucose by the liver [33]. The role of insulin in the body is:
  (i) facilitation of glucose transport through certain membranes;
  (ii) convert glucose to glycogen;
  (iii) slowdown of gluconeogenesis;
  (iv) regulation of lipogenesis.

- Hyperglycemia : A condition in which the pancreas either does not secrete sufficient amount of insulin or for unknown reason the secreted insulin does not help muscle and liver cells to uptake glucose. This will rise the glucose concentration level in the body and the condition is referred as hyperglycemia.

- Hypoglycemia : A condition in which extra amount of insulin secreted by pancreas which lower the glucose concentration below the normal physiological range.

- Insulin resistance : A condition in which cells of the body fail to respond to normal actions of hormone insulin. The cells become resistant to insulin and unable to use it effectively which leads to high blood glucose level. Also $\beta$ cells of the pancreas subsequently release the hormone insulin, which further increase the blood insulin level in the body. Often the condition remain undetected and contribute to occurrence of type 2 diabetes mellitus [34]. The exact reason behind the insulin resistance is still unknown but some factors i.e lack of exercise, obesity, unbalanced diet, physical inactivity may cause the insulin resistance.

- Insulin sensitivity : is a general phenomenon in the body and can be measured in different way through studies. Insulin sensitivity describe the sensitivity of the body to the effects of insulin. Insulin sensitive body requires smaller amount of insulin to lower blood glucose level than the person who have low sensitivity.

- Glucose effectiveness : Ability of glucose to enhance its own disappearance independent of insulin presence [35].

- AIRglucose : First phase insulin response [36].

- DI (Disposition index) : Ability of pancreatic $\beta$ cells to compensate for insulin resistance [36].

- $\phi_1$ : First phase pancreatic responsivity [37].

- $\phi_2$ : Second phase pancreatic responsivity [37].

- Ultradian oscillations : An ultradian oscillation is a recurrent period or cycle repeated throughout a 24 hour day [38].

- Gluconeogenesis : is a process of generation of glucose from non carbohydrate carbon substitutes such as glycerol, lactate and glycogenic amino acids [39].

- Lipogenesis : is a process of conversion of acetyl-Coenzyme A into fatty acids [40].

- Insulin pump: It is a small electronic device about the size of a paser used to control the raised glucose concentration in the body by delivering precise doses of rapid acting insulin 24 hr a day through a continuous subcutaneous insulin infusion (CSII).

  Basal dose : is the amount of insulin delivered continuously for normal functioning of the body.

  Bolus dose : is the additional amount of insulin which can be delivered in the body to maintain the glucose concentration.

- Artificial pancreas : It is used to control blood glucose level of diabetic people by providing the substitute of healthy pancreas. Improper functioning of $\beta$ cells of the pancreas motivates the researchers to develop substitutes of insulin [41]. The goal of the artificial pancreas is to improve insulin replacement therapy, and to ease the insulin therapy for the type 1 diabetic people.

- Insulin lispro : Insulin lispro is a rapid acting insulin analogue and it was the first insulin analogue to enter in the market in 1996 [42]. Insulin lispro has a shortened delay of onset.

- Insulin aspart : Insulin aspart is also a rapid acting insulin analog and is manufactured from the human insulin by changing a single amino acid.

- Insulin glargine : Insulin glargine developed by rDNA technology in 2002 is a long acting basal insulin analogue, given once daily to help in controlling the raised blood glucose level.

- Time delays : In the whole glucose - insulin regulatory system some delays are observed. These delays are :
  (i) A time delay in insulin secretion either the insulin secreted from the pancreas or by insulin pump.
  (ii) A time delay in inhibition in hepatic glucose production.
  (iii) A time delay in insulin action to lower the glucose concentration.

## 1.6 Testing and treatment therapies for diabetes

Diabetes is a common disease, yet every individual needs unique care and treatment. People with diabetes and their families should be encouraged to know about the latest medical therapies and approaches to deal with the disease.

### 1.6.1 Glucose tolerance tests for diagnosis of disease

A number of glucose tolerance tests have been developed over the years and applied in clinical experiments [37,43–46]. Glucose tolerance tests helps to diagonize if a person has diabetes or not.

- A1c : is a blood test that provides information about a person's average blood glucose level over the past 3 months. The A1C test is also named as hemoglobin A1c, HbA1c, or glycohemoglobin test [47].

- FSIGTT (Frequently sampled intravenous glucose tolerance test) : is a blood test to measure the blood glucose level in which nothing (drink and eat) is given for 8

to 12 hr before the test. If the glucose level is found $> 126$ $mg/dl$ (7.0 $mmol/l$) then the person is prone to have diabetes.

- OGTT (Oral glucose tolerance test) : In OGTT, a glass of glucose liquid (75 $mg$) is given to the individual and blood samples are collected over 2 hr following the glucose infusion. If the glucose level is $> 200$ $mg/dl$ (11.1 $mmol/l$) then the person may prone to diabetes.

- IVGTT (Intravenous glucose tolerance test) : A test in which glucose is injected intravenously and blood samples are collected following the glucose injection. IVGTT and FSIGTT are used to test insulin sensitivity or response to high plasma glucose concentration level. In these test plasma glucose and serum insulin are sampled frequently and the individual need to fast for 8-10 hr before test. A bolus of 0.33 $g/kg$ body weight [48] is given and is administered into an antecubital vein in approximately 2.5 $min$. Insulin sensitivity can be determined by taking information from the sampled data.

### 1.6.2 Treatment therapies for diabetes

Diabetes is an incurable condition that can be improved through administration of insulin or by adopting sedentary lifestyle.

**1. Lifestyle**

- Healthy eating
- Regular exercise
- Eating balanced diet
- Involved in physical activities
- Play outdoor games

**2. Oral medication**

In type 2 diabetes, blood glucose control is often controlled by proper meal planning, weight loss and exercise timely. If these measures are not able to bring blood glucose levels down near the normal range then the next step is to take oral medicine. Some

of the medicines recommended by doctors are : Alpha-Glucosidase Inhibitors (acarbose, miglitol), Biguanides (metformin-alogliptin, metformin-canagliflozin, metformin-glipizide, metformin-glyburide), DPP-4 Inhibitors (alogliptin, alogliptin and pioglitazone, linagliptin), Meglitinides (nateglinide and repaglinide) and many more [49].

**3. Insulin infusion**

Blood glucose level should be monitored regularly for better living. Insulin is the most potent agent to lower blood glucose, is rapidly effective and is easily titrated [50, 51]. However, insulin is a high-alert medication which requires accurate monitoring and standardized protocols to minimize risks while maximizing benefits [52, 53]. Intravenous infusion is the preferred route to deliver insulin in critical care, labor and delivery. Type 1 diabetics and severe cases of type 2 diabetes who were treated with insulin require subcutaneous insulin infusion [54].

**(3.a) Continuous Subcutaneous Insulin Infusion (CSII)**

CSII and multiple daily insulin injection therapy are effective means of diabetes management with the goal of achieving near to normal level of blood glucose and improved lifestyle in severely affected diabetics Working of insulin pump is done in CSII style [55]. Insulin pump is not only for treatment of type 1 diabetics but also provide a feasible alternative for type 2 diabetes for exogenous injection of insulin [56–58]. The recommended insulin analogues for insulin pumps are [49] :

- short-acting : regular (R) (Humulin, Novolin, and other brands)
- rapid-acting: insulin aspart (NovoLog, FlexPen), insulin glulisine (Apidra), insulin lispro (Humalog)
- intermediate-acting: insulin isophane (Humulin, Novolin, Iletin)
- long-acting: insulin detemir (Levemir), insulin glargine (Lantus).

Rapid acting insulin analogs are appropriate for insulin pumps. The stability of these insulin in pumps has been confirmed.

Depending upon the severity of disease (Type 1 diabetes), artificial pancreas may be considered as the future of CSII.

**(3.b) Artificial pancreas**

All insulin pumps used for diabetic treatment follow the open loop approach i.e. insulin is injected in the body without the prior knowledge of blood glucose level. A risk in the open loop control in hypoglycemia. Many researchers have been making great efforts in developing technology that will close the loop. The objective was to develop a system that combines continuous blood glucose monitoring with an insulin pump and thus works as an artificial pancreas. The idea of artificial pancreas came in 2005 from Dr. Edward R. Damiano. He met with Dr. Steven Russell in order to design and get a medical perspective on his proposed idea.

**Working of artificial pancreas**

The artificial pancreas has four components in order to make it work.

- A glucose sensor and transmitter that measures the glucose levels continuously.
- It transmits the information to a receiver that displays the glucose levels for the patients at regular intervals.
- This is connected to a small computer which calculates how much insulin is required.
- Then via bluetooth the small computer give command to insulin pump to release the required amount of insulin into the patient [41].

## 1.7 Development of mathematical model for diabetes

The two main variables involved in glucose - insulin regulatory system of human body which can be observed or manipulate clinically are blood glucose level, $G$, and the blood insulin level, $I$.

Let $G(t)$ and $I(t)$ represents the glucose and insulin concentration at time $t \geq 0$. The model comprises of :-
(Rate of change of glucose concentration) $\frac{dG(t)}{dt}$ = glucose production - glucose utilization and
(Rate of change of insulin concentration) $\frac{dI(t)}{dt}$ = insulin production - insulin utilization.

Glucose production : When glucose level drops below the basal level $G_b$, glucose is either

released from the liver or given orally. Glucose is obtained from the food we eat in the form of starch or sucrose. Glucose is also consumed through oral glucose intake, meal ingestion, glucose infusion.

Hence,

$$\frac{dG(t)}{dt} \propto (G_b - G(t)) \tag{1.7.1}$$

Glucose utilization : The presence of insulin induces the metabolism of sugar, hence lowering the blood sugar level. Higher amount of blood sugar level or insulin level makes the utilization faster, hence the product of two levels is an adequate representation for glucose utilization.

$$\frac{dG(t)}{dt} \propto -G(t)I(t) \tag{1.7.2}$$

Hence rate of change of glucose concentration may be modeled as :

$$\frac{dG(t)}{dt} = a(G_b - G(t)) - bG(t)I(t) \tag{1.7.3}$$

where $a$ and $b$ are the sensitivities of glucose gradient to low blood glucose level and presence of insulin respectively.

Insulin production : If the blood sugar level rises above its fasting level, insulin is secreted by $\beta$ cells of the pancreas or infused by outer source (Insulin pump or artificial pancreas) in case of diabetic people. Hence

$$\frac{dI(t)}{dt} = \begin{cases} c(G(t) - G_b), \text{if } G(t) > G_b \\ 0, \text{if } G(t) \leq G_b \end{cases} \tag{1.7.4}$$

Insulin utilization : Insulin itself degrades by separate biochemical process. Hence

$$\frac{dI(t)}{dt} \propto -eI(t), I(t) \geq 0 \tag{1.7.5}$$

Hence rate of change of insulin concentration may be modeled as :

$$\frac{dI(t)}{dt} = c(G(t) - G_b)^+ - eI(t) \tag{1.7.6}$$

where $c$ and $e$ are sensitivities of insulin gradient to high glucose level and insulin level.

Hence model for diabetes is given as below :

$$\frac{dG(t)}{dt} = a(G_b - G(t)) - bG(t)I(t) \tag{1.7.7}$$

$$\frac{dI(t)}{dt} = c(G(t) - G_b)^+ - eI(t) \tag{1.7.8}$$

where $a$, $b$, $c$ and $e$ are the parameters defined above.

After the development of this basic model, many models have been developed which involved ordinary differential equation (ODE) and delay differential equation (DDE) models, as discussed below :

### 1.7.1 Ordinary differential equations (ODE) mathematical models

Researchers have proposed man ODE models till date to explain various phenomena in glucose - insulin dynamics [6, 37, 71]. A year wise development in ODE models will be presented in this section.

Bolie [59] developed an ODE minimal model to evaluate the coefficients of normal blood glucose regulation. The differential equations for glucose - insulin regulatory system is written as :

$$\frac{dx(t)}{dt} = p - \alpha x + \beta y \tag{1.7.9}$$

$$\frac{dy(t)}{dt} = q - \gamma x - \delta y \tag{1.7.10}$$

where $x$ represents the deviation in insulin concentration from their mean physiological value, $y$ represents the deviation in glucose concentration from their mean physiological value, $p$ is the intravenous injection functions $\dot{I}$ (rate of insulin injection) divided by extracellular compartment value, $q$ is the intravenous injection functions $\dot{G}$ (rate of glucose injection) divided by extracellular compartment value, $\alpha$ denotes the sensitivity of insulinase activity to elevate insulin concentration, $\beta$ denotes the sensitivity of pancreatic insulin to elevate glucose concentration, $\gamma$ represents the combined sensitivity of liver glycogen storage and tissue glucose utilization to elevate insulin concentration and $\delta$ represents the combined sensitivity of liver glycogen storage and tissue glucose utilization to elevate glucose concentration [59].

In 1964, Ackerman et al. [60] reviewed a model to predict the blood glucose level by simulating the behavior of human regulating system. He compared the predictions made during OGTT to regulate the blood glucose and blood insulin concentration. In 1970, Segre et al. [61] considered a 2 compartment model and analysed glucose and insulin control mechanism in 26 normal, 16 diabetic and 8 obese subjects. Glucose level for all the three groups were determined by infusing glucose (0.5 gm/min for about 300 min). In 1978, Ruby et al. [62] discussed a model to indicate the roles of both insulin and glucagon as regulators of blood glucose. The simulation results suggest that insulin plays the most important role in the control of hyperglycemia and glucagon is an important regulatory hormone under conditions of hypoglycemia when the blood glucose value falls below 50 mg/dl. In 1979, Bergman et al. [63] discussed the studies which led to definition and measurement of the characteristic parameters of metabolic regulation. The parameters presented a novel and powerful way of metabolic regulation, which provides an improved means for investigating the environmental, dietary and activity related factors which alter the regulation of metabolism in mammalian species. In 1979, Bergman and Cobelli [46] estimated the insulin sensitivity after evaluating a mathematical model of glucose disappearance. Seven mathematical models of glucose uptake were compared to find the glucose disappearance. The parameter of the model were estimated from a single IVGTT, to estimate the insulin sensitivity. In 1980, Toffolo et al. [64] proposed the minimal model for the insulin kinetics in dog. The proposed minimal model was used for the physiological studies of insulin secretary function in dog by using IVGTT and proposed the idea to apply the model for the pathophysiological studies in man also. Toffolo compared six mathematical models to study the insulin kinetics and found that the model (discussed by him) is superior in explaining insulin dynamics with respect to all aspects. In 1981, Bergman et al. [37] introduced two separate mathematical models : one for glucose kinetics and other for insulin kinetics. Insulin model produce the parameters : $\phi_1$, $\phi_2$, responsivity of $\beta$ cells to glucose, whereas glucose model produce the insulin sensitivity ($S_I$) parameter during IVGTT. In 1984, Defronzo et al. [65] examined the tissue sensitivity to insulin in 36 control subjects and 19 insulin dependent diabetics using insulin clamp technique. Following hyperinsulinemia, suppression of hepatic glucose production was $\sim$ 95 % in both diabetics and controls, suggested that peripheral tissues are primarily responsible for observed impairment in insulin mediated glucose uptake. In 1985, Bergman et al. [66] examined the different approaches introduced by re-

searchers for the evaluation of insulin sensitivity. He reviewed pancreatic suppression test ( [67–69]), glucose clamp ( [67,68]), and minimal model approach ( [37,70]) to find the effect of closed loop feedback relation between insulin action and insulin secretion. In 1986, Pacini and Bergman [71] proposed mathematical model for measuring two main factors - insulin sensitivity and pancreatic responsivity to control glucose tolerance. Bergman proposed MINMOD (Minimal modelling Approach) - a computer program to identify the model parameters $S_G$, $S_I$, $\phi_1$, $\phi_2$ and analyzed FSIGTT data. In 1990, Welch et al. [72] determined the exogenous infusion of insulin in the minimal model FSIGTT analysis. The information about insulin mediated glucose uptake and non insulin mediated glucose uptake, insulin sensitivity and insulin secretion was also extracted. In 1991, Sturis et al. [6] developed a six dimensional ODE model. Later in 2001, Tolic et al. [7] simplified the model and the model has been the basis of many DDE models [17, 73–77]. In 1991, M.E. Fisher [78] presented a mathematical model for glucose insulin interaction in the blood system. Mathematical optimization techniques are applied to mathematical model to derive insulin infusion program. A semi - closed algorithm is proposed for continuous insulin delivery to diabetic patients. In 1995, Coates et al. [79] studied the minimal model (MINMOD) analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT) depends on an adequate insulin response to the glucose load. In MINMOD, subjects having non insulin dependent diabetes mellitus (NIDDM) were not included. Hence, the technique has been modified by using intravenous bolus of insulin. Also they compared estimates of insulin sensitivity derived from minimal modeling of a 4 hr insulin modified FSIVGTT and the glucose clamp in subjects with NIDDM. In 1997, Vicini et al. [80] showed that 2CMM (2 compartment minimal model) provide indexes of glucose effectiveness ($S_G$), insulin sensitivity ($S_I$) and plasma clearance rate ($PCR$). The limitation of one compartment minimal model [81] was also overcome by providing the plausible profile of endogenous glucose production. In 2000, Topp et al. [8] developed a $\beta IG$ model for $\beta$ cell mass, insulin and glucose kinetics for diabetes. In 2001, Ryan et al. [82] modified the mathematical model of $\beta$ cell mass, insulin and glucose kinetics for diabetes developed by Topp et al. [8]. The effects of insulin receptor dynamics which was very important in the pathogenesis of diabetes was included. He also showed that insulin sensitivity can be increased by 36 % due to exercise and required insulin level can also be decreased to maintain the glucose concentration. The system of equations improves the quantitative prediction of $\beta$ cell mass values and provides a theoretical justification

for the fact. In 2000, Gaetano and Arino [48] proposed another model known as "dynamical model" in order to overcome the limitations and drawbacks of the coupled minimal model. They reported that unstable steady state does not exists for the model while Li et al. [83] found that these models can posses unstable positive steady states producing oscillatory solutions. In 2002, Cobelli et al. [84] proposed a new approach to estimate insulin sensitivity from an OGTT using an "integral equation". Three different model : Piecewise linear (P), Spline (S) and dynamic (D) were presented in the paper to determine rate of appearance of oral glucose in plasma ($R_a$). All the three models estimated the insulin sensitivity. In 2002, Derouich and Boutayeb [85] introduced the effect of physical activities and exercise via parameters in a mathematical model given by Bergman et al. [37] and compared the behavior of normal, NIDD and IDD people. The new added parameters demonstrated the effect of physical exercise on the diabetic body. In 2002, Mari et al. [86] investigated $\beta$ - cell function and its relationship to insulin sensitivity by choosing 17 normal volunteers. Insulin secretion and insulin sensitivity were measured by applying mathematical model on meal test (MT) and oral glucose tolerance test (OGTT) with the help of euglycemic insulin clamp technique. In 2003, Toffolo and Cobelli [87] introduced a new improved version of 2 compartment minimal model (2CMM) [80]. The new improved version of 2CMM, proved a more reliable and precise parameter of glucose metabolism during an IVGTT. In 2004, Dellaman et al. [88] used the reference method : tracer 2 step method and compared the results on database of 88 subjects. The method was compared with the Homeostasis Model Assessment (HOMA) [89, 90], Quantitative Insulin Sensitivity (QUICK) [91], MATSUDA - De Fronzo [92] to measure the insulin sensitivity during an OGTT. The results confirmed the rate of appearance of glucose absorption and insulin sensitivity accurately by using Oral Minimal Model (OMM). In 2005, DallaMan et al. [93] presented a labelled Oral Minimal Model ($OMM^*$) by adding a tracer to the oral dose and labelled insulin sensitivity ($S_I^*$). $OMM^*$ not only estimates the labelled rate of appearance of oral glucose in plasma ($R_a^*$) but also accurately measure $S_I^*$. In 2005, R.N. Bergman [36] considered the minimal model and showed that insulin sensitivity or insulin sensitivity index ($S_I$) can be calculated from parameters of minimal model by performing frequently sampled IVGTT, measure glucose and insulin, fit the data to the minimal model and calculate insulin sensitivity. Also he showed that product of insulin sensitivity and insulin secretion would be approximately constant i.e. insulin sensitivity $\times$ insulin secretion = disposition index ($S_I \times AIR_{glucose} = \text{DI}$). In 2006, Boutayeb

et al. [35] presented a mathematical model for the size of a population of diabetes mellitus. The non linear case was discussed and critical values of the population were analysed for stability. In 2006, Bergman et al. [94] performed dimensional analysis of MINMOD and found that with non dimensionalization, pathological DI is naturally defined in the model and it has the meaning of insulin sensitivity at unit first phase pancreatic response. Using simulated data and human FSIVGTT data they found the new approach which provide highly correlative parameter estimates to the original dimensional formulation. In 2006, Wang et al. [95] formulated a mathematical model to deal with the question about heterogeneity between young and adult onset type 1 diabetes (T1D). It was found that if autoimmunity is initiated then the turnover is slow, a stable steady state can exist with the $\beta$ cell turnover is rapid. In 2007, Silber et al. [96] developed an integrated model for healthy and type 2 diabetic (T2D) patients to regulate the glucose and insulin concentration by using IVGTT data form 30 healthy and 42 diabetic individuals. Analysis of all the data by non linear mixed effect modelling was performed in NONEM. In 2007, Silber et al. [97] extended the previously developed integrated model [96] for glucose - insulin regulatory system by including the OGTT in healthy volunteers by simulation and bootstrap of the model. The new model developed was based on incretin effect (i.e oral glucose provocations results in stronger insulin response compared to intravenous provocations). In 2007, Roy and Parker [98] extended the minimal model [37], and included the major effects of exercise on plasma glucose and insulin concentration level in the body. In 2008, an attempt has been made by Gaetano et al. [99], to discuss the progression of type 2 diabetes (T2D) through mathematical model. A model of the pancreatic islet compensation was formulated by the help of some physiological assumptions and compared with the model developed by Topp et al. [8]. The model was found more robust and useful for clinical purpose through assessment of the related parameters. In 2008, Stahl and Johansson [100] made an attempt to show how system identification and control may be used to estimate predictive quantitative models which can be used in designing of optimal insulin regimens. In 2008, Periwal et al. [101] examined various mathematical models analogues with the minimal model of glucose disposal (MMG) to quantify the combined influence of insulin on lipolysis and glucose disposal during an insulin - modified frequently sampled intravenous glucose tolerance tests (FSIGT). The tested models contain compartments of plasma free fatty acids (FFA), glucose and insulin. Out of 23 models, the best fitted model was selected by using Bayesian model compar-

ison method which minimized model complexity. In the best model, insulin suppressed lipolysis via. a Hill function through a remote compartment that acted both on FFA and glucose simultaneously, and glucose dynamics obeyed the classic MMG. In 2010, Pacini et al. [102] compared the insulin sensitivity index ($S_I$) and glucose effectiveness ($S_G$). The common protocols are regular (rFSIGT) and an insulin modified test (mFSIGT), with an additional insulin administration at 20 min. Both FSIGTs with minimal model analysis provide the same $S_I$, which was a very robust index. In 2011, Javier et al. [103] extended the model of Topp et al. [8] by proposing two models : one to show the effects of adipose tissue on insulin sensitivity and second to show the effect of fat accumulation on the regulatory system. He also discussed three different formulations for fat accumulation : a linear case and two nonlinear cases where the relationship between fat accumulation, insulin and glucose was discussed.

The mechanism behind the glucose - insulin dynamics is very complicated and the mathematical models developed so far play an increasingly important role to understand the complex biological phenomenon. Different aspects of diabetes are targeted by different types of models ranging from clinical studies to health service research [104]. No doubt numerous mathematical models exists in the literature which attempt to address the complexity of the disease, still an imbalance exists between the current knowledge given by experimental approach and their mathematical representation [104].

Most of the ODE models were developed to evaluate the diagnostic tests such as intravenous glucose tolerance test (IVGTT), oral glucose tolerance test (OGTT), meal glucose tolerance test (MGTT) etc. The aim of these tests were to estimate the insulin sensitivity ($S_I$), glucose effectiveness ($S_G$), disposition index (DI), insulin secretion, insulin action and $\beta$ cell function.

### 1.7.2 Delay differential equation (DDE) mathematical models

Delay differential equations (DDE) have been used in mathematical models in many areas of biology and medicine, such as epidemiology, population biology, physiology, cell mobility, immunology etc. [105, 106]. Delayed effects often exists in the glucose - insulin metabolic system. The three physiological time delays occurring in glucose - insulin dynamics are : delay in insulin secretion stimulated by elevated glucose concentration by $\beta$ cell of the pancreas, delay in inhibition in hepatic glucose production, delay in insulin

absorption and insulin action (time needed for plasma insulin to cross the endothelial barriers and become interstitial insulin that helps the body cells (muscles, adipose tissue etc.) to consume glucose) [6, 75, 107]. Hence the delay terms need to be taken in account when modeling the glucose - insulin regulatory system to match the physiology of human body. The general approach to include the technique of compartment split by introducing auxiliary variable in ordinary differential equations (ODE) and delay differential equations (DDE) mathematical models are constructed by using explicit time delays either in discrete or distributed form [42, 48].

Modeling of DDE mathematical models can be grouped according to their functions/purpose include and models:

- used to analyze the ultradian insulin secretion oscillations [6, 74, 75].
- used with diagnose tests.
- related to insulin therapies;
- to take intracellular activity of $\beta$ - cells into account.

In 1991, Sturis et al. [6] developed a six dimensional ODE mathematical model. Sturis incorporated a delay term in the model and reported that oscillations depends on the existence of a delay between increment in insulin concentration and corresponding effect on glucose production. Also the model does not exhibit oscillations if the delay term is omitted. Oscillations were damped for very short delay ($< 25$ *min*) and for very large delay ($> 50$ *min*) and sustained oscillations obtained in the range of 25-50 *min* with period of 95-140 *min*.

The DDE mathematical model for the glucose - insulin regulatory system is :

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))\, f_4(I(t)) + f_5(I(t)) \tag{1.7.11}$$

$$\frac{dI}{dt} = f_1(G(t)) - d_i I(t) \tag{1.7.12}$$

with the initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0$, $G(t) \equiv G_0$ and $I(t) \equiv I_0$ for $t \geq 0$. The functions $f_i$, i = 1,2,3,4,5 and their values are taken from [6] as the shape of the functions are more important than their forms [74]. The shapes of the functions are shown in

Figure 1.1.

$$f_1(G) = \frac{Rm}{1 + exp((C_1 - G/V_g)/a_1)} \tag{1.7.13}$$

$$f_2(G) = U_b(1 - exp(-G/(C_2 V_g))) \tag{1.7.14}$$

$$f_3(G) = \frac{G}{C_3 V_g} \tag{1.7.15}$$

$$f_4(I) = U_0 + \frac{(U_m - U_0)}{1 + exp(-\beta log(I/C_4(1/V_i + 1/Et_i)))} \tag{1.7.16}$$

$$f_5(I) = \frac{Rg}{(1 + exp(\alpha(I/V_p - C_5)))} \tag{1.7.17}$$

- $G_{in}$ is glucose infusion rate.
- $f_1(G(t))$ represents insulin secretion.
- $f_2(G(t))$ represents glucose utilization independent of insulin.
- $f_3(G(t))f_4(I(t))$ represents insulin mediated glucose utilization.
- $f_5(I(t))$ represents total glucose production.
- $d_i$ is insulin degradation rate.

In 2006, Li et al. [107] proposed a model by incorporating two explicit time delay for better understanding of the glucose - insulin regulatory system. It was reported in the study that time delay of insulin secretion stimulated by the elevated glucose concentration may be one of the possible cause for ultradian insulin secretion oscillation. The numerical simulation focussed on detecting the bifurcation points on a single parameter out of the four parameters. : delay ($\tau_1$), delay ($\tau_2$), constant glucose infusion rate $G_{in}$ and insulin degradation rate $d_i$. In 2007, Li et al. [75] studied the mathematical model analytically and numerically by varying two parameters simultaneously in DDE models. It was stated that the delays in the glucose - insulin regulatory system were critical for ensuring the sustained oscillations of insulin secretion. In fact the delay in insulin secretion and newly synthesized insulin become remote insulin is more critical than delay in hepatic glucose production. The simulations also reveal that the delay $\tau_1$ has to be extremely large ($>$

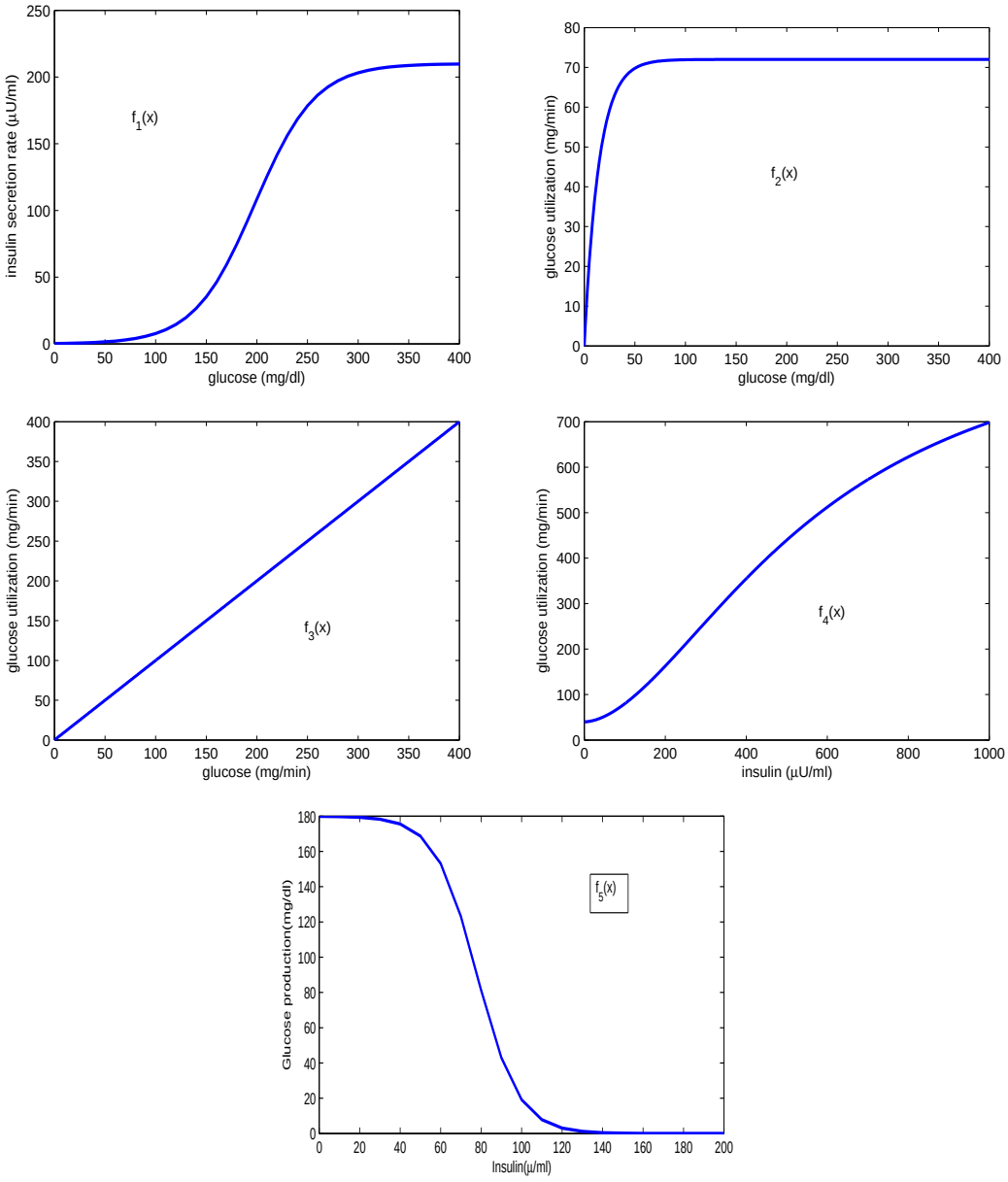


Figure 1.1: The shapes of the functions $f_1$, $f_2$, $f_3$, $f_4$ and $f_5$.

400 min) to produce any sustained oscillations, which clearly falls out of the normal physiological range. In 2007, Panunzi et al. [108] proposed a new, discrete single delay model (SDM) for the glucose - insulin regulatory system. The model was applicable to intravenous glucose tolerance test (IVGTTs) as well as to multiple injection and infusion schemes. The model was considered for the determination of insulin sensitivity from the IVGTT. In 2007, Wang et al. [73] modeled the insulin therapies using a delay differential equation model. The model was studied both quantitatively and qualitatively and the analytical results corresponds to ultradian insulin secretion oscillation. In 2009, Wang et al. [109] proposed a new model for insulin therapy for both types of diabetes - type 1 and type 2 in which the insulin degradation rate assumes Michaelis - Menten kinetics. The results showed that pancreatic insulin secretion can be mimic by exogenous insulin infusions.

Basal dose and bolus dose are the two types of insulin doses which simulate the insulin pulsatile secretion and ultradian secretion in an oscillatory manner, respectively [42]. Insulin analogue exists in hexameric, dimeric and monomeric states and hexameric form is the predominant state after the subcutaneous injection of soluble insulin. The hexameric form dissociates into dimeric and monomeric form which can penetrate the capillary membrane and can be absorbed into plasma [110].

In 2009, Li et al. [42] proposed the ODE mathematical models to stimulate the dynamics of rapid acting insulin analogue of the whole metabolic system. In 2009, Li and Johnson [111] considered the explicit delay $\tau > 0$ for transformation of hexameric to dimeric form and demonstrate the plasma insulin concentration profile and compared with the experimental data but the range of the delay term was not figured out.

## 1.8 The organization of thesis

The work presented in this thesis investigate ordinary differential equation mathematical model and delay differential equation mathematical model to explore various aspects in understanding the glucose -insulin dynamics for better management of the disease in affected population.

The thesis entitled “Mathematical modeling of diabetes” containing 8 chapters which are arranged in the form :

Chapter 1 : Chapter 1 is introductory in nature which gives a short review of the work done in the field till now about the physiology of diabetes through important mathematical equations. In this chapter, literature survey has been conducted which describe the types of diabetes, its diagnosis, risk factors, symptoms and treatment of disease. The basic mathematical model is discussed in the chapter which explains the glucose - insulin dynamics precisely and clearly. The purpose of this chapter is to provide the motivation behind the work carried out in the thesis.

Chapter 2 : In chapter 2, the effect of vitamin D on glucose - insulin dynamics of normal and diabetic people has been discussed. Maintenance of glucose concentration for diabetic people is very important and challenging. Though our body is a complex structure and it is difficult to find out one reason behind any abnormality, but it has been reported in the literature that when type 1 diabetics were tested they were found having vitamin D deficiency. Since then medical practitioner started considering vitamin D as a vital factor in diabetes. Vitamin D improves insulin sensitivity, decrease the insulin resistance and increases insulin secretion in our body. Hence an attempt has been made to analyze glucose - insulin concentration under the effect of vitamin D, by inducing parameters for relevant phenomena in mathematical model proposed by Bergman et al. [71]. The effect of vitamin D on dynamics of glucose - insulin regulatory system for diabetics has been discussed. The results of numerical simulations suggest that presence of vitamin D helps in regulating the glucose and insulin concentration in normal, T1DM and T2DM people. The work reported in the chapter has been accepted as a research paper entitled, "Dynamics and control of glucose - insulin regulatory system in diabetics using vitamin D".

Chapter 3 : Obese people have always been on a high risk of consistent raised glucose concentration. In this chapter, we analyze the effect of FFA together with obesity on the glucose - insulin dynamics of NIDD people through a mathematical model. Indexing HDMR method is proposed to get a polynomial based structure to measure the glucose level in a normal body. For this purpose data set of 90 normal people is used for the study. An attempt has been made to capture the glucose and insulin concentration levels for NIDD people having raised level of FFA and obesity through numerical simulation of the model. It has been observed from the simulation of the model that elevated level of plasma FFA inhibit glucose uptake, glucose utilization, decrease insulin sensitivity and increase insulin resistance in NIDD people as compared to normal people. The work

reported in the chapter has been published in two research papers entitled, "Study of the effects of FFA and obesity on diabetes through numerical simulation of the mathematical model" and "Application of I-HDMR in glucose - insulin dynamics".

Chapter 4 : Diabetes is not just a single disease but it brings many health related problems and hence affect our organs. Diabetes, if uncontrolled, can affect both the nervous system and circulatory system. In this chapter, an attempt has been made to capture the changes in glucose - insulin dynamics of central nervous system, liver and kidney which are severely affected by diabetes through mathematical modeling and simulation. The numerical simulation of the mathematical models explains that decreased volume of glucose and insulin space may be one of the possible reasons behind the prolonged raised glucose level in the central nervous system, liver and kidney of the diabetic people. The work reported in the chapter has been published as a research paper entitled, "Dynamical system for glucose - insulin space in different organs of diabetics".

Chapter 5 : The most widely used model in physiological research on the metabolism of glucose is "minimal model", which describes intra venous glucose tolerance test (IVGTT) experimental data well with the smallest set of identifiable and meaningful parameters [46, 71]. This model was used for the study of time delay occurs in insulin secretion by Li et al. Literature confirms that there is a delay occur in insulin action also but not much attention has been paid on the numerical range of this delay. This motivated us to further extend the model by incorporating the second time delay for insulin action. The extended model has been analyzed for stability and then numerical simulation is being carried out using Matlab 2012b. From the simulation results, we have concluded that sustained periodic oscillations are observed for both the time delays. Also, the simulation shows that after introducing the delay in insulin action, the delay length of insulin secretion proposed by Li et al. has been shortened, which can be proved important in maintaining the glucose level after delivery of insulin. The work reported in the chapter has been communicated in the paper entitled, "Study of two time delays in IVGTT glucose - insulin dynamical system".

Chapter 6 : In chapter 6, ranges of time delays in glucose - insulin dynamics of type 1 diabetics using artificial pancreas has been quantified. Time delay in insulin secretion, its absorption and action is a point of consideration in artificial pancreas as it may prove fatal in the extreme situation. The present mathematical model deals with two time delays out of which one occur in insulin secretion and second in its absorption and action. The

model assess the change in glucose - insulin dynamics after the induction of different values of these time delays in their respective range. Also, simulation is performed over the model to quantify the amount of two time delays to avoid diabetic comma, which has not been explored much. The work reported in the chapter has been published as a research paper entitled, "Quantitative analysis of time delays of glucose - insulin dynamics using artificial pancreas".

Chapter 7 : In chapter 7, we extend our attempt of modeling the closed - loop control of glucose concentration level by considering three time delays instead of two time delays for the proper functioning of artificial pancreas. The three delays which are taken in the present study are in insulin secretion, in inhibition in hepatic glucose production stimulated by insulin and in time taken by insulin to reach interstitial compartment to lower glucose level (i.e. glucose utilization delay or insulin action delay). Our analytical and numerical results shows that periodic and sustained oscillations of glucose and insulin concentration exists for type 1 diabetic people and delay in insulin secretion may be one of the major possible reason behind the occurrence of ultardian oscillations. We have also found out more feasible range of all three time delays from the simulation of present model, which may be proved very useful in better designing and improved functioning of artificial pancreas. The work reported in the chapter has been communicated in the paper entitled, "Quantitative and stability analysis of three time delays in glucose and insulin oscillations profile using artificial pancreas".

Chapter 8 : Management of type 1 diabetes and severe type 2 diabetes rely on exogenous insulin or insulin analogues to control raised blood glucose concentration. Insulin lispro and insulin aspart are rapid acting insulin analogue which have a shortened delay of onset and are easily absorbed in the bloodstream. Insulin analogue exists in hexameric, dimeric and monomeric states and hexameric form dissociates into dimeric and monomeric form which can penetrate the capillary membrane and can be absorbed into plasma. For different insulin analogues the transformation of hexameric state into dimeric and monomeric state takes different time which will be considered as first time delay in the present study. More the time it will take in this transformation, utilization of insulin in the body will be delayed which will be termed as second time delay. Therefore, an attempt has been made to find the ranges of these two time delays for the concoction of better rapid acting insulin analogues for better management of glucose and insulin concentration in diabetics through DDE model. The model has been analyzed for the

stability and then simulation has been carried out using Matlab 2012b. The profile of plasma insulin concentration level obtained from the simulation of the model are in good agreement with previously observed results for the quantified range of both the time delays. The work reported in the chapter has been communicated in the paper entitled, "Modeling the dynamics of plasma insulin concentration level of insulin analogues in type 1 diabetes using two explicit time delays".

# Chapter 2

# Dynamics and control of glucose - insulin dynamics using vitamin D

In this chapter,[1] the effect of vitamin D on glucose - insulin dynamics of normal and diabetic people has been discussed. Maintenance of glucose concentration for diabetic people is very important and challenging. Though our body is a complex structure and it is difficult to find out one reason behind any abnormality, but it has been reported in the literature that when type 1 diabetics were tested they were found having vitamin D deficiency. Since then medical practitioner started considering vitamin D as a vital factor in diabetes. It has been reported that vitamin D improves insulin sensitivity, decreases insulin resistance and increases insulin secretion in our body. Hence an attempt has been made to analyze glucose - insulin concentration under the effect of vitamin D, by inducing parameters for relevant phenomena in mathematical model. The effect of vitamin D on dynamics of glucose - insulin regulatory system for diabetics has been discussed. The results of numerical simulations proves that presence of vitamin D helps in overall regulation of the glucose and insulin concentration in normal, T1DM and T2DM people.

[1]The results of this chapter has been accepted as a research paper entitled "Dynamics and control of glucose - insulin regulatory system in diabetics using vitamin D" in *Mathematics in computer science.*

## 2.1 Introduction

Recent studies have shown that deficiency of vitamin D results in reduction of insulin secretion and thus in hyperglycemia, which leads to diabetes if it persists for long duration [112]. Optimal profile of insulin release for diabetics has been discussed by Nilam et al. [113]. Vitamin D deficiency was significantly associated with increased diastolic blood pressure, increased triglycerides levels and reduced high density lipoprotein cholesterol [114]. A review states evidence of strong link between abnormal glucose - insulin dynamics and deficiency of vitamin D [115]. Vitamin D also plays a role in the pathogenesis of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with a special emphasis on the direct effects of vitamin D on pancreatic cells [116]. Evidence from animal and human studies suggest that vitamin D may play an important role in modifying risk of T2DM and hypertension. Vitamin D has both direct and indirect effects on various mechanisms related to the pathophysiology of T2DM and hypertension, including pancreatic beta cell dysfunction and impaired insulin action [117]. Till the time, the casual link between vitamin D, T2DM and hypertension, remained to be determined. Most of the research have conducted in the United States on local People suffering from diabetes, either T1DM or T2DM. Insulin resistance is a risk factor for T2DM, and recent studies have shown a strong relation among insulin resistance and vitamin D deficiency.

Vitamin D is a powerful substance that our body usually produces on its own with the help of sunlight which enable our body to produce a powdery substance that converts into vitamin D. Vitamin D is obtained from exposure to sunlight, fortified foods and dietary supplements. When our skin is exposed to solar ultraviolet radiation (wavelength 290 - 350 $nm$), 7 - dehydrocholesterol is converted to previtamin ($D_3$) which is rapidly converted to cholecalciferol ($D_3$). Ergocaliferol ($D_2$), obtained from food along with cholecalciferol ($D_3$), is converted into 25 - hydroxyvitamin D in the presence of vitamin D - 25 - hydroxylase in the liver, which is the major circulating metabolite and used to determine a patient's vitamin D status [112, 114–117]. Almost all 25 - hydroxyvitamin D is bound to circulate DBP (vitamin D - binding protein) and is filtered by the kidneys and reabsorbed by the proximal convoluted tubules. The biologically inactive 25 - hydroxyvitamin D must be converted in the kidneys to active 1, 25 - hydroxyvitamin D by 1 - alpha hydroxylase. Finally, the active 1, 25 - hydroxyvitamin D can bind to VDR - RXR (vitamin D receptor - retinoic acid X - receptor complex) in the intestine, bone and

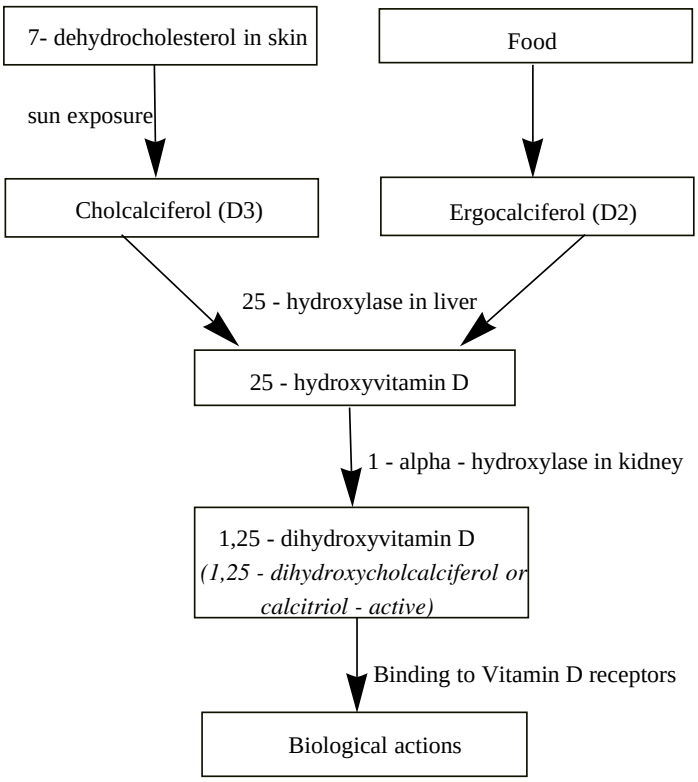


Figure 2.1: Mechanism of synthesis of Vitamin D.

parathyroid glands. VDRs are present in pancreatic $\beta$ cells and vitamin D is essential for normal insulin secretion [118]. ( See Figure 2.1 for the mechanism of synthesis of vitamin D).

Islet cell insulin secretion is reduced in vitamin D - deficient animals and can be corrected by vitamin D supplementation [118–120]. The impact of vitamin D deficiency on $\beta$ cell function seen in vitro and in vivo animal models has been matched by vitamin D studies in human volunteers undergoing hyperglycaemic clamps [121]. Epidemiological studies have shown that vitamin D deficiency might increase the incidence of autoimmune disease, such as T1DM genetically at risk individuals [122]. Vitamin D appears to affect exclusively the insulin response to glucose stimulation, while it does not appear to influence basal insulinemia [123, 124]. Vitamin D may have a beneficial effect on insulin action by stimulating the expression of insulin receptor thereby enhancing insulin

responsiveness for glucose transport [125]. Association between low vitamin D level and decreased insulin sensitivity has been reported in cross- sectional studies [121, 125–131]. Based on available data from recent studies, vitamin D supplementation is considered to be a potential and inexpensive therapy, which not only decrease the risk, but also improves glycemic parameters in T2DM [132]. The positive effects of vitamin D on insulin secretion and sensitivity and secondary its action on inflammation can be seen through available clinical and epidemiological data [133].

American Academy of Pediatrics recommended to start 400IU soon after birth and continuing through childhood and adolescence [134]. Canadian cancer society recommended a daily dose of 1000IU per day for adults [134]. Since literature shows that vitamin D increases insulin sensitivity [125], decreases insulin resistance [132] and improves insulin action [125] in the body [135], therefore parameters have been introduced for these three phenomenon in minimal model [37]. These parameters will throw an insight to estimate the effects of different dosage of vitamin D in normal, NIDD and IDD. Stability analysis is carried out for the proposed model which confirms the positive and bounded solution of the model.

## 2.2 Mathematical model

Glucose is stored in liver and peripheral tissues, including muscle tissues. Glucose utilization process is controlled by insulin, which enhances glucose uptake. Also, an increase in glucose concentration augments pancreatic release of insulin. This feedback loop leads to difficulties in interpretation of test results. To overcome this problem, the whole system is decomposed into two independent components [43] : (i) the effect of insulin to accelerate glucose uptake and (ii) the effect of glucose to enhance insulin secretion.

The two subsystems have been described in mathematical terms and the mathematical model given by Bergman et al. [71] is given as :

$$\frac{dG(t)}{dt} = -X(t)G(t) - p_1(G(t) - G_b); G(0) = G_0 \tag{2.2.1}$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b); X(0) = X_0 \tag{2.2.2}$$

$$\frac{dI(t)}{dt} = p_5(G(t) - G_c)^+t - p_4(I(t) - I_b); I(0) = I_0 \tag{2.2.3}$$

where, $G(t)$ $[mg/dl]$ represents glucose concentration at time t, $X(t)$ $[min^{-1}]$ represents remote insulin concentration at time t, $I(t)$ $[\mu U/ml]$ represents the interstitial insulin at time t, $G_c$ $[mg/dl]$ represents the threshold level of glucose above which the endogenous insulin secretion will be stimulated, $G_b$ $[mg/dl]$ represents the basal glucose level and $I_b$ $[\mu U/ml]$ denotes the basal insulin level. The parameters $p_i$ $(p_i > 0)$, i = 1,2,3,4,5 are defined in Table 2.1 .

To model the effects of vitamin D on glucose - insulin dynamics, we take into account four major factors [135]: (i) vitamin D help the cells in glucose uptake i.e. it increases glucose effectiveness (ii) it improves insulin sensitivity of the body (iii) insulin secretion is increased due to vitamin D (iv) it decreases insulin resistance.

To observe the changes in glucose - insulin dynamics due to the above said effects of vitamin D, four new parameters $v_j$ $(v_j > 0)$, j = 1,2,3,4 have been introduced in the model (2.2.1 - 2.2.3) for which explanation is as follows:

- $v_1$ $[min^{-1}]$ represents effect of vitamin D on muscles and fat cells to utilize glucose so it is incorporated with parameter $p_1$ which represents glucose effectiveness.

- $v_2$ deals with the effect of vitamin D on muscles and fat cells to increase insulin sensitivity, hence incorporated in the term containing $X(t)G(t)$.

- Since vitamin D affects pancreas to increase the secretion of insulin, hence $v_3$ $[ml(\mu\text{U})^{-1}min^{-2}]$ is combined with $p_3$ which explains the same phenomena.

- $v_4$ $[min^{-1}]$ represents effect of vitamin D in increasing utilization of the insulin, therefore combined with parameter $p_4$.

After incorporating the above new parameters in the minimal model, the extended model is as follows :

$$\frac{dG(t)}{dt} = -v_2X(t)G(t) - p_1v_1(G(t) - G_b); G(0) = G_0 \quad (2.2.4)$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3v_3(I(t) - I_b); X(0) = X_0 \quad (2.2.5)$$

$$\frac{dI(t)}{dt} = p_5(G(t) - G_c)^+t - p_4v_4(I(t) - I_b); I(0) = I_0 + I_b \quad (2.2.6)$$

where

$$(G(t)-G_c)^+t=\begin{cases}(G(t)-G_c)t, if G(t)>G_c\\ 0, if G(t)\leq G_c\end{cases}$$

## 2.3 Positive and bounded solutions of the model

**Proposition 1.** *: Let $(G(t),X(t),I(t))$ be a solution of system (2.2.4-2.2.6) with $G(0) = G_0 > 0$, $X(0) = X_0 > 0$ and $I(0) = I_0 > 0$, then $G(t) > 0$, $X(t) > 0$, $I(t) > 0$ and also bounded above for all $t > 0$.*

*Proof.* **(i)** $G(t)$ **is positive.**
Eqn.(2.2.4) can be written as

$$\frac{dG(t)}{dt}+[v_2X(t)+p_1v_1]G(t) = p_1v_1G_b$$

The solution is given by

$$G(t) = \frac{p_1v_1G_b\int_0^t f(u)du+G_0}{f(t)} \tag{2.3.1}$$

where

$$f(t) = e^{\int_0^t[v_2X(s)+p_1v_1]ds}>0$$

Since $p_1 > 0$, $v_1 > 0$, $G_b > 0$, $G_0 > 0$ and $f(u) > 0$, therefore right hand side of the eqn.(2.3.1) is positive. Hence $G(t) > 0$.

**(ii)** $I(t)$ **is positive.**
Now eqn.(2.2.6) implies

$$\frac{dI(t)}{dt} = p_5(G(t)-G_c)^+t-p_4v_4(I(t)-I_b)$$

$$\frac{dI(t)}{dt}+p_4v_4(I(t)-I_b) = p_5(G(t)-G_c)^+t$$

The solution is given by

$$I(t) = I_b + I_0 e^{-p_4 v_4 t} + \int_0^t p_5 (G(u) - G_c)^+ e^{-p_4 v_4 (t-u)} u du \tag{2.3.2}$$

Since the integral term in the right hand side of the eqn.(2.3.2) is non-negative, therefore,

$$I(t) \geq I_b + I_0 e^{-p_4 v_4 t}, \forall t \geq 0 \tag{2.3.3}$$

which implies

$$I(t) \geq I_b > 0, \forall t \geq 0 \tag{2.3.4}$$

Hence, at any time the level of $I(t)$ will never be lesser than $I_b$.

**(iii)** $X(t)$ **is positive.**

Eqn.(2.2.5) can be written as

$$\frac{dX(t)}{dt} + p_2 X(t) \quad = \quad p_3 v_3 (I(t) - I_b)$$

The solution is given by

$$X(t) - X_0 e^{-p_2 t} = \int_0^t p_3 v_3 e^{-p_2 (t-u)} (I(u) - I_b) du$$

From eqn.(2.3.3),

$$I(t) - I_b \geq I_0 e^{-p_4 v_4 t}, \forall t \geq 0$$

After solving

$$X(t) - X_0 e^{-p_2 t} \geq \begin{cases} \frac{I_0 p_3 v_3 (e^{-p_4 v_4 t} - e^{-p_2 t})}{p_2 - p_4 v_4}, \text{if } p_2 \neq p_4 v_4 \\ I_0 p_3 v_3 e^{-p_2 t} t, \text{if } p_2 = p_4 v_4 \end{cases}$$

Since the right hand side of the above expression is non-negative, therefore

$$X(t) \geq X_0 e^{-p_2 t} > 0, \forall t \geq 0 \tag{2.3.5}$$

Hence, $X(t)$ always exceeds than $X_0$ for all time $t$.

**(iv)** $G(t)$ **is bounded.**

From eqn.(2.2.4),

$$\frac{dG(t)}{dt} = -v_2 X(t) G(t) - p_1 v_1 (G(t) - G_b), G(0) = G_0$$

Therefore,

$$\frac{dG(t)}{dt} \leq -p_1 v_1 (G(t) - G_b)$$

Let $P(t) = G(t) - G_b$. Then,

$$\frac{dP}{dt} + p_1 v_1 P \leq 0$$

which implies

$$\begin{aligned} P(t) &\leq P(0) e^{-p_1 v_1 t}, \forall t > 0 \\ G(t) - G_b &\leq (G(0) - G_b) e^{-p_1 v_1 t} \\ &< (G(0) - G_b), \forall t > 0 \end{aligned}$$

which implies

$$G(t) < G(0), \forall t > 0.$$

Since $G(t) > 0$ and $G(t) \leq G(0)$, this implies $G(t)$ is bounded.

Hence we can conclude that all the solutions $G(t)$, $X(t)$, $I(t)$ are positive, $G(t)$ is bounded (hence remain finite for all $t \geq 0$). The boundedness of X(t) and I(t) will be discussed in the next section. □

## 2.4 Stability analysis of mathematical model

In this section, stability analysis of the system (2.2.4-2.2.6) has been discussed.

**Theorem 2.4.1.** *(Comparison Theorem [136]): Let $\phi_{1,i}(t)$ be a solution of the ordinary differential equations*

$$\frac{dx_i}{dt} = f_i(x,t), i = 1,2.....n$$

*and $\phi_{2,i}(t)$ be a solution of a second system*

$$\frac{dx_i}{dt} = g_i(x,t), i = 1,2.....n$$

*satisfying the same initial conditions $\phi_{1,i}(t_0) = \phi_{2,i}(t_0) = x_{i,0}$, i = 1,2....n, over the interval $a \leq t \leq b$. $f_i, g_i$ are defined on $U \times [a,b]$ and $U \subset R^n$ is an open domain. Hence $f_i, g_i : U \times [a,b] \to R$ are continuous functions such that $f_i < g_i$ [$f_i > g_i$] on U. Then, $\phi_{1,i}(t) \leq \phi_{2,i}(t)[\phi_{1,i}(t) \geq \phi_{2,i}(t)]$ for all t in the interval [a, b].*

To check the stability of the model at the equilibrium point, $G_c = G_b$ (Preposition I.5, [48]) is taken in the eqn.(2.2.6) of the model. Let us consider the model, given by eqns. (2.2.4–2.2.6).

For conciseness of notation, define

$g(t) = (G(t) - G_b), x(t) = S(t), i(t) = (I(t) - I_b), q_1 = p_1v_1; q_2 = v_2G_b; q_3 = p_3v_3; q_4 = p_4v_4$

We may write system (2.2.4–2.2.6) in the form:

$$\frac{dg(t)}{dt} = -v_2x(t)g(t) - q_2x(t) - q_1g(t) \tag{2.4.1}$$

$$\frac{dx(t)}{dt} = -p_2x(t) + q_3i(t) \tag{2.4.2}$$

$$\frac{di(t)}{dt} = p_5H(g(t))t - q_4i(t) \tag{2.4.3}$$

Where $H \equiv H(g(t))$ is the unit step function :

$$H(g(t)) = \begin{cases} 0, \text{if } g(t) < 0 \\ 1, \text{if } g(t) > 0 \end{cases} \tag{2.4.4}$$

From the structure of the system, we note that, since the first term on the right - hand side of (2.4.3) is non - zero only when $g > 0$, any instability would arise only if g were maintained above zero i.e., $G > G_b$ for all $t \geq 0$.

Using the Comparison Theorem 2.4.1, we may establish certain inequalities in the solutions to (2.2.4–2.2.6) that will enable us to determine the stability of the system.

Suppose $g(0) < 0$ $(i.e., G(0) < G_b)$. Then H = 0, and from equations (2.4.1–2.4.3) we see that $g(t)$, $x(t)$ and $i(t)$ decay to zero, and hence the system is stable for $G(0) < G_b$.

From the eqn.(2.4.1), and using the Comparison Theorem 2.4.1 (where H = 1), we have :

$$\begin{aligned} \frac{dg}{dt} &= -q_1 g - q_2 x - v_2 g x \\ &\leq -q_1 g - q_2 x_{min} - v_2 g x_{min} \\ &= -Qg - q_2 x_{min}, \end{aligned}$$

where $Q = q_1 + v_2 x_{min}$

The solution is given by

$$g(t) \leq g(0)e^{-Qt} - \frac{q_2 x_{min}}{Q}(1 - e^{-Qt}) \tag{2.4.5}$$

and

$$\begin{aligned} \frac{dg}{dt} &\leq -Qg(0)e^{-Qt} - q_2 x_{min} e^{-Qt} \\ &< 0, \forall t \geq 0 \end{aligned}$$

which is negative.

At $t \to \infty$, eqn.(2.4.5) $g(0)e^{-Qt} - \frac{q_2 x_{min}}{Q}(1 - e^{-Qt})$ becomes $\frac{-q_2 x_{min}}{Q} < 0$

From this, we conclude that, if $g(0) > 0$ (i.e.,$G(0) > G_b$), the right-hand-side of (2.4.5) decreases to zero after a finite time T, so that g(t) passes through 0 after a time $T_G$, where $T_G \leq T$. Also, at $t = T_G$, H becomes zero.

From eqn.(2.4.3),

$$\begin{aligned}\frac{di}{dt} &= p_5 Hgt - q_4 i \\ &= p_5 H(g(t))g(t)t - q_4 i\end{aligned}$$

The solution is given by

$$i(t) = i(0)e^{-q_4 t} + p_5 e^{-q_4 t}\int_0^t H(g(s))sg(s)ds \tag{2.4.6}$$

Now, the integral on the right in (2.4.6) is bounded above by

$$\int_0^{T_G} sg(s)ds < \infty$$

which implies $i(t) \leq i_{max}$ i.e. $i(t)$ is bounded above for $t \geq 0$. Also from eqn.(2.4.6), $i(t) \geq i_{min}$ for some finite $i_{min}$ i.e. $i(t)$ is bounded below for all $t \geq 0$. Hence $i(t)$ is bounded.

Similarly, using the eqn.(2.4.2) and Theorem 2.4.1, we have

$$\frac{dx}{dt} = -p_2 x + q_3 i \leq -p_2 x + q_3 i_{max}$$

The solution is given by

$$\begin{aligned}x(t) &\leq x(0)e^{-p_2 t} + \frac{q_3 i_{max}}{p_2}(1 - e^{-p_2 t}) \\ &\leq x(0) + \frac{q_3 i_{max}}{p_2} \\ &\equiv x_{max}\end{aligned}$$

implies $x(t)$ is bounded above.

Now, from the eqn.(2.4.2), and using the Comparison Theorem 2.4.1,

$$\frac{dx}{dt} = -p_2 x + q_3 i \geq -p_2 x + q_3 i_{min}$$

The solution is given by

$$x(t) \geq x(0)e^{-p_2 t} + \frac{q_3 i_{min}}{p_2}(1 - e^{-p_2 t}) \tag{2.4.7}$$

which implies $x(t)$ is bounded below for $t \geq 0$.
Hence, $x(t)$ is bounded.

Hence we can say that if $G(0) < G_b$, then the system (2.2.4–2.2.6) is stable and if $G(0) > G_b$, then the solutions of (2.2.4–2.2.6) are bounded for all $t \geq 0$.

## 2.5 Analysis of model

Behavior of the model will be discussed at the equilibrium point, as it is necessary to analyze a mathematical model in the neighborhood of equilibrium point for its stability. Therefore, to determine the effect of vitamin D on glucose disappearance, and insulin sensitivity after a glucose bolus, a modification has been introduced in the model (2.2.4–2.2.6) to include a glucose source. The modified model is given as:

$$\begin{aligned}
\frac{dG(t)}{dt} &= -v_2 X(t)G(t) - p_1 v_1 (G(t) - G_b) + G_{in}(t), \\
\frac{dX(t)}{dt} &= -p_2 X(t) + p_3 v_3 (I(t) - I_b), \\
\frac{dI(t)}{dt} &= p_5 (G(t) - G_c)^{+} t - p_4 v_4 (I(t) - I_b),
\end{aligned}$$

where $G_{in}(t)$ is the glucose infusion rate per unit of volume at time $t$ which is assumed to be constant for the stability analysis.

### 2.5.1 Equilibrium condition

At equilibrium $(G, X, I) = (G^*, X^*, I^*)$, we have

$$X^* = \frac{p_3 v_3 (I^* - I_b)}{p_2}$$

$$G^*_{in} = v_2 X^* G^* + p_1 v_1 (G^* - G_b)$$

where $G^*_{in}$ represents the constant rate of injection of glucose

$$G^* = \frac{p_1 v_1 G_b + G^*_{in}}{\frac{v_2 p_3 v_3 (I^* - I_b)}{p_2} + p_1 v_1}$$

Define $I = I^* - I_b$, then the function $G^*(I)$ is given by

$$G^*(I) = \frac{p_1 v_1 G_b + G^*_{in}}{\frac{v_2 p_3 v_3 I}{p_2} + p_1 v_1} \tag{2.5.1}$$

We see that $G^*$ is a decreasing function of I and

$$\lim_{I \to 0} G^*(I) = G_b + \frac{G^*_{in}}{p_1 v_1} \tag{2.5.2}$$

and

$$\lim_{I \to \infty} G^*(I) = 0 \tag{2.5.3}$$

Eqn.(2.5.2) shows that in absence of insulin, the presence of vitamin D does not lower the glucose concentration, and a risk of hyperglycaemia may occur in case of IDD and NIDD.

On the other hand eqn.(2.5.3) also does not lead to hypoglycemia as the total required amount of insulin is given by an external source is finite.

## 2.6 Numerical simulation and results

The model (2.2.4–2.2.6) is numerically simulated by using Matlab 2012b. To carry the numerical simulation, the values of parameters $p_i$, i = 1,2,3,4,5 are given in Table 2.2, Table 2.3 and Table 2.4. $G_b$ [$\sim 100\ mg/dl$] [137], $G_c$ [$\sim 100\ mg/dl$] [137] are taken for the numerical simulation of the model. According to the literature, vitamin D helps to regulate the glucose - insulin regulatory system. Hence the values of the parameters of vitamin D are assumed according to their compatibility with other parameters $(p_1, p_2, p_3, p_4, p_5)$ and their effect on different mechanism. The new parameters $v_i$, i = 1,2,3,4 will take two set of values corresponding to varying dosage of vitamin D. The values of the new

parameters $v_i$, i = 1,2,3,4 which are introduced to assess the effect of vitamin D on glucose - insulin dynamics are given in the Table 2.2, Table 2.3 and Table 2.4. Then comparisons were made in the glucose - insulin dynamics corresponding to these different set of values. Graphs are plotted for each case (normal, NIDD, and IDD) to capture the effect of vitamin D in lowering the glucose level near to basal value.

### 2.6.1 Normal case

In normal case, $\beta$ cells produces enough insulin and utilized properly in the body. Therefore, $I_e \geq 0$ and $I_b \geq 0$ are considered for numerical simulation. For the glucose - insulin dynamics, the values of parameters $p_1, p_4, G_0, I_0$ are taken from the Bergman et al. paper [71]. The values of parameters $p_2, p_3, p_5$ were considered from the average normal values in humans. The values of the parameters for the normal case are given in Table 2.2. Vitamin D is crucial for our metabolism and stamina but excess of vitamin D can be proved fatal also. It can be seen in Figure 2.2 that in normal case excess of vitamin D can bring the glucose level near to 50 $mg/dl$ which lead to hypoglycemia. It is also reported that excess intake of vitamin D may lead to various problems in metabolism which is also verified from Figure 2.2. Therefore, it is suggested that external dose of vitamin D should be consumed under the prescription of medical practitioner.

### 2.6.2 NIDD (Non insulin dependent diabetes) case

In NIDD case, $\beta$ cells produces enough insulin but not utilized by the body properly due to insulin resistance of the body. Therefore, $I_e \geq 0$ and $I_b \geq 0$ are considered for numerical simulation. The values of the parameters ($p_1$ to $I_0$) are considered from the paper [72]. Lower value of glucose effectiveness ($S_G$) and insulin sensitivity ($S_I$) are the main reason behind the consistent raised glucose concentration. Therefore, $S_G$ and $S_I$ are lower taken than the normal case [72]. The parameter $p_2$ has less effect on original minimal model so we take the value of $p_2$ same as in the normal case, $p_3$ is derived from $p_2.S_I$, where $S_I = (p_3/p_2)$ was obtained by parametric estimation for the NIDD data with basal values ($G_b$ and $I_b$) and peak glucose values comparable to the normal data. The parameter $p_5$ is taken as 10% of the $p_5$ value for the normal case. The values of the parameters for the NIDD case are given in Table 2.3. Dose of vitamin D helps to lower the glucose concentration from 175 $mg/dl$ to 150 $mg/dl$ that can be seen in Figure 2.3.

Since 150 $mg/dl$ is still not in physiological range, reason behind is that for numerical simulation sole effect of vitamin D is considered without any medical treatment.

### 2.6.3 IDD (Insulin dependent diabetes) case

In IDD case, either no insulin is secreted by $\beta$ cells or little amount is secreted which is not utilized properly by the body. Therefore, $I_e = 0$ and $I_b = 0$ are considered. Glucose - insulin is completely disturbed because of which $S_G$ and $S_I$ are further decreased and hence less value of $S_G$ and $S_I$ are taken as compared to normal case. The values of the parameters ($p_1$ to $I_0$) are considered from the paper [138]. Value of $p_2$ is taken within the normal range and the parameters $p_4$, $I_0$ were obtained by linear regression of log transformed IDD data. The value of $p_5$ is taken as very small, as the IDD cases have lower response to pancreas [85, 138]. The values of the parameters for the IDD case are given in Table 2.4. Dose of vitamin D helps to lower the glucose concentration from 180 $mg/dl$ to 160 $mg/dl$ that can be seen in Figure 2.4. This amount of glucose concentration is still higher than the normal value, but it is proved that even without medical treatment, vitamin D can be helpful in lowering down the glucose concentration.

## 2.7 Conclusion and future scope

A mathematical model containing the effect of vitamin D on plasma glucose - insulin dynamics was developed. The principle goal was to extend the Bergman Minimal model [71] by adding suitable parameters to capture the physiological phenomenon induced by vitamin D. The added terms in the proposed model are linear and as well as non linear in nature, and thus we tried to maintain the simplistic approach of the original model. The model captured the effect of vitamin D on glucose - insulin dynamics in which it is confirmed that the important parameters which determine insulin sensitivity, pancreatic responsivity, and glucose effectiveness have a significant impact on the model.

People belonging to poor families, having low income and suffering from diabetes all over the world are struggling to get just the necessary amount of insulin, and it is very difficult for them to fight with the disease as the treatment involves insulin therapy which is very costly. This motivates us to find an approachable way to control the disease and make us to focus on the vitamin D which not only increases the insulin sensitivity but also decreases insulin resistance and increases inulin secretin in our body. To the best

of our knowledge, it is the first model which incorporates the effects of vitamin D via parameters. This illustration confirms that we should include a dose of vitamin D in our daily routine, especially for the persons who are involved in the industrial sector and do indoor jobs. Each individual should adjust the dosage of vitamin D according to his/her situation.

In future, we will try to develop a mathematical model to find the exact amount of vitamin D needed to be given to the diabetic patients, according to the severity of the disease and lifestyle. Such model will be of great help to the diabetic community which is increasing very rapidly.

| Parameters | Units | Explanation | References |
|---|---|---|---|
| $p_1$ | $min^{-1}$ | represents glucose effectiveness | [37] |
| $p_2$ | $min^{-1}$ | fractional rate of insulin appearance in interstitial compartment | [37] |
| $p_3$ | $(min^{-2})(\mu\text{U/ml})^{-1}$ | contribution of plasma insulin to the remote compartment from interstitial compartment | [37] |
| $p_4$ | $min^{-1}$ | clearance of plasma insulin | [37] |
| $p_5$ | $(min^{-2})(\mu\text{U/ml})(mg/dl)^{-1}$ | degree by which glucose exceeds threshold or baseline glucose level | [37] |

Table 2.1: Explanation of the parameters of model.

| Para | Normal | With varying amount of Vit. D | With varying amount of Vit. D | Ref |
|---|---|---|---|---|
| $p_1$ | 0.0399 | 0.0399 | 0.0399e | [71] |
| $p_2$ | 0.0200 | 0.0200 | 0.0200 | [71] |
| $p_3$ | 0.00004 | 0.00004 | 0.00004 | [71] |
| $p_4$ | 0.257 | 0.257 | 0.257 | [71] |
| $p_5$ | 0.001 | 0.001 | 0.001 | [71] |
| $G_0$ | 287 | 287 | 287 | [71] |
| $I_0$ | 351 | 351 | 351 | [71] |
| $v_1$ | - | 0.30 | 0.25 | - |
| $v_2$ | - | 0.75 | 0.75 | - |
| $v_3$ | - | 0.95 | 0.90 | - |
| $v_4$ | - | 0.60 | 0.50 | - |

Table 2.2: Values of parameters for normal case.

| Para | NIDD | With varying amount of Vit. D | With varying amount of Vit. D | Ref |
|---|---|---|---|---|
| $p_1$ | 0.014 | 0.014 | 0.014 | [72] |
| $p_2$ | 0.0200 | 0.0200 | 0.0200 | [72] |
| $p_3$ | 0.00000128 | 0.00000128 | 0.00000128 | [72] |
| $p_4$ | 0.129 | 0.129 | 0.129 | [72] |
| $p_5$ | 0.0001 | 0.0001 | 0.0001 | [72] |
| $G_0$ | 438 | 438 | 438 | [72] |
| $I_0$ | 1322 | 1322 | 1322 | [72] |
| $v_1$ | - | 0.20 | 0.15 | - |
| $v_2$ | - | 0.85 | 0.85 | - |
| $v_3$ | - | 0.90 | 0.85 | - |
| $v_4$ | - | 0.55 | 0.35 | - |

Table 2.3: Values of parameters for NIDD case.

| Para | IDD | With varying amount of Vit. D | With varying amount of Vit. D | Ref |
|---|---|---|---|---|
| $p_1$ | 0.016 | 0.016 | 0.016 | [138] |
| $p_2$ | 0.043 | 0.043 | 0.043 | [138] |
| $p_3$ | 0.0000038 | 0.0000038 | 0.0000038 | [138] |
| $p_4$ | 0.02676 | 0.02676 | 0.02676 | [138] |
| $p_5$ | 0.0000001 | 0.0000001 | 0.0000001 | [138] |
| $G_0$ | 300 | 300 | 300 | [138] |
| $I_0$ | 51 | 51 | 51 | [138] |
| $v_1$ | - | 0.12 | 0.10 | - |
| $v_2$ | - | 0.90 | 0.90 | - |
| $v_3$ | - | 0.95 | 0.90 | - |
| $v_4$ | - | 0.48 | 0.40 | - |

Table 2.4: Values of parameters for IDD case.

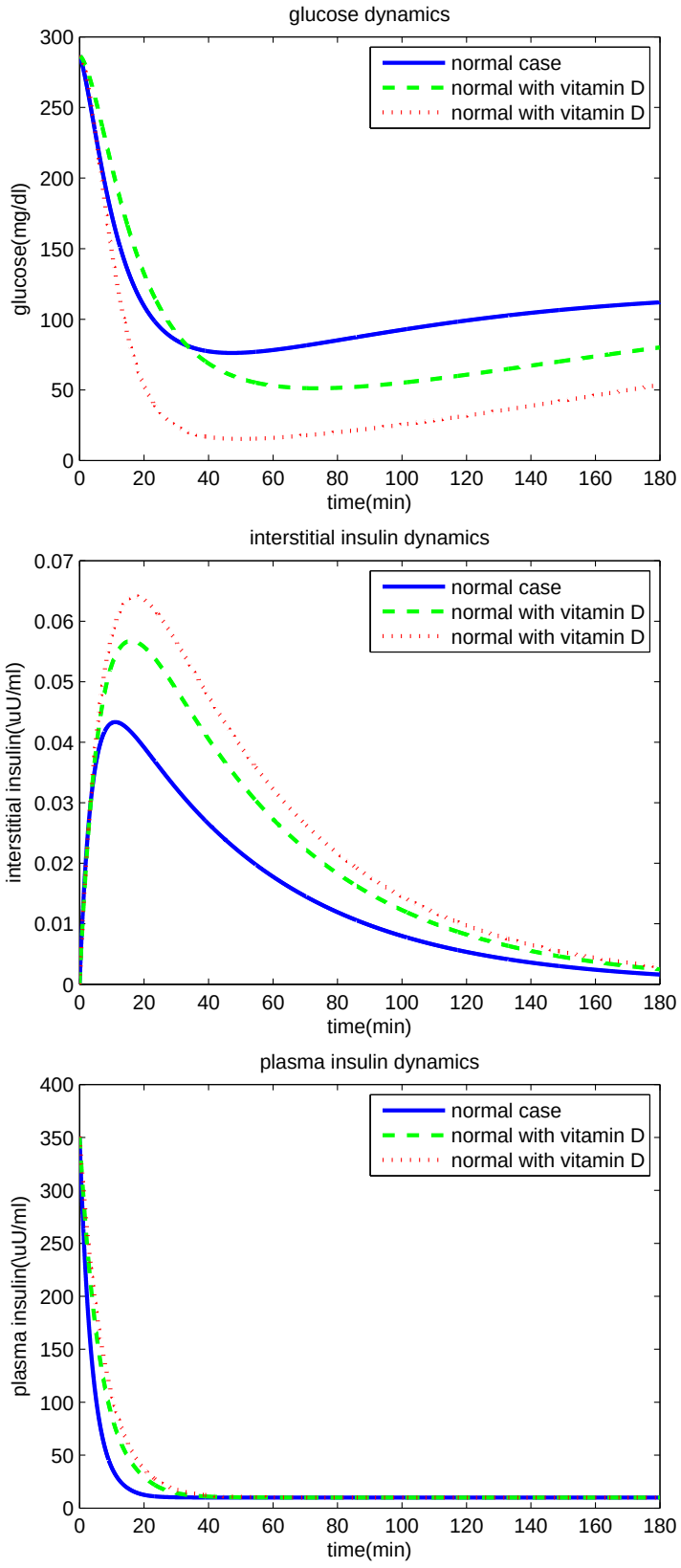


Figure 2.2: Comparison of glucose concentration level of normal people for three different cases (one without vitamin D and two with varying amount of vitamin D) is shown in fig (a). Interstitial insulin peaks are compared and can be seen in fig (b). Plasma insulin concentration level for all three cases are shown in fig (c).

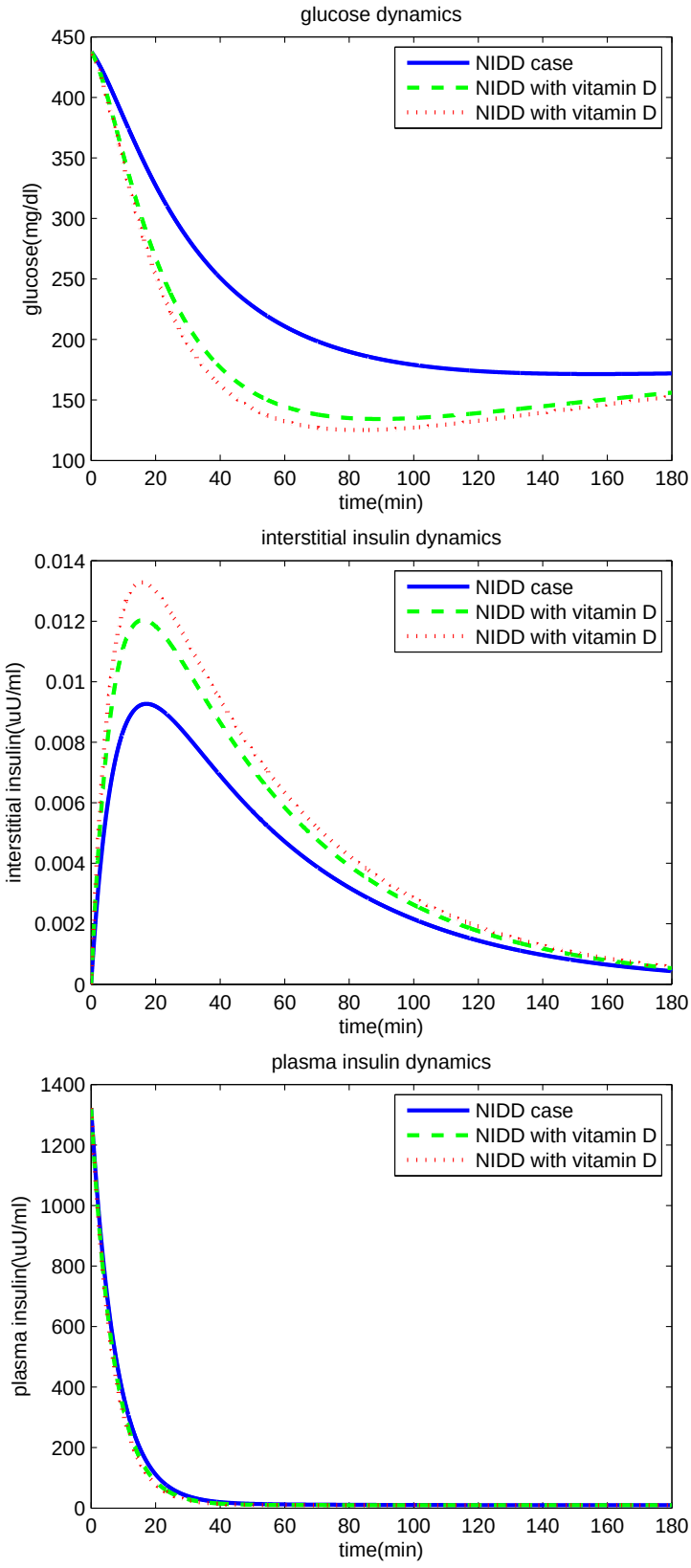


Figure 2.3: Comparison of glucose concentration level of NIDD people for three different cases (one without vitamin D and two with varying amount of vitamin D) is shown in fig (a). Interstitial insulin peaks are compared and can be seen in fig (b). Plasma insulin concentration level for all three cases can be seen in fig (c).

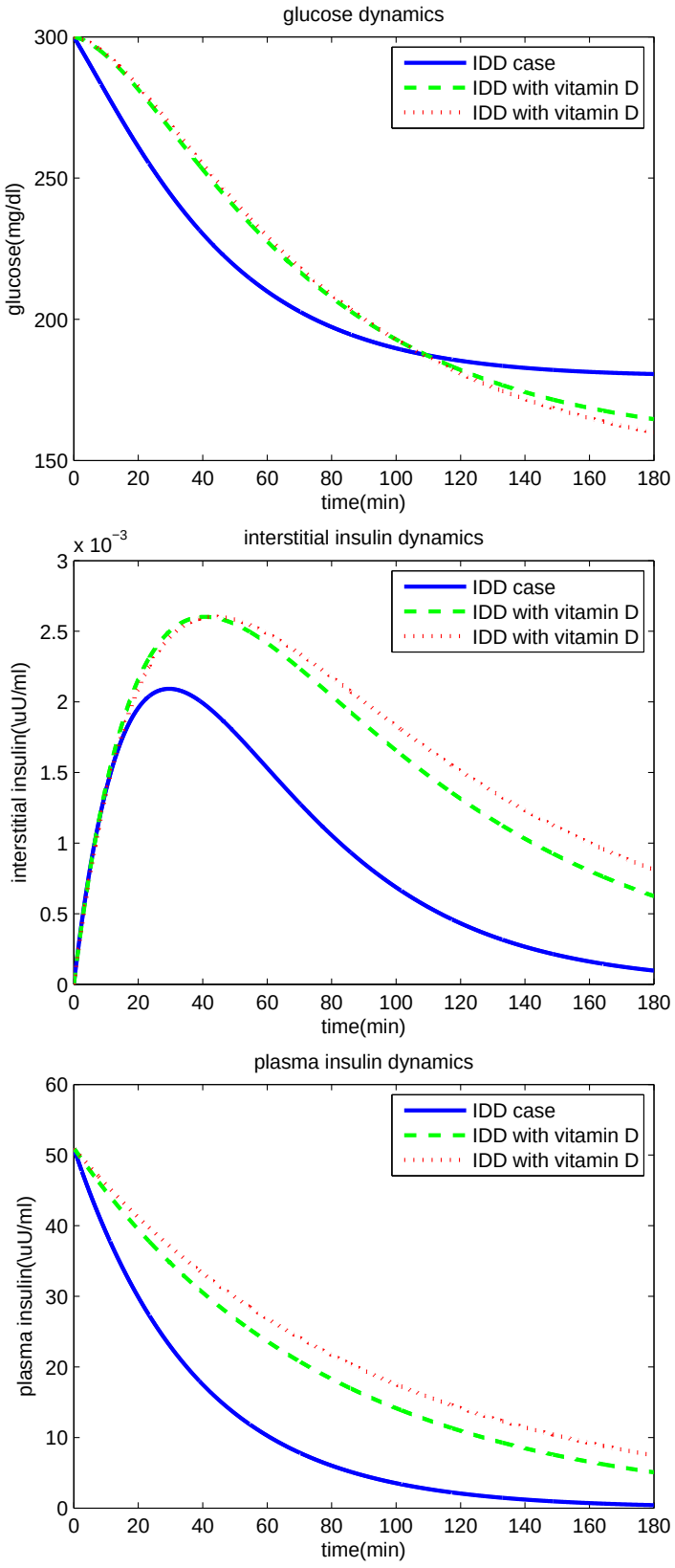


Figure 2.4: Comparison of glucose concentration level of IDD people for three different cases (one without vitamin D and two with varying amount of vitamin D) is shown in fig (a). Peak of interstitial insulin for all the cases are compared and can be seen in fig (b). Plasma insulin concentration level for all three cases can be seen in fig (c).

# Chapter 3

# Effects of FFA and obesity on diabetes

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Obese people have always been on a high risk of consistent raised glucose concentration. The aim of this chapter,[1] is to analyze the effect of FFA together with obesity on the glucose - insulin dynamics of NIDD people through a mathematical model. An attempt has been made to capture the glucose and insulin concentration levels for NIDD people having raised level of FFA and obesity through numerical simulation of the model. It has been observed from the simulation of the model that elevated level of plasma FFA inhibit glucose uptake, glucose utilization, decrease insulin sensitivity and increase insulin resistance in NIDD people as compared to normal people. Also Indexing HDMR method is proposed to get a polynomial based structure to measure the glucose level in a normal body. For this purpose a data set of 90 normal people is used for the study.

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[1]The results of this chapter have been published in two research papers entitled "Study of the effects of FFA and obesity on diabetes through numerical simulation of the mathematical model" in *Journal of mathematics and system science*, **5** (2015) doi: 10.17265/2159-5291/2015.06.004 and "Application of I-HDMR in glucose - insulin dynamics" in *International conference on mathematical sciences* (2014).

## 3.1 Introduction

Obesity has been a growing health problem in the first half of the 20th century. The earliest identified discussions on the need for an organisation addressing obesity took place in Great Britain in 1961. The first meeting of the "Obesity Association" was held in London in 1967. In the 1970s, the field of obesity research began to blossom in Europe. If 70s was a decade of foundation laying, 80s was a time of consolidation and construction, witnessing the birth of the International Association for the Study of Obesity (IASO). The 90s was the decade of maturation, and several important developments increased IASO's prominence on the international scene. The 6th, 7th and 8th ICOs were held respectively in Kobe, Japan in 1990; Toronto, Canada in 1994; and Paris, France in 1998, with attendance that reached 3000. In August 2002, following an extensive strategic review process, IASO and IOTF merged to become a single entity capable of confronting the challenges posed by the global obesity epidemic in the 21st century. The newly incorporated IASO became a registered NGO in the WHO system when the IOTF's work with the WHO was formalised [139].

Insulin resistance can have many causes [140], but so far obesity is considered to be the major cause in the developed countries. The exact reason, how obesity cause insulin resistance in not fully known so far. But in US, obesity is approaching epidemic proportion where more than 2/3 of all adults are either overweight or obese [141].

Obesity is associated with elevated plasma free fatty acids (FFA) levels, with insulin resistance and hyperinsulinemia, two important cardiovascular risk factors for diabetes [142]. Obesity has a great impact on the glucose effectiveness and insulin sensitivity of any human body system. Infact Hofman et al. [143] found that insulin sensitivity was approximated 80 % lower in obese horses than in non obese horses, an effect similar to reported 76 % reduction in insulin sensitivity in obese vs. non - weight humans [144]. Lowering of plasma FFA levels would improve insulin resistance, hyperinsulinemia and glucose tolerance in obese non diabetic and diabetic subjects.

Free Fatty Acids (FFA) are one of the outcomes of the food digestion process and these acids are described as "free" because they are freely transported in the bloodstream without the help of any other carrier and source [145]. Fatty acids are called essential fatty acids as they are required by the human body but cannot be provided in sufficient quantity by other substrates, hence must be obtained from food [145]. The relationship between

obesity, FFA and type 2 diabetes is explained in Figure 3.1. FFA not only increase

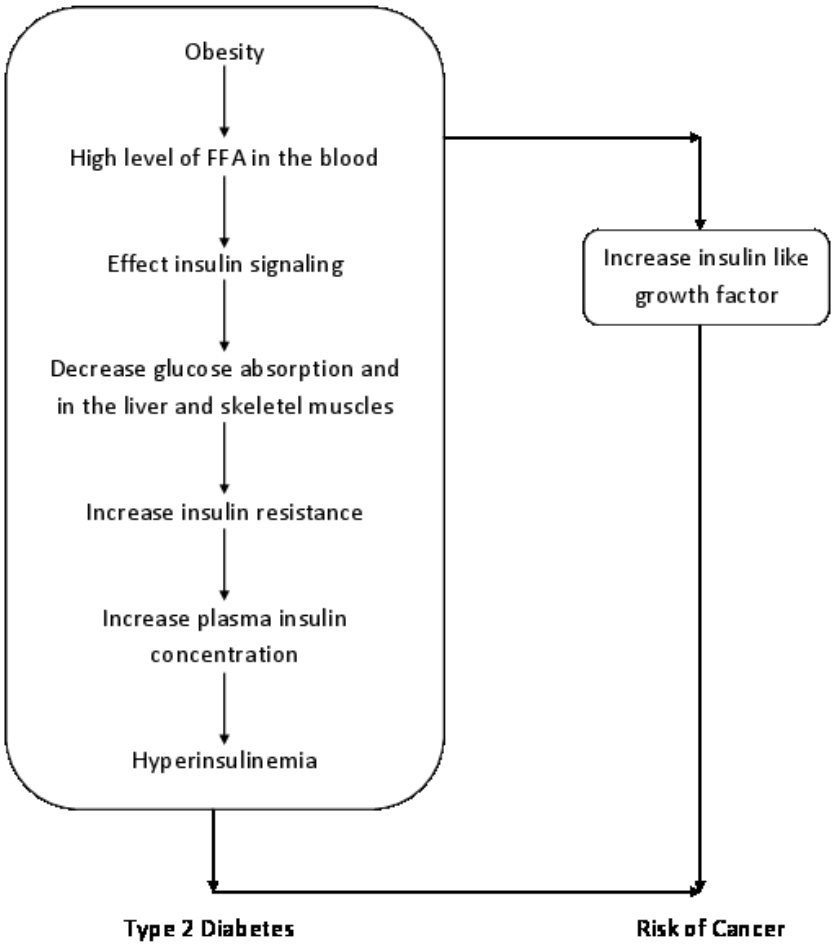


Figure 3.1: Relationship of obesity, FFA and type 2 diabetes

insulin resistance [146–148] but also affect insulin secretion in normal as well as diabetic people [149]. Glycogen synthesis in euglycemic diabetes patients were decreased to an even greater degree than rate of glucose uptake (-72 vs - 53%) [148]. FFA and glycerol increased insulin suppressed hepatic glucose production and thus caused insulin resistance in the whole body. Glucose uptake decreased by $\sim$50 % (from 8.8 to 4.2 $mg/kg/min$) when FFA concentration rose from $\sim$50 to $\sim$750 $\mu M$. When FFA concentration rose from $\sim$50 to $\sim$500 $\mu M$, glucose uptake decreases by $\sim$3 $mg/kg/min$, CHO oxidation and glucagon

synthesis also decreases. Decline in glucose uptake, which occurred when plasma FFA concentration rose further ($\sim 550$ to $\sim 750\ \mu M$), was caused exclusively by a decrement in glycogen synthesis [147].

Mathematical modeling of the glucose - insulin dynamics of the diabetic patient affected by the elevated FFA plasma level and obesity will help to find the ways to maintain the glucose concentration in physiological range. To the time, theoretical evidences are given by many researchers about the strong link between raised FFA level, obesity and diabetes but still it is unfold mathematically.

Since it is evident from the past research articles that FFA and obesity are closely associated with diabetes, therefore an attempt has been made to analyze the effect of elevated FFA level and obesity on the glucose - insulin dynamics of diabetic people. Theoretical changes suggested by Boden has been incorporated in the mathematical model and then simulation has been carried out by using Matlab 2012b. There is a strong relation between obesity and FFA [150], which are amongst the main factors responsible for occurrence of type 2 diabetes. FFA also cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis [151]. On the basis of theoretical results obtained by Boden and Chen (1995), the effect of physiological elevation of plasma FFA on the glucose and insulin concentration level for obese people having type 2 diabetes through a mathematical model will be discussed in the present study. Indexing HDMR will be used to propose a polynomial based structure to calculate the glucose concentration by taking a data set of 90 healthy subjects.

## 3.2 Mathematical model

The minimal model [37] for the glucose - insulin dynamics is given as

$$\frac{dG(t)}{dt} = -X(t)G(t) - p_1(G(t) - G_b); G(0) = G_0 \tag{3.2.1}$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b); X(0) = X_0 \tag{3.2.2}$$

$$\frac{dI(t)}{dt} = -p_4(I(t) - I_b) + p_5(G(t) - G_c)^+t; I(0) = I_0 + I_b \tag{3.2.3}$$

where, $G(t)$ $[mg/dl]$ represents glucose concentration at time t, $X(t)$ $[min^{-1}]$ represents remote insulin concentration at time t, $I(t)$ $[\mu U/ml]$ represents the interstitial insulin at

time t, $G_b$ $[mg/dl]$ represents the basal glucose level, $G_c$ $[mg/dl]$ represents the threshold glucose level of glucose above which the endogenous insulin secretion will be stimulated and $I_b$ $[\mu U/ml]$ represents the basal insulin level. The parameters $p_i$ $(p_i > 0)$, i = 1,2,3,4,5 are given in Table 2.1.

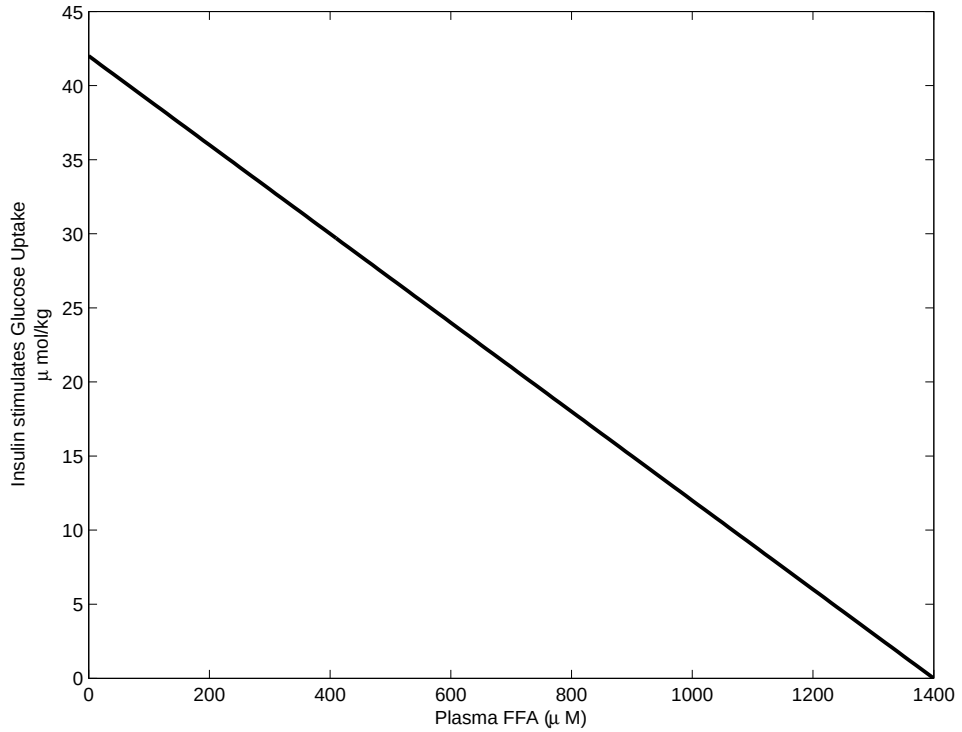


Figure 3.2: Relationship between insulin stimulated glucose uptake and plasma FFA.

Elevated level of plasma FFA level and insulin simulated glucose uptake by the cells of the body shows a linear relationship implies if the level of FFA increases, glucose uptake by the cells decreases [145], shown in Figure 3.2. Total stimulated (insulin stimulated plus basal) glucose uptake has been inhibited by 40–50 % in isoglycemic and in euglycemic patients at plasma FFA concentration of $\sim 950$ and $\sim 550$ $\mu M$ [148] respectively, hence the expression $-X(t)G(t)$ in the first equation of the model (3.2.1–3.2.3) is changed to $-(0.5)X(t)G(t)$. This will lead to a change in the first equation of minimal model. Also as reported by Boden peripheral insulin sensitivity and hence whole insulin sensitivity decreases which is represented by $p_3$ in eqn.(3.2.2). Hence there will be a change in the numerical value of $p_3$ which will be reflected in the simulation of the modified model. FFA is found to have an affect on peripheral insulin resistance which is represented by $p_5$ in eqn.(3.2.3) and hence we allow the value of parameter $p_5$ to vary. After making the above discussed changes, the modified mathematical model for the glucose - insulin

dynamics of NIDD people is given below :

$$\frac{dG(t)}{dt} = -(0.5)X(t)G(t) - p_1(G(t) - G_b); G(0) = G_0 \tag{3.2.4}$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b); X(0) = X_0 \tag{3.2.5}$$

$$\frac{dI(t)}{dt} = -p_4(I(t) - I_b) + p_5(G(t) - G_c)^+t; I(0) = I_0 + I_b \tag{3.2.6}$$

## 3.3 Stability analysis of mathematical model

To check the stability of the model at the equilibrium point, $G_c = G_b$ is taken in the eqn.(3.2.6) of the model.

Consider the model (3.2.4–3.2.6). Let us define $g(t)$ = ($G(t)$ - $G_b$), $x(t) = S(t)$, $i(t)$ = ($I(t)$ - $I_b$)

We may write system (3.2.4–3.2.6) in the form:

$$\frac{dg(t)}{dt} = -(0.5)x(t)g(t) - G_bx(t) - p_1g(t) \tag{3.3.1}$$

$$\frac{dx(t)}{dt} = -p_2x(t) + q_3i(t) \tag{3.3.2}$$

$$\frac{di(t)}{dt} = p_5H(g(t))t - q_4i(t) \tag{3.3.3}$$

Where $H \equiv H(g(t))$ is the unit step function :

$$H(g(t)) = \begin{cases} 0, \text{if } g(t) < 0 \\ 1, \text{if } g(t) > 0 \end{cases} \tag{3.3.4}$$

To determine the stability of the model (3.2.4–3.2.6), we may establish certain inequalities in the solutions to (3.2.4–3.2.6)

Let $g(0) < 0$ $(i.e., G(0) < G_b)$. Then H = 0, and from equations (3.3.1–3.3.3) we see that $g(t)$, $x(t)$ and $i(t)$ approaches to zero, and hence the system is stable for $G(0) < G_b$.

From the eqn.(3.3.1), and using the Comparison Theorem 2.4.1 (where H = 1), we have :

$$\begin{aligned}\frac{dg}{dt} &= -p_1 g - G_b x - (0.5)gx \\ &\leq -p_1 g - G_b x_{min} - (0.5)gx_{min} \\ &= -Pg - G_b x_{min},\end{aligned}$$

where $P = p_1 + (0.5)x_{min}$

The solution is given by

$$g(t) \leq g(0)e^{-Pt} - \frac{G_b x_{min}}{P}(1 - e^{-Pt}) \tag{3.3.5}$$

and

$$\begin{aligned}\frac{dg}{dt} &\leq -g(0)Pe^{-Pt} - G_b x_{min} e^{-Pt} \\ &< 0, \forall t \geq 0\end{aligned}$$

which is negative.

At $t \to \infty$, eqn.(3.3.5) $g(0)e^{-Pt} - \frac{G_b x_{min}}{P}(1 - e^{-Pt})$ becomes $\frac{-G_b x_{min}}{P} < 0$

Hence, we can say that if $g(0) > 0$ (i.e.,$G(0) > G_b$), the right-hand-side of (3.3.5) decreases to zero after a finite time T, so that $g(t)$ passes through 0 after a time $T_G$, where $T_G \leq T$. Also, at $t = T_G$, H becomes zero.

From eqn.(3.3.3),

$$\frac{di}{dt} = p_5 Hgt - p_4 i$$

The solution is given by

$$i(t) = i(0)e^{-p_4 t} + p_5 e^{-p_4 t} \int_0^t H(g(s))sg(s)ds \tag{3.3.6}$$

Now, the integral on the right in (3.3.6) is bounded above by

$$\int_0^{T_G} sg(s)ds < \infty$$

which implies $i(t) \leq i_{max}$ i.e. $i(t)$ is bounded above for $t \geq 0$. Also from eqn.(3.3.6), $i(t) \geq i_{min}$ for some finite $i_{min}$ i.e. i(t) is bounded below for all $t \geq 0$. Hence $i(t)$ is bounded.

Similarly, using the eqn.(3.3.2) and Theorem 2.4.1, we have

$$\frac{dx}{dt} = -p_2x + p_3i \leq -p_2x + p_3i_{max}$$

The solution is given by

$$\begin{aligned} x(t) &\leq x(0)e^{-p_2t} + \frac{p_3i_{max}}{p_2}(1-e^{-p_2t}) \\ &\leq x(0) + \frac{p_3i_{max}}{p_2} \\ &\equiv x_{max} \end{aligned}$$

Hence, $x(t)$ is bounded above.

Now, from the eqn.(3.3.2),

$$\frac{dx}{dt} = -p_2x + p_3i \geq -p_2x + p_3i_{min}$$

The solution is given by

$$x(t) \geq x(0)e^{-p_2t} + \frac{p_3i_{min}}{p_2}(1-e^{-p_2t}) \tag{3.3.7}$$

which implies $x(t)$ is bounded below for $t \geq 0$.
Hence, $x(t)$ is bounded.

Hence we can say that if $G(0) < G_b$, then the system (3.3.1–3.3.3) is stable and if $G(0) > G_b$, then the solutions of (3.3.1–3.3.3) are bounded for all $t \geq 0$.

## 3.4 Numerical simulation and results

On the basis of above results, numerical simulation has been carried out by using Matlab 2012b. Boden suggested that for every 100 $\mu M$ increase in plasma FFA, peripheral insulin sensitivity decreased by $\sim$ 8 % [145], and whole insulin sensitivity decreased by approximately 76 % in obese people as compared to normal subjects [144]. The value of $p_3$ in the model (3.2.4–3.2.6) is taken as 8 % of the value $p_3$ used for normal subjects, hence $p_3 = 0.0000024$, obtained from the relation $S_I = p_3/p_2$ (insulin sensitivity of the normal people), $S_I^{'} = S_I - 76\%\ S_I$ (insulin sensitivity for the NIDD people) and $p_2 = 0.0200$. FFA could account for maximally 50 % of peripheral insulin resistance in patients with type 2 diabetes [145], hence the value of the parameter $p_5$ in the model (3.2.4–3.2.6) is 50 % more of the value $p_5$ used for normal subjects, therefore $p_5 = 0.0015$ is taken for the numerical simulation. The values of all the parameters for normal and NIDD people are given in Table 3.2.

Elevated level of plasma FFA cause decrement in insulin sensitivity and increment in insulin resistance, because of which glucose level does not reach to the normal basal value. This effect is shown in Figure 3.3. Comparison between the changes in glucose and insulin concentration in normal and elevated FFA in NIDD people is shown in Figure 3.4. First graph of Figure 3.4(a) depicts that glucose level approaches to physiological basal level faster in normal people than in NIDD with elevated FFA.

It is also observed that more time is taken by NIDD people with elevated FFA than normal to attain nearly same glucose level. The effects of elevated FFA in insulin level can be seen from second and third Figure 3.4. These graphs shows that more insulin is required in NIDD with elevated FFA to perform the same action than in normal, which can be understood as the need of external insulin in NIDD with elevated FFA.

The biggest challenge in the model (3.2.1–3.2.3) is to find the values of the parameters. To get rid of this problem, an endeavor has been made to establish a polynomial relation among the various important parameters of the body. To establish such a relation, first of all ranking has been done of the parameters to list out most important parameter affecting glucose - insulin dynamics.

| Sr. no. | Parameters | Rank value |
|---|---|---|
| 1. | BMI | 0.051325 |
| 2. | age | 0.02418 |
| 3. | sex | 0.020057 |
| 4. | weight | 0.01167 |
| 5. | height | 0.01054 |
| 6. | thigh | 0.008436 |

Table 3.1: The selected parameters with their rank value

## 3.5 Preparing data set

We are going to deal with data set of 90 normal people and around 30 attributes, out of which 60 are training nodes and 30 are testing nodes. Some of the attributes are listed below: age of patient (years), body mass index of patient (bmi), blood insulin (mcg/dl), c-peptide, fast blood sugar (fbs) (mg/dl), urine in blood ($\mu$U/ml), creatinine (mg/dl), total cholesterol (mg/dl), triglyceride (mg/dl), high density lipoprotein (hdl) (mg/dl), low density lipoprotein (ldl) (mg/dl), very low density lipoprotein (vldl), sex (male or female), height (cms), weight (kg), oral glucose tolerance test (ogtt2hr), suberosal (ss), thigh (cms) and many more.

A feature selection method used to select the significant parameter out of 50 parameters. For this purpose, info gain attribute ranking method is applied to the data sets at WEKA. It is known that the hdl and ldl levels have inverse ratio. For this reason, only one parameter is selected to increase the performance of I-HDMR method. If both hdl and ldl stay within the first five features, the one with the higher rank will be selected. Another point is not to use fbs and glucose in urine level together in the modeling process as high level fast blood sugar (fbs) causes glucose in urine.

The selected parameters are Body mass Index(BMI), Age, Sex, Weight, Height, Thigh circumference. The rank value of the parameters are given in Table 3.1.

## 3.6 Methods

In this section the details of the Indexing HDMR method used to find the glucose level are given. Also, the steps of the algorithm are discussed below. I-HDMR has the ability to partition a given multivariate random data and to obtain an analytical structure for

the given interpolation problem and to find testing data location in the index space.

The equation of the HDMR method for a given multivariate function is as follows :

$$\begin{aligned} f(x_1.....x_n) &= f_0 + \sum_{i_1=1}^{N} f_{i_1}(x_{i_1}) \\ &\quad + \sum_{\substack{i_1,i_2=1 \\ i_1<i_2}}^{N} f_{i_1} f_{i_2}(x_{i_1}, x_{i_2}) \\ &\quad + f_{1,2.....N}(x_1, x_2....x_N) \end{aligned}$$

This expansion is a finite sum and is composed of $2^N$ components such as a constant, N univariate terms, N(N - 1)/2 bivariate terms and so on. The purpose of this method is to construct a unique representation for the given multivariate function. The "bivariate HDMR approximation" can be given by the following relation:

$$\begin{aligned} f(x_1.....x_n) &\approx f_0 + \sum_{i_1=1}^{N} f_{i_1}(x_{i_1}) \\ &\quad + \sum_{\substack{i_1,i_2=1 \\ i_1<i_2}}^{N} f_{i_1} f_{i_2}(x_{i_1}, x_{i_2}) \end{aligned}$$

However, we know that HDMR method can partition the multivariate data having orthogonality geometry in which the class values at all possible nodes of the problem domain should be known [152]. This domain can be described as $P \equiv P_1 \times P_2 \times ..... \times P_N$, $P_j \equiv \xi_j^1 .....\xi_j^{n_j}$, $1 \leq j \leq N$, where N is the number of parameters in the problem, $n_1, n_2, ..., n_N$ are the number of different values that the parameters can take and the set P stands for the cartesian product set constructed through all possible parameter values of the given problem which satisfies the orthogonal geometry need for the HDMR method. Therefore, there are $n_1 \times n_2 \times .... \times n_N$ nodes in this set. The training data set does not include the class values at all nodes of the problem domain. The nodes at which the class values are known, are distributed arbitrarily inside the given domain.

This structure has a non-orthogonal geometry. I-HDMR method constructs an algorithm to obtain an orthogonal geometry from this non-orthogonal geometry to make HDMR applicable to the data partitioning process in order to determine an analytical structure for the given problem.

### 3.6.1 Algorithm

The steps of I-HDMR algorithm can be expressed as follows:

Step 1. Evaluate the prime factors of training nodes which is 60. The factors are 2, 2, 3, 5. The following assignments are done for glucose level:

$$n_1 = 2,\ n_2 = 2,\ n_3 = 3,\ n_4 = 5$$

Step 2. Specify the index sets for glucose level.
Step 3. Construct a cartesian product set by using the index sets given in Step 2. The general structure of this set is given above.
Step 4. Sort the given training set by class values in ascending order.
Step 5. Construct a one-to-one mapping between the given training set nodes and the cartesian product set of Step 3.
Step 6. Build an analytical structure for each I-HDMR component through partitioned data sets.
Step 7. Find out the appropriate training node for each testing node.
Step 8. Determine the location of each testing node in the index space.
Step 9. Insert the values of testing node location into analytical structure and evaluate the class of testing node under consideration.

## 3.7 Findings

The main task of this work is to model the given data by using the Indexing HDMR method and to build a planning structure for glucose level. The accuracy, sensitivity and root mean squared error (RMSE) results will be found out for glucose level and method. The evaluations will be done by using Perl programming language. We will try to establish a polynomial relation between the selected parameters and the glucose level.

The polynomial structure may be of the form:

$$\begin{aligned} f(x_1, x_2 \ldots\ldots x_6) &= a_0 x_1 + a_1 x_2 + \ldots\ldots + a_5 x_6 \\ &\quad + a_6 x_1 x_2 + \ldots\ldots + a_{10} x_1 x_6 \\ &\quad + a_{11} x_2 x_2 + \ldots\ldots + a_{14} x_2 x_6 \\ &\quad + a_{15} x_3 x_1 + \ldots\ldots + a_{20} x_6 x_6 \\ &\quad + a_{21} x_1 x_2 x_3 + \ldots\ldots\ldots\ldots\ldots \end{aligned}$$

where $f$ represents glucose concentration level, $x_i, i = 1,2,3,4,5,6$ are the above selected parameters based on their rank value and $a_j$ are the constant coefficients. This relation can be used to calculate the glucose concentration by having the value of 6 parameters which are available without any advance test. Therefore, this polynomial may be proved extremely useful for the individuals to keep close check on glucose level once the values of $a_i$ are known.

## 3.8 Conclusion and future scope

The present mathematical model shows that elevated level of plasma FFA inhibit glucose uptake, glucose utilization, decrease insulin sensitivity and increases insulin resistance in NIDD people. It also explained the need of external insulin in NIDD with elevated FFA. To explore the effects of obesity and elevated FFA in normal and NIDD subjects BMI (body mass index) is selected as most effective parameter among all sorted parameters to form a polynomial.

In future, a relation will be formulated among various physiological parameters which includes BMI, age, sex etc and glucose level for diabetic patients with medication and without medication.

| Parameters | Value for normal | References | Value for NIDD | References |
|---|---|---|---|---|
| $p_1$ | 0.0399 | [71] | 0.014 | [72] |
| $p_2$ | 0.0200 | [71] | 0.0200 | [72] |
| $p_3$ | 0.00004 | [71] | 0.0000024 | - |
| $p_4$ | 0.257 | [71] | 0.129 | [72] |
| $p_5$ | 0.001 | [71] | 0.0015 | - |
| $G_0$ | 287 | [71] | 392 | [72] |
| $I_0$ | 351 | [71] | 1322 | [72] |

Table 3.2: The values of the parameters.

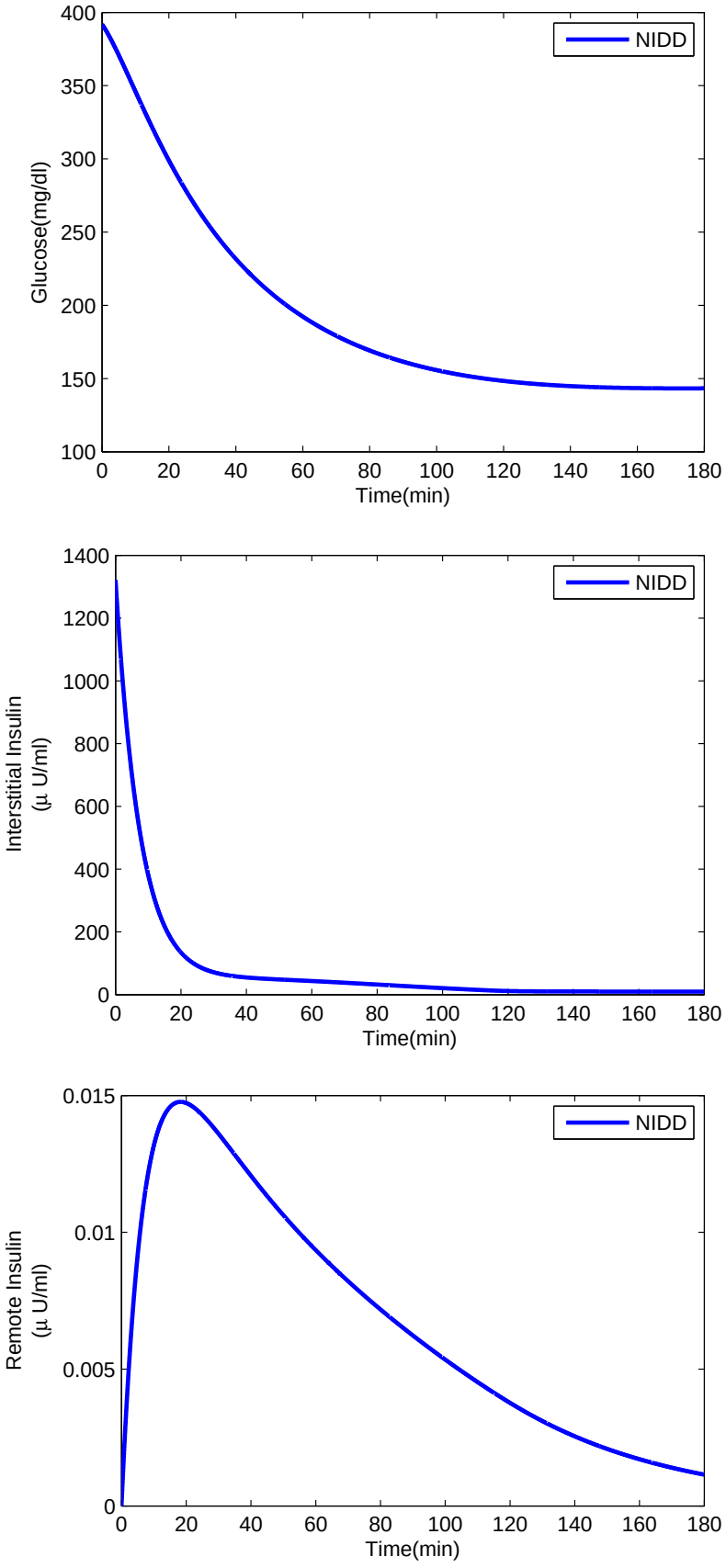


Figure 3.3: Glucose - Insulin dynamics for NIDD people.

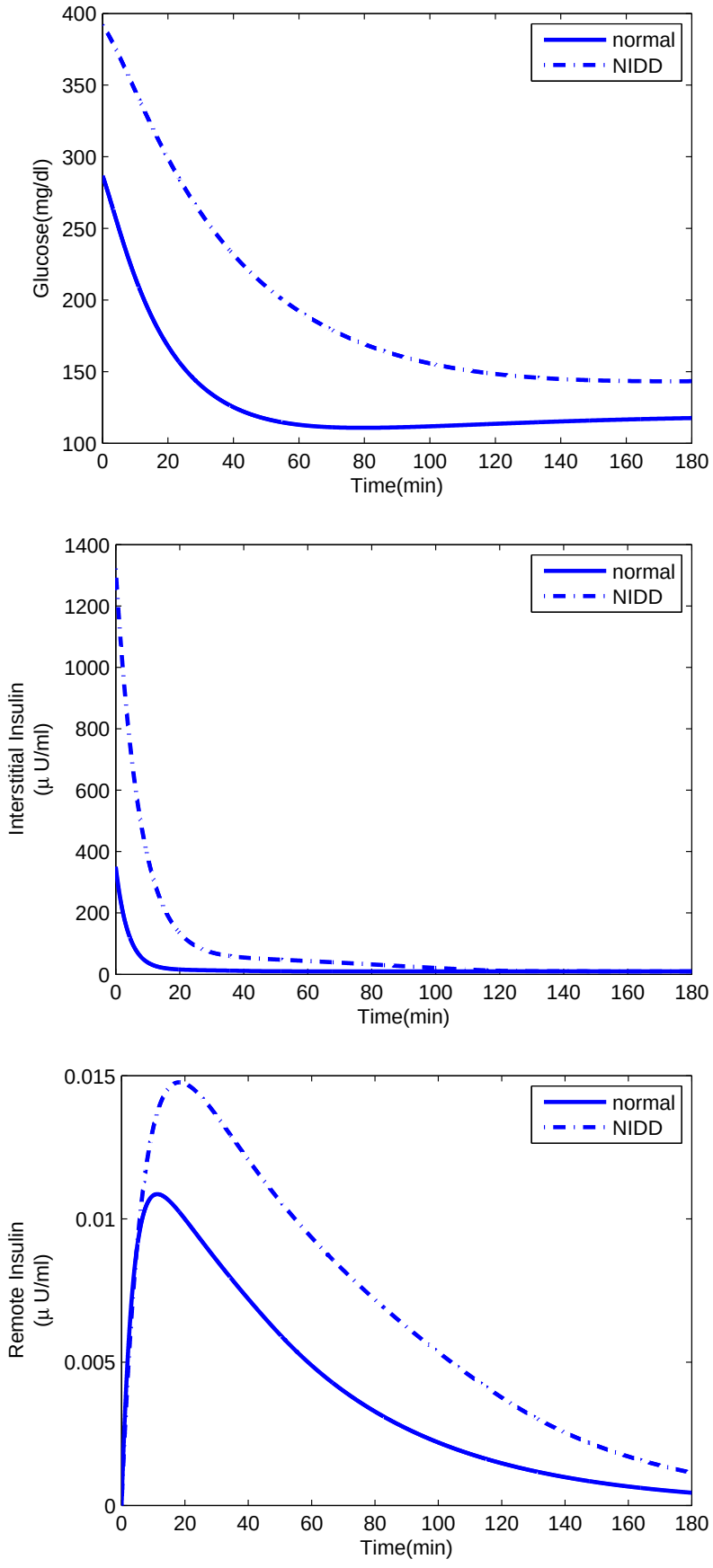


Figure 3.4: Comparison of glucose - insulin dynamics for normal and NIDD people.

# Chapter 4

# Dynamical system for glucose - insulin space in organs of diabetics

Diabetes is not just a single disease but it brings many health related problems and affect our organs. Diabetes, if uncontrolled, can affect both the nervous system and circulatory system. In this chapter,[1] an attempt has been made to capture the changes in glucose - insulin dynamics of central nervous system, liver and kidney which are severely affected by diabetes through mathematical modeling and simulation. The numerical simulation of the mathematical models explains that decreased volume of glucose and insulin space may be one of the possible reasons behind the prolonged raised glucose level in the central nervous system, liver and kidney of the diabetic people.

[1]The results of this chapter has been published in a research paper entitled "Dynamical system for glucose - insulin space in different organs of diabetes" in *Communication in Mathematical Biology and Neuroscience*, **9** (2016).

## 4.1 Introduction

Diabetes affects our blood vessels and nerves and therefore can affect any part of the body. As these two systems involved in almost all body functions resulting diabetes leads to many health related complications and sometimes leads to failure of the multiple organs. However, certain organs of our body are affected more than other organs for e.g brain, heart, kidney, liver and pancreas.

It is clinically proved that type 2 diabetes may increase the risk of failure of many major organs in the body, directly and indirectly. The following parts of the body which may be affected by the diabetes depends upon the severity of the disease : eye, heart, kidney, liver, nervous system and the reproduction system. In diabetes, nervous system fails first and later all other systems. It motivates us to find the possible reason behind the raised glucose concentration in the respective organs whose functioning are impaired by the diabetes.

Diabetes affect the CNS in several ways. Diabetes increases the stroke risk and overdose with insulin or oral intake can permanently damage the brain. Diabetes changes brain transport, blood flow and metabolism [153]. The brain system fails first which puts pressure on the islet system, causing further decomposition in the brain system that ends in type 2 diabetes. The vessels in the brain can also become damaged by hyperglycemia, and there is some evidences that this damage contributes to a progressive decline in brain function [154, 155]. Frequent exposure to high glucose levels likely diminishes mental capacity, as higher HbA1c levels have been associated with a greater degree of brain shrinkage [156].

Continued excessive sugar levels in the kidney affect the glomeruli, or the blood filtering units of the kidneys. In diabetes, the flow of blood through the kidneys increases and glomeruli have to work harder resulting the kidneys get larger in size than normal. Diabetes is among the leading cause of kidney failure [157]. Nearly one third of kidney failure patients are diabetics.

Liver plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production and detoxification [158]. Several roles are played by liver like carbohydrate metabolism, formation of glycogen, breakdown of glycogen, synthesis of glucose from certain amino acids and many more. In diabetics, fat is accumulated in the liver

resulting excess deposition of fat in the liver and decreased removal of fat increase the size of liver. An enlarged liver and enzyme abnormalities are characteristics of fatty liver. The National Institute of Diabetes and Digestive and kidney disease reports that 10 to 20% of Americans have fatty liver [159].

The whole body models provide very important quantitative information about the glucose - insulin dynamics. It is important but at the same time remarkably difficult also to measure the physiological changes in the glucose - insulin dynamics at the organ level. Here, for all three organs; CNS, kidney and liver, mathematical models have been developed separately for each organ, to analyze the effect of volume of glucose and insulin space on the glucose - insulin dynamics of diabetic people. The mathematical model has been checked for its stability properties, positive and bounded solutions of the system are also discussed in further section of the chapter.

It can be concluded from the results obtained from numerical simulation of the model that decreased volume for glucose and insulin space (plasma and remote compartments) may be one of the major reason for the raised glucose level in type 2 diabetics. Other possible reasons together with the decreased volume of glucose and insulin space for the raised glucose concentration (hyperglycemia) in each organ of the body are discussed at the end of each section.

## 4.2 Model derivation

Insulin and glucose are the two main factors in the glucose - insulin endocrine metabolic regulatory system. The glucose - insulin dynamics of human body is shown graphically in Figure 4.1. By applying law of conservation of mass, we attempt to model the glucose - insulin dynamics of three organs (CNS, Kidney and Liver) which are severely affected by the long term persistence of diabetes in human body. Let G(t) and I(t) are the glucose and insulin concentration at time $t \geq 0$, then

$$\frac{dG}{dt} = \text{Glucose production - Glucose utilization}$$
$$\frac{dI}{dt} = \text{Insulin production - Insulin utilization}$$

On the basis of conservation law, we discuss the mathematical models to capture the physiological changes of the glucose - insulin dynamics in various organs of human body.

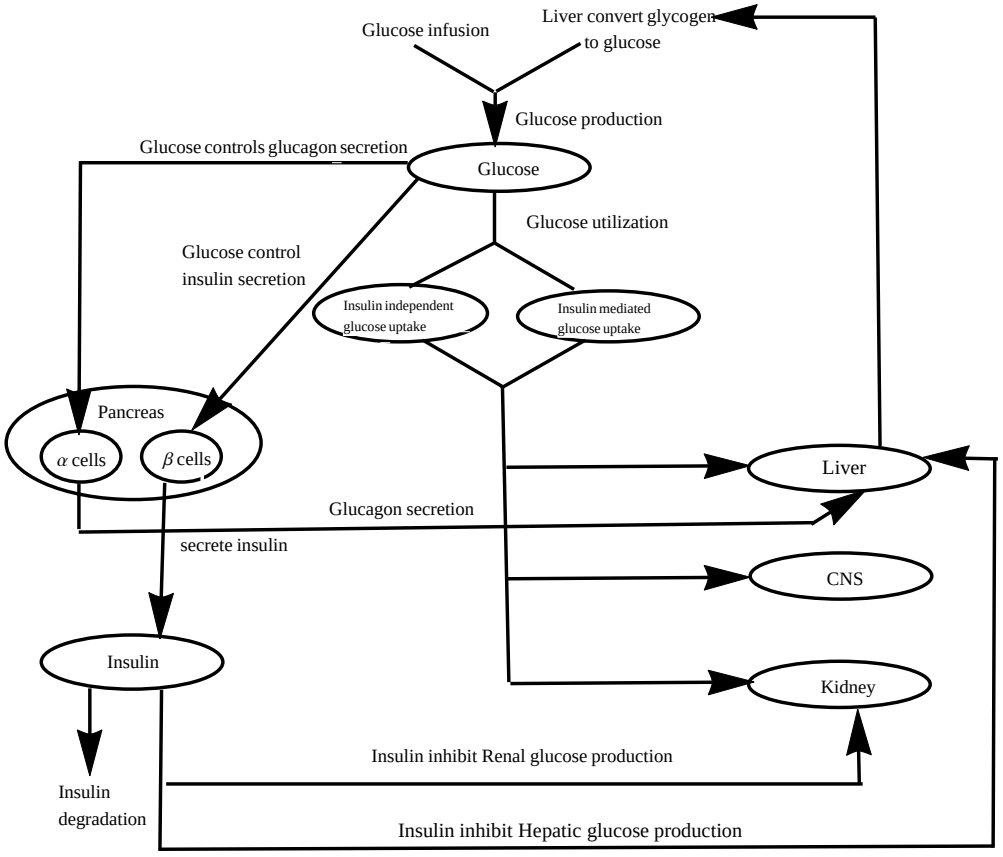


Figure 4.1: Glucose - Insulin dynamics of the human body

## 4.3 Mathematical model

The mathematical model for glucose - insulin dynamics of the whole body [7] is given as :

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))\,f_4(I(t)) + f_5(I(t)) \tag{4.3.1}$$

$$\frac{dI}{dt} = f_1(G(t)) - d_i I(t) \tag{4.3.2}$$

with initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G(t)$ represents the glucose concentration and $I(t)$ represents the insulin concentration at time $t$.

- $G_{in}$ is glucose infusion rate.
- $f_1(G(t))$ represents insulin secretion.
- $f_2(G(t))$ represents glucose utilization independent of insulin.
- $f_3(G(t))\,f_4(I(t))$ represents insulin mediated glucose utilization.
- $f_5(I(t))$ represents total glucose production.
- $d_i$ is insulin degradation rate.

The functions $f_i$, i = 1, 2, 3, 4, 5 are given below [7] :

$$f_1(G) = \frac{Rm}{1 + exp((C_1 - G/V_1)/a_1)}$$

$$f_2(G) = U_b(1 - exp(-G/(C_2 V_1)))$$

$$f_3(G) = \frac{G}{C_3 V_1}$$

$$f_4(I) = U_0 + \frac{(U_m - U_0)}{1 + exp(-\beta log(I/C_4(1/V_2 + 1/Et_i)))}$$

$$f_5(I) = \frac{Rg}{(1 + exp(\alpha(I/V_3 - C_5)))}$$

where,

- $V_1$ represents volume of glucose space.
- $V_2$ represents volume of remote insulin compartment.
- $V_3$ represents volume of plasma insulin compartment.
- $t_i$ is time constant for remote insulin degradation.
- $E$ is the rate constant for exchange of insulin between plasma and remote compartment.

## 4.4 Mathematical model for central nervous system (CNS)

Brain controls and governs the action of all parts of human body and approximately 25 % of total body glucose is required for the proper functioning of the brain. Brain also maintain the glucose homeostasis i.e the balance of insulin and glucagon to maintain the blood glucose. Normal glucose regulation in the body depends upon the link between insulin produced by $\beta$ cells and signal in hypothalamus. Initially, the brain was considered to be an insulin-insensitive tissue, and the uptake of glucose was an insulin-independent process [160]. However, subsequent studies demonstrated the existence of Insulin Receptors in the brain [161]. Type 2 diabetes appears to be the result of failure of both brain centered system and pancreatic islet system.

The magnitude of the glucose utilization dependent on insulin may not seems large, because it is superimposed on background of insulin independent glucose uptake. A 15 % increase in brain glucose uptake secondary to insulin stimulation may have clinical significance [162].

The mathematical model for glucose - insulin dynamics of the whole body [7] is given in (4.3.1-4.3.2). In model (4.3.1-4.3.2), the functions $f_i$, i = 1,2,3,4,5 represents the physiological changes occurred in the glucose - insulin dynamics of the human body.

Rosenzweig in 1980 demonstrated the presence of insulin in brain of rat and human in higher concentration than in plasma [163]. In 1986, Darrel illustrated that insulin is produced within the CNS, specifically by neurons within the CNS of rats [164]. Insulin in the brain has been found at level higher level than plasma. It has been reported that high concentration of insulin are maintained in the CNS compartment compared to plasma levels and the CNS insulin concentration is not affected by alternations in plasma

insulin concentration [165]. This phenomena has been represented by $\gamma$ in eqn.(4.4.2) of the model (4.4.1-4.4.2).

The functions which are included in the mathematical model for CNS are given as :

- $f_1(G_B(t))$ represents insulin secretion but there is no significant production of insulin takes place in CNS hence not considered in the CNS model.
- $f_2(G_B(t))$ represents glucose utilization independent of insulin and according to the literature available, glucose uptake in brain is almost non insulin mediated [160], hence the function is included in the model.
- $f_3(G_B(t))\,f_4(I_B(t))$ represents insulin mediated glucose utilization, it has already been demonstrated that insulin mediated glucose uptake take place in brain, hence the functions are considered for the CNS model.
- $f_5(I_B(t))$ represents glucose production and there is no direct glucose production in the brain, hence the function is not included in the model.

Hence, the glucose - insulin regulatory system for Central Nervous System is

$$\frac{dG_B}{dt} = G_{in} - f_2(G_B(t)) - f_3(G_B(t))\,f_4(I_B(t)) \tag{4.4.1}$$

$$\frac{dI_B}{dt} = -d_i I_B(t) + \gamma \tag{4.4.2}$$

with initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$. $G_B(t)$ represents glucose concentration in the brain, $I_B(t)$ represents insulin concentration in the CNS at time $t$. The functions $f_i$, i = 2,3,4 have been found behaving in the manner given below. The functions are modeled as :

$$f_2(G_B) = U_b^{'}(1 - exp(-G_B/(C_2V_1^{'})))$$

$$f_3(G_B) = G_B/(C_3V_1^{'})$$

$$f_4(I_B) = U_0^{'} + \frac{(U_m - U_0^{'})}{1 + exp(-\beta log(I/C_4(1/V_2^{'} + 1/Et_i)))}$$

where

- $V_1^{'}$ represents volume of glucose space in CNS.
- $V_2^{'}$ represents volume of remote insulin compartment.
- $\gamma$ denotes the insulin concentration in the brain.
- $U_b^{'}$ denotes the rate of glucose utilization with respect to glucose concentration i.e non insulin mediated glucose uptake.
- $U_0^{'}$ denotes the glucose utilization rate with respect to plasma insulin i.e insulin mediated glucose uptake in the CNS.

## 4.5 Mathematical model for liver

Liver plays an important role to maintain the homeostasis of glucose level in the body for normal people. But for diabetic people, $\alpha$ and $\beta$ cells are impaired in action and hence the working of liver is also disturbed due to which glucose absorption and production from the liver is also disturbed and resulting the glucose level either lowers down or raised very much leads to hypoglycemia or hyperglycemia respectively. In type 2 diabetes, increased level of insulin resistance leads to increase hepatic glucose production [166].

It was found in the study that hepatic glucose production in obese type 2 diabetic patients may be increased by 12% compared to healthy people. The reason for including insulin production function in second differential equation of the model is that insulin is able to suppress hepatic glucose production about 25% of the values measured at fasting insulin concentration in the morning both in the healthy and in type 2 diabetic people [167]. The liver seems to be very sensitive and important organ to insulin in both normal and type 2 diabetics because maximal suppression is obtained at insulin concentration about 30 to 50 $\mu U/min$. Endogenous glucose production can be considered as sum of all glucose production by kidney, intestines, liver, glucose intake and even muscles, and here hepatic glucose production is used synonymous with total endogenous glucose production. Hepatic glucose production was found more in type 2 diabetics due to a reduced insulin sensitivity of liver cells. Increased amount of hepatic glucose production add to the degree of hyperglycemia in diabetic people [167]. Splanchnic glucose production was higher in diabetic than in non diabetic people. Thus, excessive insulin induced suppression of splanchnic glucose release is also impaired [168].

The functions which are included in the mathematical model of Liver are given as :

- $f_1(G_L(t))$ represents insulin secretion and almost glucose utilization in the liver is insulin mediated, hence the function is included in the model.
- $f_2(G_L(t))$ represents glucose utilization independent of insulin and some amount of glucose uptake in the liver is also non insulin mediated, hence included in the model.
- $f_3(G_L(t))f_4(I_L(t))$ represents insulin mediated glucose utilization, hence incorporated in the model.
- $f_5(I_L(t))$ represents hepatic glucose production.

Hence, the glucose - insulin regulatory system for liver is :

$$\frac{dG_L}{dt} = G_{in} - f_2(G_L(t)) - f_3(G_L(t))f_4(I_L(t)) + f_5(I_L(t)) \quad (4.5.1)$$

$$\frac{dI_L}{dt} = f_1(G_L(t)) - d_i I_L(t) \quad (4.5.2)$$

with initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G_L(t)$ represents glucose concentration in liver and $I_L(t)$ represents insulin production in liver at time $t$. The functions $f_i$, i = 1,2,3,4,5 are given as :

$$f_1(G_L) = \frac{R_m^{'}}{1 + exp((C_1 - G_L/V_1^{''})/a_1)}$$

$$f_2(G_L) = U_b(1 - exp(-G_L/144V_1^{''}))$$

$$f_3(G_L) = G_L/(C_3 V_1^{''})$$

$$f_4(I_L) = U_0 + \frac{U_m - U_0}{1 + exp(-\beta log(I_L/C_4(1/V_2^{'} + 1/Et_i)))}$$

$$f_5(I_L) = \frac{R_g^{'}}{(1 + exp(\alpha(I_L/V_3^{'} - C_5)))}$$

where,

- $V_1^{''}$ represents volume of glucose space in liver.
- $V_2^{'}$ represents volume of remote insulin compartment.
- $V_3^{'}$ represents volume of plasma insulin compartment.
- $R_m^{'}$ represents the rate of insulin secretion.
- $R_g^{'}$ represents the rate of hepatic glucose production.

## 4.6 Mathematical model for kidney

Besides liver, kidney is the only organ capable of generating sufficient glucose (gluconeogenesis) to release in the blood by its reabsorption and excretion [169–171]. The kidneys are designed to filter plasma, reabsorb glucose and excrete substances that must be eliminated from the body. The basic functions of the kidney is regulation of fluid, body fluid osmolality, excretion of metabolic waste, hormone secretion and maintain glucose balance [172, 173]. The primary mechanism of the kidney include release of glucose into the circulation via gluconeogenesis, glucose uptake from the circulation to satisfy the kidney's energy needs and reabsorption of glucose at the level of the proximal tubule [172]. Diabetes is characterized by increased rate of glucose turnover (Glucose production - Glucose utilization) in the human body. Increased glucogenesis is considered to be one of the major reason of overproduction of glucose in type 2 diabetics [174, 175]. It was observed that approximately 25 % of systemic glucose production is contributed by renal glucose production and renal glucose uptake accounts for 20 % of systemic glucose removal indicate an important role of the human kidney to maintain the glucose homeostasis [176]. The observation also provide a possible explanation that why people with renal failure are more prone to develop hypoglycemia [177, 178]. In case of type 2 diabetic people, renal glucose release is inscribed in both the postprandial and post absorptive states, implies the kidney's distribution to the hyperglycemia [171]. A 3-fold increase in renal glucose release was observed in patients with diabetes verses normal [179], while as hepatic glucose release increased by only 30% in the diabetic state. During hypoglycemia, the 2-fold increase in renal glucose production rates in normal subjects, and not observed in patients with diabetes [180].

Renal glucose reabsorption tends to increase with plasma glucose levels, upto plasma concentration of 180 mg/dl to 200 mg/dl [172]. In patients with diabetes, the kidneys may

be susceptible to the effects of hyperglycemia, as kidney cells are unable to decrease glucose transport rates to prevent intracellular hyperglycemia in states of increased glucose concentration [181]. The possible reason behind is that may be insulin fails to suppress renal glucose production in diabetic patients. Diabetic kidney diseases are more common in type 2 diabetic people and is one of the reason for kidney failure.

The functions which are included in the mathematical model for kidney are given as:

- $f_1(G_K(t))$ represents insulin secretion and glucose utilization is controlled by the insulin hence incorporated in the model.
- $f_2(G_K(t))$ represents glucose utilization independent of insulin and some glucose uptake in the kidney is also non insulin mediated, hence the function is included in the model.
- $f_3(G_K(t))\,f_4(I_K(t))$ represents insulin mediated glucose utilization, hence incorporated in the model.
- $f_5(I_K(t))$ represents renal glucose production.

Hence, the glucose - insulin regulatory system for kidney is :

$$\frac{dG_K}{dt} = G_{in} - f_2(G_K(t)) - f_3(G_K(t))\,f_4(I_K(t)) + f_5(I_K(t)) \tag{4.6.1}$$

$$\frac{dI_K}{dt} = f_1(G_K(t)) - d_i I_K(t) \tag{4.6.2}$$

with initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G_K(t)$ represent the glucose concentration in kidney and $I_K(t)$ represent the insulin concentration in kidney at time $t$. The functions $f_i$, i = 1,2,3,4,5 are given below :

$$f_1(G_K) = \frac{R_m''}{1 + exp((C_1 - G_K/V_1'')/a_1)}$$

$$f_2(G_K) = U_b(1 - exp(-G_K/144V_1''))$$

$$f_3(G_K) = G_K/(C_3 V_1'')$$

$$f_4(I_K) = U_0 + \frac{U_m - U_0}{1 + exp(-\beta log(I_K/C_4(1/V_2^{'} + 1/Et_i)))}$$

$$f_5(I_K) = \frac{R_g^{''}}{(1 + exp(\alpha(I_K/V_3^{'} - C_5)))}$$

where,

- $V_1^{''}$ represents volume of glucose space in kidney.
- $R_m^{''}$ represents rate of insulin secretion.
- $R_g^{''}$ represents rate of renal glucose production.

## 4.7 Positive and bounded solutions of mathematical model

In this section, we will show the solutions $(G(t), I(t))$ of system (4.3.1-4.3.2) are positive and bounded.

**Proposition 2.** *: Let $(G(t), I(t))$ be a solution of system (4.3.1-4.3.2) with $G(0) = G_0 > 0$, $I(0) = I_0 > 0$, then $G(t)$ and $I(t)$ are positive and bounded for all $t > 0$.*

*Proof.* **(i) $G(t)$ is positive.**
The solution of model (4.3.1-4.3.2) with given initial condition exists and is unique for all $t \geq 0$. If there exists a $t_0 > 0$ such that $G(t_0) = 0$ and $G(t) > 0$ for $0 < t < t_0$, then $G^{'}(t_0) \leq 0$. So we have

$$\begin{aligned} 0 \geq G^{'}(t_0) &= G_{in} - f_2(G(t_0)) - f_3(G(t_0))\, f_4(I(t_0)) + f_5(I(t_0)) \\ &= G_{in} - f_2(0) - f_3(0)\, f_4(I(t_0)) + f_5(I(t_0)) \\ &= G_{in} + f_5(I(t_0)) > 0 \end{aligned}$$

which is a contradiction, hence implies $G(t) > 0$ for all $t > 0$.
Hence, $G(t)$ is positive.

**(ii) $G(t)$ is bounded.**
If $\lim_{t\to\infty} \sup G(t) = \infty$, then there exist a sequence $\{t_n\}_{n=1}^{\infty} \uparrow \infty$ such that $\lim_{n\to\infty} G(t_n) = \infty$ and $G(t_n^{'}) \geq 0$. Thus $0 < G^{'}(t_n) = G_{in} - f_2(G(t_n)) - f_3(G(t_n))\, f_4(I(t_n)) + f_5(I(t_n)) \leq G_{in} -$

$f_2(G(t_n)) - k_4 f_3(G(t_n)) + K_5$, and therefore

$$\begin{aligned} 0 \leq \lim_{n\to\infty} G^{'}(t_n) &\leq G_{in} - \lim_{n\to\infty} f_2(G(t_n)) - k_4 \lim_{n\to\infty} f_3(G(t_n)) + K_5 \\ &\leq G_{in} - K_2 - k_4 \lim_{x\to\infty} f_3(x) + K_5 < 0 \end{aligned}$$

(The steady state of the system (4.3.1-4.3.2) is unique, hence

$$\lim_{x\to\infty} f_3(x) > (G_{in} - K_2 + K_5)/k_4).$$

This contradiction shows that there exist a $K_G > 0$ such that $G(t) < K_G$ for all $t > 0$ implies $G(t)$ is bounded above.

Hence, $G(t)$ is bounded.

**(ii)** $I(t)$ **is positive and bounded.**

Eqn.(4.3.2) can be written as

$$\begin{aligned} \frac{dI}{dt} &= f_1(G(t)) - d_i I(t) \\ \frac{dI(t)}{dt} + d_i I(t) &= f_1(G(t)) \end{aligned}$$

The solution is given by

$$\begin{aligned} I(t)e^{d_i t} &= I(0) + \int_0^t f_1(G(t))e^{d_i t} dt \\ I(t) &= I(0)e^{-d_i t} + e^{-d_i t} \int_0^t f_1(G(t))e^{d_i t} dt \end{aligned}$$

which implies, I(t) $\geq$ I(0)$e^{-d_i t}$, At $t \to \infty$, I(t) $> 0$, implies I(t) is positive.
At steady point, I(t) = $d_i^{-1} f_1(x)$, Since $|f_1(x)| \leq K_1$, therefore I(t) $\leq d_i^{-1} K_1$ = K, hence I(t) is bounded.

Hence the solution $(G(t), I(t))$ of the model (4.3.1-4.3.2) are positive and bounded. □

## 4.8 Stability analysis of mathematical model

To discuss the stability analysis of the model (4.3.1-4.3.2), we assume that all functions $f_i$, i = 1,2,3,4,5 satisfies the following conditions [75] :

(i) $\beta$ cells of the pancreas secrete insulin to control the glucose concentration level and since pancreas stop releasing insulin when the glucose concentration is abundant, hence $f_1(x) > 0$ and $f_1'(x) < 0$ for $x > 0$. Since the highly raised glucose concentration saturate the secretion of insulin, hence the amount of insulin secreted by pancreas is finite and so we take $\lim_{x\to\infty} f_1(x) = K_1$ for $x > 0$. Some amount of insulin can also be secreted by pancreas without the glucose stimulation, hence we assume $f_1(0) = k_1 > 0$.

(ii) The function $f_2(x)$ represents the insulin - independent glucose utilization, it is clear that $f_2(0) = 0$, $f_2(x) > 0$ and $f_2'(x) > 0$ for $x > 0$. Also the utilization of glucose is limited, we assume that $\lim_{x\to\infty} f_2(x) = K_2$ and $f_2'(x) < K_2'$ for $x > 0$.

(iii) The insulin - dependent utilization of glucose in the body is represented by the function $f_3(G(t))f_4(I(t))$, so it can be written as $f_3(0) = 0$, $f_3'(x) > 0$, $f_4(0) = k_4 > 0$, $f_4(x) > 0$ and $f_4'(x) > 0$ for $x > 0$. From [75], we assume that there exists constants $k_3 > 0$, $K_4 > 0$ such that $0 < f_3(x) \leq k_3 x$, $\lim_{x\to\infty} f_4(x) = K_4$ for $x > 0$.

(iv) $f_5$ denotes the total glucose production and since organs stops releasing glucose when the insulin concentration is abundant, hence $f_5(x) > 0$, and $f_5'(x) < 0$ for $x > 0$, and $\lim_{x\to\infty} f_5(x) = 0$. Amount of glucose produced by liver is small and it takes some time also, so there exists $K_5$ such that $f_5(x) \leq K_5$ for $x > 0$, and $f_5(0) = k_5$.

Consider the linearized system of model (4.3.1-4.3.2) about the steady point ($G^*$, $I^*$):

$$\frac{dG}{dt} = -AG(t) - BI(t) \tag{4.8.1}$$

$$\frac{dI}{dt} = CG(t) - d_i I(t) \tag{4.8.2}$$

where, A= $f_2'(G^*)$ + $f_3'(G^*)f_4(I^*)$, B = $f_3(G^*)f_4'(I^*)$ - $f_5'(I^*)$, C = $f_1'(G^*)$

The characteristic equation is given as :

$$\lambda^2 + a\lambda + b = 0$$

in which, $a$ = A + $d_i$, $b$ = A$d_i$ - BC.

Apply Routh - Hurwitz Criterian on the characteristics polynomial to prove the system as stable and for that we need to show the following conditions :

(i) $a = \mathrm{A} + d_i > 0$
(ii) $b = \mathrm{A}d_i - \mathrm{BC} > 0$
(iii) $\mathrm{A} > 0$

*Proof.* (i) $a = f_2'(x) + f_3'(x) f_4(x) + d_i$,

since $f_2'(x) > 0$, $f_3'(x) > 0$, $f_4(x) > 0$ and $d_i > 0$ implies a $> 0$.

(ii) $b = (f_2'(x) + f_3'(x) f_4(x))d_i - (f_3(x) f_4'(x) - f_5'(x)) f_1'(x)$,

since $f_2'(x) > 0$, $f_3'(x) > 0$, $f_4(x) > 0$, $f_5'(x) < 0$, $d_i > 0$, $f_4(x) > 0$, $f_4'(x) > 0$ and $f_1'(x) < 0$ implies b $> 0$.

(iii) $\mathrm{A} = f_2'(G^*) + f_3'(G^*) f_4(I^*) > 0$,

From part (i) it can be seen that all the terms of A are $> 0$. □

Hence it is concluded that the mathematical model (4.3.1-4.3.2) which represents the glucose - insulin dynamics for normal people is stable. To avoid the repetition, the stability analysis of the remaining mathematical models are not discussed.

## 4.9 Numerical simulation

We used Matlab 2012b to simulate the mathematical models numerically. The results of our simulation reveals the possible reasons behind the raised glucose concentration in CNS, liver and kidney which are severely affected by the diabetes, if it persists long in the human body.

The total glucose space for the severe diabetic people is 124.47 $ml/kg$ or 9.68775 $l$ [182]. Out of which 1.04 % i.e 0.8112 $l$ of body weight is taken for the CNS and 11.41 % i.e 8.8765 $l$ of the total body weight is taken for the remaining compartments (liver and kidney). The total volume space for the insulin is 10.92 $l$ or 14.04 % of body weight, out of which 3.131 $l$ is for the plasma insulin compartment and 7.800 $l$ is for remote insulin compartment [183]. The average weight of human body is assumed to be 77.8 $kg$

throughout the paper.

### 4.9.1 Normal

Mathematical model (4.3.1-4.3.2) is numerically simulated to observe the glucose and insulin concentration in normal body. The values of the parameters which are taken in the numerical simulation are given in Table 4.1.

### 4.9.2 Central Nervous System

(i) To find the direct impact of volume of glucose and insulin space on the glucose - insulin dynamics in CNS for diabetic people, the parameters $V_1^{'}$ and $V_2^{'}$ are taken and are given in Table 4.2. Since glucose uptake and glucose production are impaired in diabetics, the effected glucose concentration level are shown with the help of graphs after numerical simulation of the mathematical model (4.3.1-4.3.2).

It can be seen from the Figure 4.3(a) that after a initial dip in starting, glucose concentration starts increasing and after approximately 1.5 hrs, glucose concentration crossed the normal glucose level and approaches to 190 $mg/dl$ within 3 hrs of glucose infusion, which explains the condition of hyperglycemia in and near the CNS compartment of the diabetic people. Figure 4.3(b) depicts the insulin concentration profile. Our simulation shows that decreased volume of glucose and insulin space may be one of the major reason for raised glucose concentration in the CNS. The other possible reasons together with the decreased volume of glucose and insulin space are discussed further.

(ii) The glucose concentration is already raised in the diabetic people as the glucose utilization is impaired in diabetic people. The parameter $U_b^{'}$ denotes the rate of glucose utilization with respect to glucose concentration i.e non insulin mediated glucose uptake. The parameter $U_0^{'}$ denotes the glucose utilization rate with respect to plasma insulin i.e insulin mediated glucose uptake in CNS.

The value of $U_b$ is 72 $mgmin^{-1}$ for normal people [7]. Since the rate of glucose utilization is lower in diabetics than normal person, hence three smaller values of $U_b^{'}$ are taken (60 $mgmin^{-1}$, 50 $mgmin^{-1}$, 40 $mgmin^{-1}$) to discuss the glucose - insulin dynamics in CNS of diabetics as shown in the Figure 4.4. Also three values of $U_0^{'}$ are taken (30 $mgmin^{-1}$, 20 $mgmin^{-1}$, 10 $mgmin^{-1}$) for fixed value of $U_b^{'}$ to discuss the glucose - insulin dynamics in CNS of diabetics which can be seen in Figure 4.5

### 4.9.3 Liver

Liver plays a major role in maintaining the glucose - insulin dynamics of the body. To the time non suppressed hepatic glucose production was considered as one of the main reason behind the raised glucose concentration in the body. $R_m^{'}$ represents the rate of insulin secretion and $R_g^{'}$ represents the rate of hepatic glucose production. Figure 4.6(a) shows the glucose concentration level in liver for different values of $R_m^{'}$ (20 $\mu U min^{-1}$, 15 $\mu U min^{-1}$, 10 $\mu U min^{-1}$) with fixed value (200 $mg min^{-1}$) of the parameter $R_g^{'}$. The reason for taking the value of $R_m^{'}$ very less compared to normal people is that since maximum suppression of hepatic glucose production was observed at insulin level of about 30 $\mu U min^{-1}$ to 50 $\mu U min^{-1}$ and it fails to do so in diabetic people hence a value near to 20 $\mu U min^{-1}$ is considered. The value of the parameter $R_g^{'}$ in case of type 2 diabetics is taken as 200 $mg min^{-1}$ (12 % more than that of normal) [167], as hepatic glucose production is increased in type 2 diabetics due to the increased insulin resistance. The values of the parameters taken to discuss the glucose - insulin dynamics in liver are given in Table 4.3.

### 4.9.4 Kidney

Stumvoll [176] shows the renal glucose production (RGP) and hepatic glucose production (HGP) in the basal state and the graphs for both production are similar in shape, only the concentration differs. $R_m^{''}$ represents rate of insulin secretion and $R_g^{''}$ represents rate of renal glucose production. Infact glucose concentration produced by renal is approximately half of the glucose concentration produced by liver. Hence the value of $R_g^{''}$ is taken as 90 $mg min^{-1}$ for kidney.

In diabetic people, insulin mediated glucose uptake and glucose production are disturbed due to insulin resistance of the body and hence the raised glucose concentration in the kidney can be seen in the Figure 4.7(a) for three different values (15 $\mu U min^{-1}$, 10 $\mu U min^{-1}$, 5 $\mu U min^{-1}$) of $R_m^{''}$.

## 4.10 Results and discussion

Mathematical models for all three compartments are simulated analytically and numerically for the transient behavior of glucose and insulin profiles. The figures illustrate the

curves of glucose and insulin concentration level in CNS, kidney and liver, corresponding to the changed value of volume of glucose space and insulin space in the organs.

Compared with the observations obtained by many biologists and researchers, the obtained results confirms most of the known observations and also reveals additional insightful information for type 2 diabetics. The results are concluded in the form of list given below :

(i) The glucose concentration approaches to 110 $mg/dl$ in 3 hours after glucose infusion, which lies in the normal physiological range (70 - 110 $mg/dl$) as shown in the Figure 4.2.

(ii) Figure 4.3 reveals that decreased volume of glucose and insulin space for diabetic people affect the CNS and may be considered as one of the possible many causes of raised glucose level which may leads to diabetic comma.

Figure 4.4(a) shows that glucose concentration level in CNS compartment of a diabetic people may acquire a blood sugar concentration over 200 $mg/dl$ and reached nearly 230 $mg/dl$ if the value of $U_b^{'}$ decreases and value of $U_0^{'}$ kept fixed. The glucose concentration continuously increases as the rate of glucose utilization decreases (depend upon the severity of disease) and may leads to diabetic comma sometimes, but never exceeds the glucose infusion value even for $U_b^{'}$ tends to zero. Figure 4.4(b) demonstrate the insulin concentration level in CNS compartment.

It can be concluded from the results that decreased volume of glucose and insulin space together with the decreased rate of glucose utilization (independent of presence of insulin) may affect the glucose concentration in the CNS compartment and hence can be considered as one of the reason for hyperglycemia in the CNS.

Similarly Figure 4.5(a) demonstrate the glucose concentration level in the CNS compartment when the value of $U_0^{'}$ varies with fixed value of $U_b^{'}$. The glucose concentration in this case is nearly 270 $mg/dl$ which clearly indicates that hyperglycemia exists and impaired the functioning of CNS. Also, it can be concluded that since both the uptakes (insulin mediated and non insulin mediated) affect the glucose concentration but decreased rate of insulin mediated glucose uptake has more impact than non insulin mediated glucose uptake in keeping the raised glucose concentration in the CNS. Figure 4.5(b) depicts the insulin concentration profile.

Figure 4.4 and Figure 4.5 shows that decreased volume of glucose and insulin space with decreased rate of glucose uptake (insulin mediated and non insulin mediated) also

intimidate continuous raised blood glucose concentration in CNS. Such condition may sometime leads to brain damage and some other brain related diseases.

(iii) The glucose level goes up and a risk of diabetic comma may be occurred if the value of $R_m^{'}$ reduced further as shown in Figure 4.6(a). It is concluded from the simulation that impaired insulin production from pancreas together with decreased volume of glucose and insulin space may be the possible reasons for the raised glucose concentration in the liver. Figure 4.6(b) demonstrate the insulin concentration level in the liver. Figure 4.6 reveals that in liver raised glucose concentration are caused by impaired insulin production from pancreas together with decreased volume of glucose and insulin space.

(iv) To the time, insulin resistance and non suppressed renal glucose production were supposed to be the reason of hyperglycemia but through this study, it can be concluded clearly that decreased volume of distribution of glucose and insulin space may be one of the major reason together with impaired rate of insulin production for raised glucose concentration in the diabetic people. Figure 4.7(b) demonstrate the insulin concentration level in the kidney. The values of the parameters taken to discuss the glucose - insulin dynamics for kidney are given in Table 4.4. Figure 4.7 depicts that impaired insulin production and decreased volume of glucose and insulin space together raised the glucose concentration and leads to many diseases related to kidney and sometimes leads to kidney failure.

## 4.11 Conclusion and future scope

An attempt has been made to capture the behavior of glucose - insulin dynamics in CNS, liver and kidney as different organs have different functions to perform and hence their need of glucose is also different. Separate mathematical models have been developed for CNS, liver and kidney depending on their response towards glucose and insulin dynamics. It is concluded that decreased volume of glucose and insulin space may be one of the major possible reason for the prolonged raised glucose concentration in CNS, liver and kidney of type 2 diabetics. Other reasons behind the raised glucose concentration may vary according to the behavior and physiology of affected organs as discussed in the paper. We hope the results obtained from the analytical and numerical study of the mathematical models will be the base to explore the role of volume of glucose and insulin space on diabetes.

| Parameters | Units | Values | Parameters | Units | Values |
|---|---|---|---|---|---|
| $R_m$ | $mUmin^{-1}$ | 210 | $V_3$ | $l$ | 3 |
| $R_g$ | $mgmin^{-1}$ | 180 | $V_2$ | $l$ | 11 |
| $U_m$ | $mgmin^{-1}$ | 940 | $V_1$ | $l$ | 10 |
| $U_0$ | $mgmin^{-1}$ | 40 | $t_i$ | min | 100 |
| $U_b$ | $mgmin^{-1}$ | 72 | $a_1$ | $mgl^{-1}$ | 300 |
| $C_1$ | $mgl^{-1}$ | 2000 | $\alpha$ | $lmin^{-1}$ | 0.29 |
| $C_2$ | $mgl^{-1}$ | 144 | E | $lmin^{-1}$ | 0.2 |
| $C_3$ | $mgl^{-1}$ | 1000 | $\beta$ | | 1.77 |
| $C_4$ | $mUl^{-1}$ | 80 | $C_5$ | $mUl^{-1}$ | 26 |

Table 4.1: The values of parameters for normal case [7].

| Parameters | Units | Values | Parameters | Units | Values |
|---|---|---|---|---|---|
| $V_1^{'}$ | $l$ | 0.8112 | $V_2^{'}$ | $l$ | 7.800 |

Table 4.2: The values of parameters for CNS.

| Parameters | Units | Values | Parameters | Units | Values |
|---|---|---|---|---|---|
| $V_1^{''}$ | $l$ | 8.8765 | $V_2^{'}$ | $l$ | 7.800 |
| $V_3^{'}$ | $l$ | 3.131 | $R_g^{'}$ | $mUmin^{-1}$ | 200 |

Table 4.3: The values of parameters for liver.

| Parameters | Units | Values | Parameters | Units | Values |
|---|---|---|---|---|---|
| $V_1^{''}$ | $l$ | 8.8765 | $V_2^{'}$ | $l$ | 7.800 |
| $V_3^{'}$ | $l$ | 3.131 | $R_g^{''}$ | $mUmin^{-1}$ | 90 |

Table 4.4: The values of parameters for kidney.

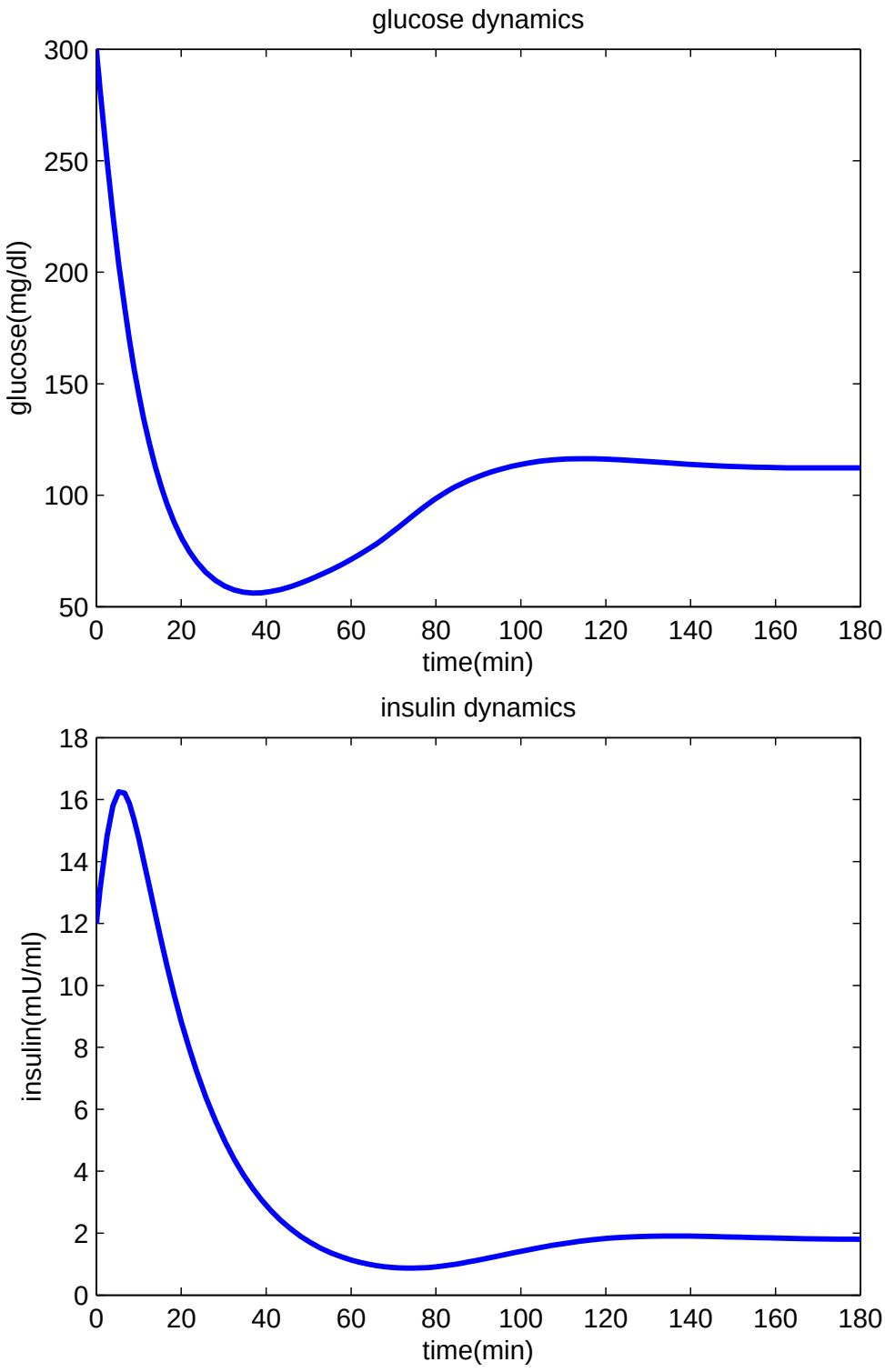


Figure 4.2: Glucose - Insulin dynamics for normal case.

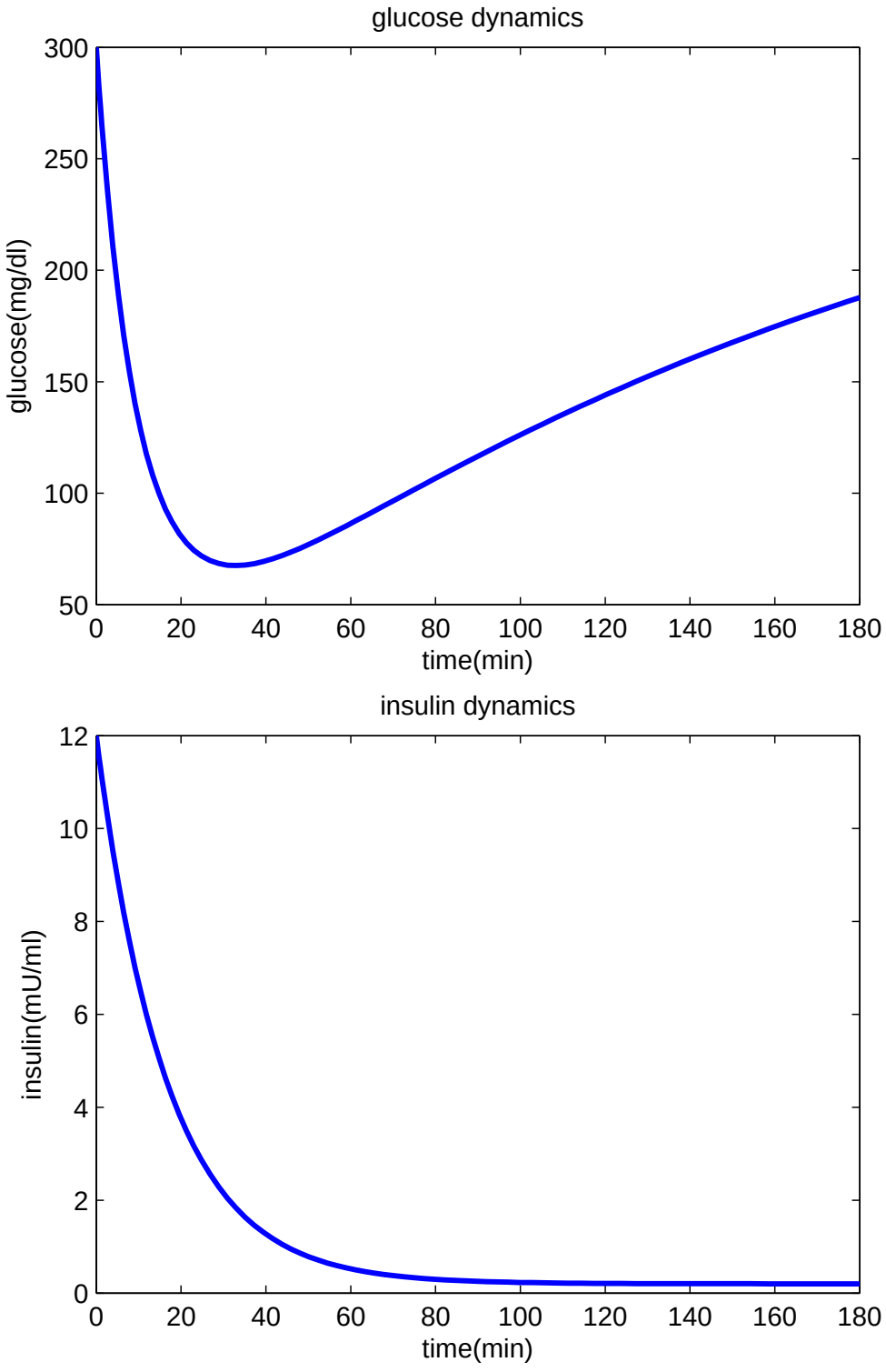


Figure 4.3: Glucose - Insulin dynamics of CNS for diabetic people with changed volume of glucose and insulin space.

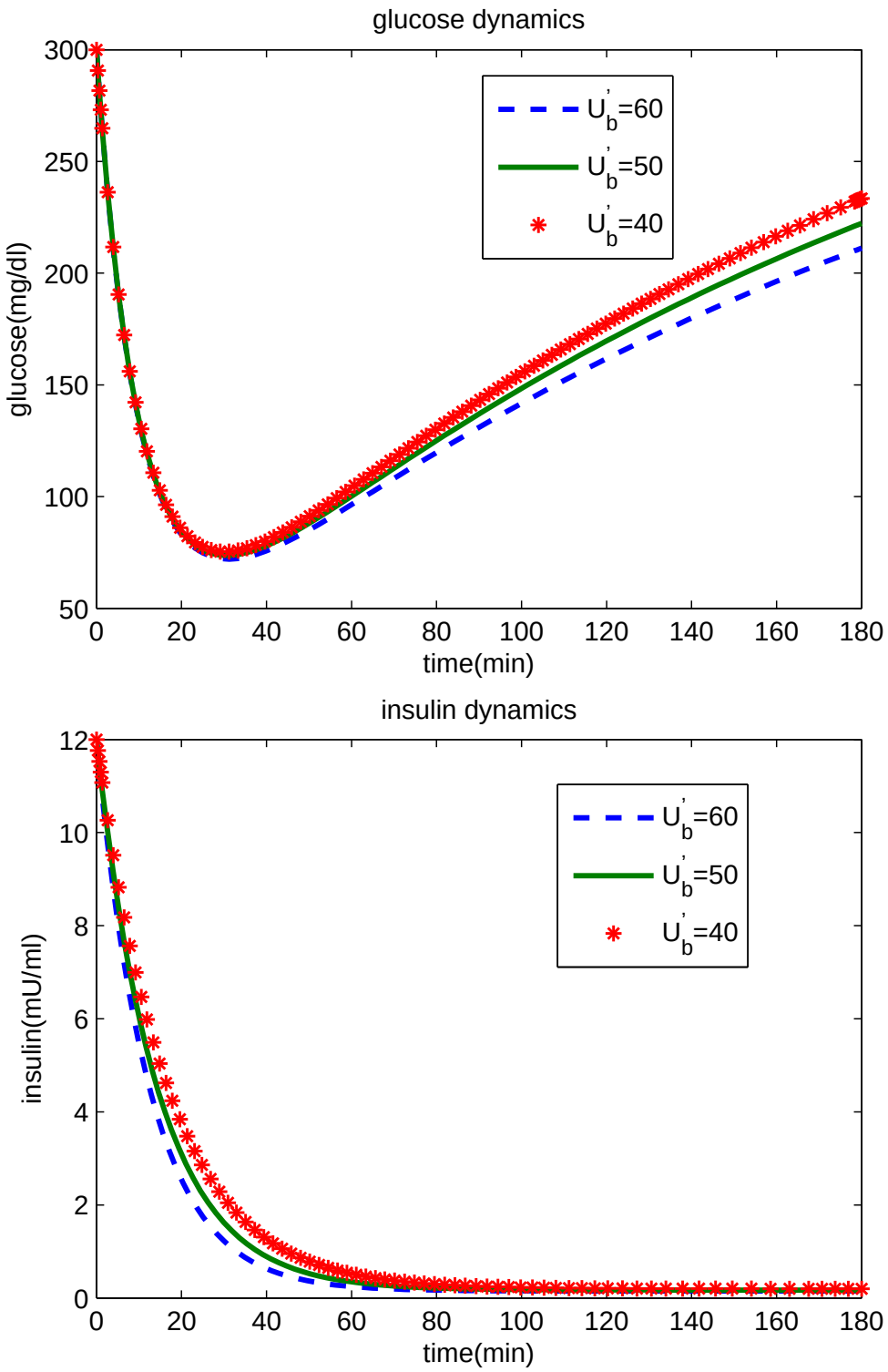


Figure 4.4: Glucose - Insulin dynamics of CNS for diabetic people for varying $U_b^{'}$.

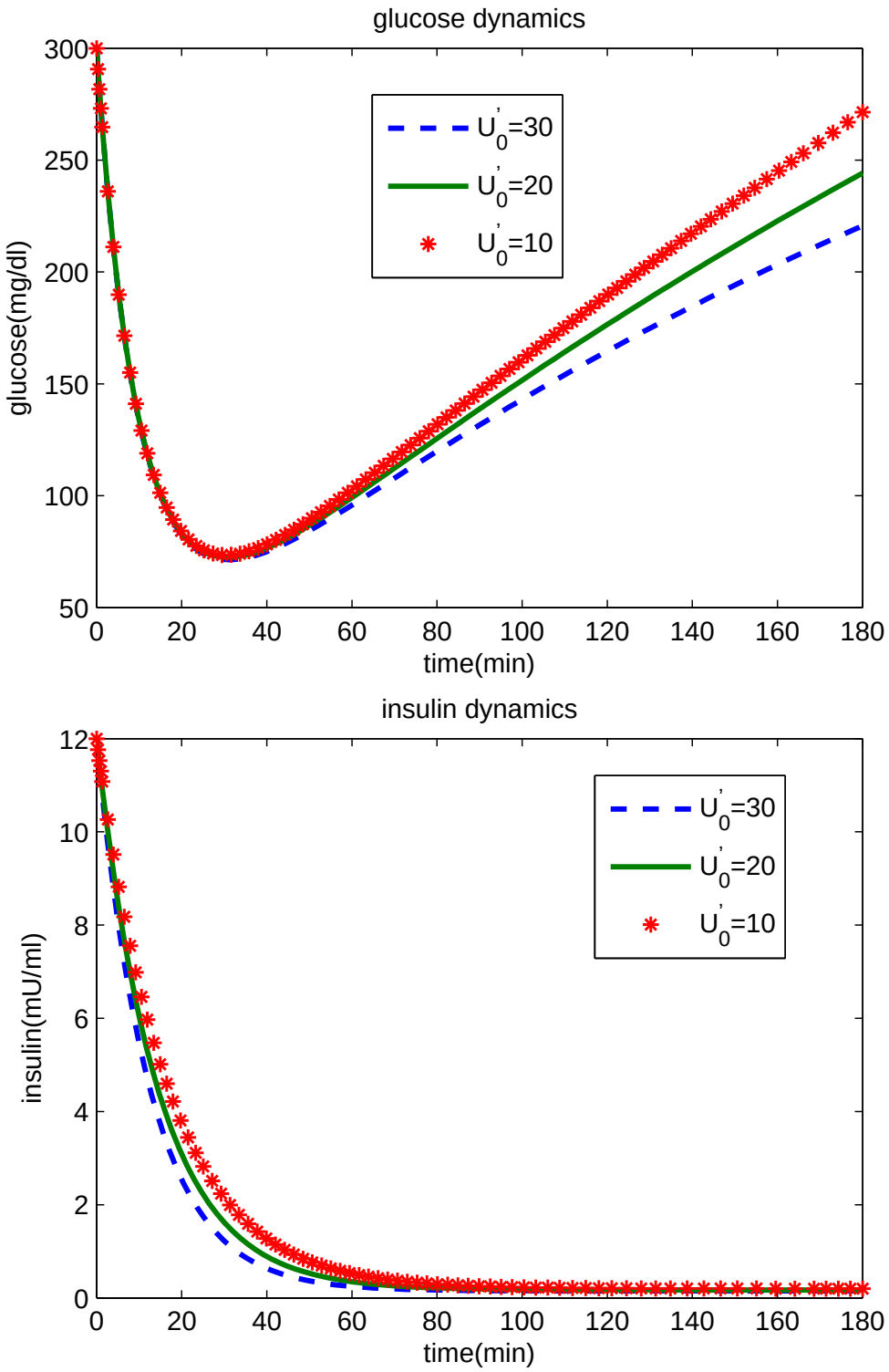


Figure 4.5: Glucose - Insulin dynamics of CNS for diabetic people for varying $U_0^{'}$.

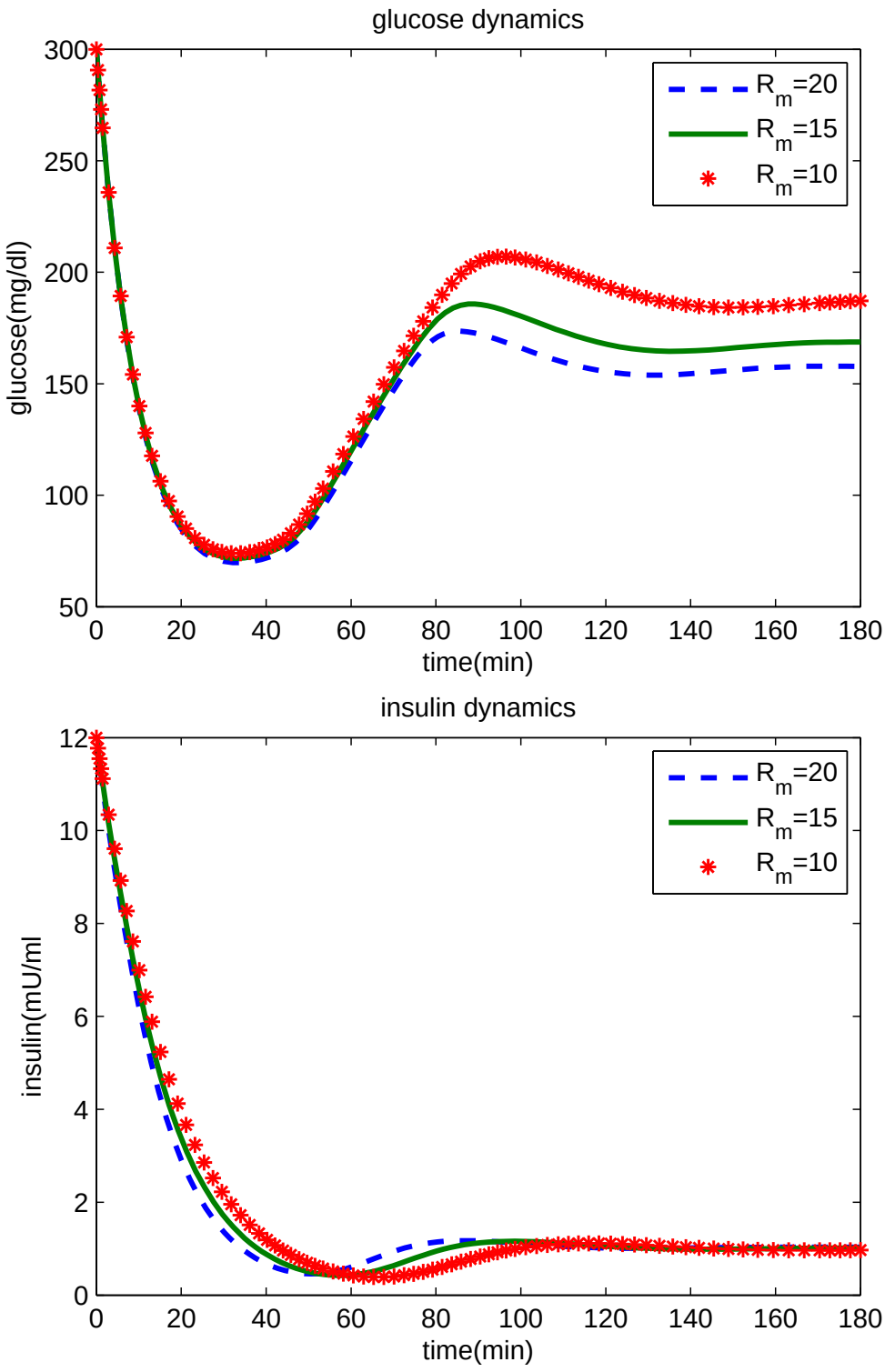


Figure 4.6: Glucose - Insulin dynamics of liver.

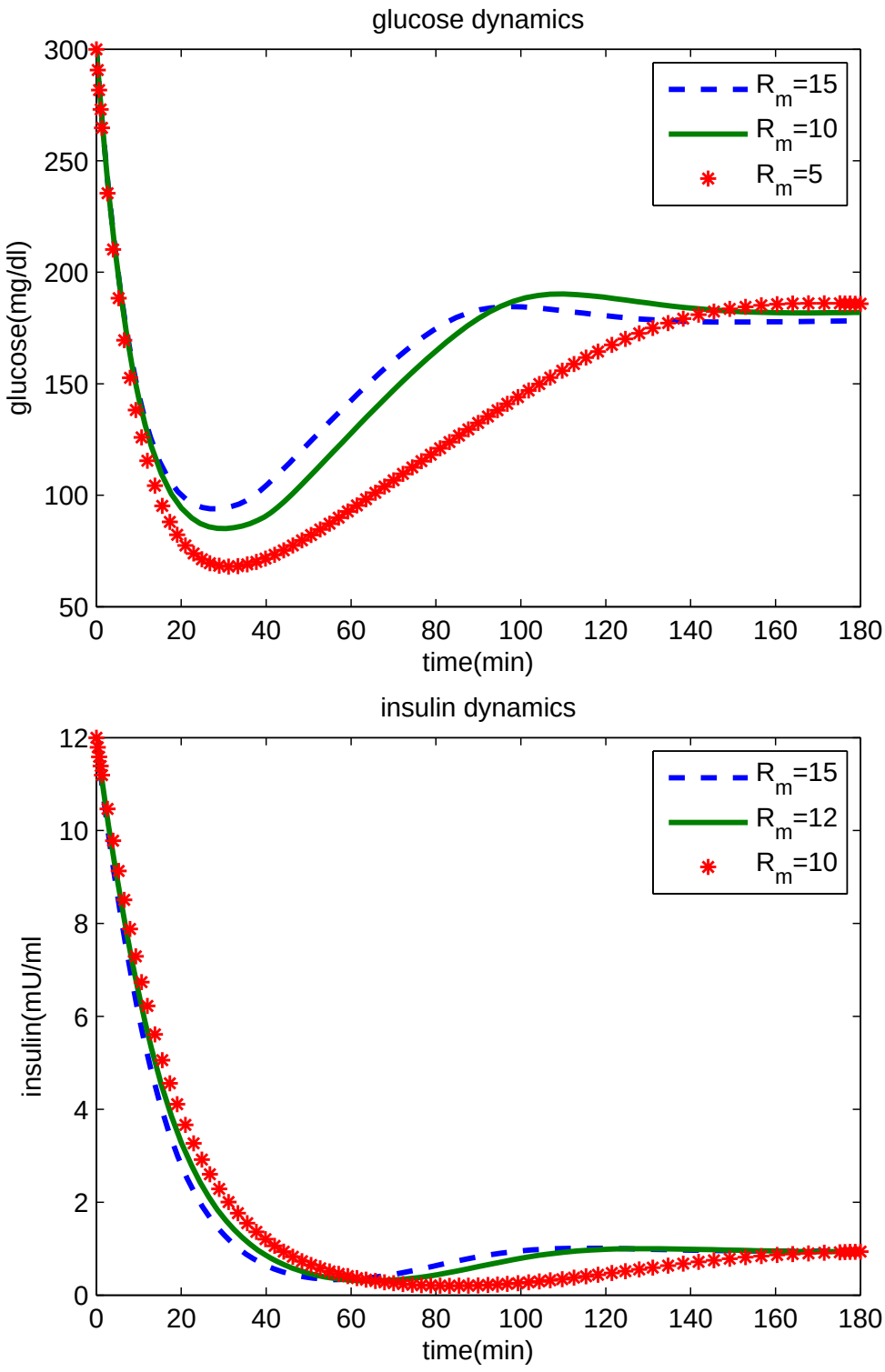


Figure 4.7: Glucose - Insulin dynamics of kidney.

# Chapter 5

# Study of two time delays in IVGTT

The most widely used model in physiological research on the metabolism of glucose is "minimal model", which describes intra venous glucose tolerance test (IVGTT) experimental data well with the smallest set of identifiable and meaningful parameters [46, 71]. This model was used for the study of time delay occurs in insulin secretion by Li et al. Literature confirms that delay occurs in insulin action also but not much attention has been paid on the numerical range of this delay. This motivated us to further extend the model by incorporated the second time delay for insulin action. In this chapter,[1] the extended model has been analyzed for stability and then numerical simulation is being carried out using Matlab 2012b. From the simulation results, we have concluded that sustained periodic oscillations are observed for both time delays. Also, the simulation shows that after introducing the delay in insulin action, the delay length of insulin secretion proposed by Li et al. has been shortened, which can be proved important in maintaining the glucose level after delivery of insulin.

[1]The results of this chapter has been communicated in a research paper entitled "Study of two time delays in IVGTT glucose - insulin dynamical system".

## 5.1 Introduction

Glucose and insulin are two important factors which maintain the glucose - insulin regulatory system and also maintain the body homeostasis. In the whole mechanism, some delays are observed (i) a delay is observed when insulin is released from pancreas stimulated by raised glucose level ($\tau_1$) [74,75] and (ii) also a delay is observed in the action of insulin to lower the raised glucose concentration ($\tau_2$) [17] as shown in Figure 5.1. It is well known that even if enough insulin is present in our body, glucose concentration will remain high because of delay in insulin action. Therefore, it is necessary to capture the delay in insulin action along with in its release from pancreas which motivated us to include this delay in the model proposed by Li et al [83].

In this chapter, a general mathematical model containing two delay terms for the glucose insulin interaction is presented. Numerical simulation is performed in Matlab 2012b and periodic solution are obtained for the various values of $\tau_1$ and $\tau_2$ as shown in the graphs for the discrete delay model. Also, the maximum possible value of delay in insulin action has been calculated which may be proved very useful in programming and designing of the devices used for external insulin delivery in severely affected diabetics.

## 5.2 Mathematical model

The general mathematical model for the glucose - insulin dynamics is given as:

$$\frac{dG(t)}{dt} = -f_1(G(t)) - f_2(G(t),I(t)) + G_{in} \tag{5.2.1}$$

$$\frac{dI(t)}{dt} = -f_3(I(t)) + f_4(H(G_t)) \tag{5.2.2}$$

Where $f_1$ represents glucose utilization independent of insulin, $f_2$ represents insulin mediated glucose utilization, $f_3$ represents insulin disappearance, $f_4$ denotes pancreatic insulin secretion simulated by raised glucose concentration and $G_{in}$ is the glucose concentration in the body.

The functions $f_1, f_2, f_3, f_4$ satisfies the following conditions :
(i) $f_1(0) = 0,\ f_1(\infty) = \infty,\ f_1^{'}(x) > 0;$
(ii) $f_2(0,0) = 0,\ f_{2x}(x,y) > 0,\ f_{2y}(x,y) > 0,\ f_2(x,0) = 0,\ f_2(0,y) = 0,\ f_2(x,\infty) = \infty,\ f_2(\infty,y) <$

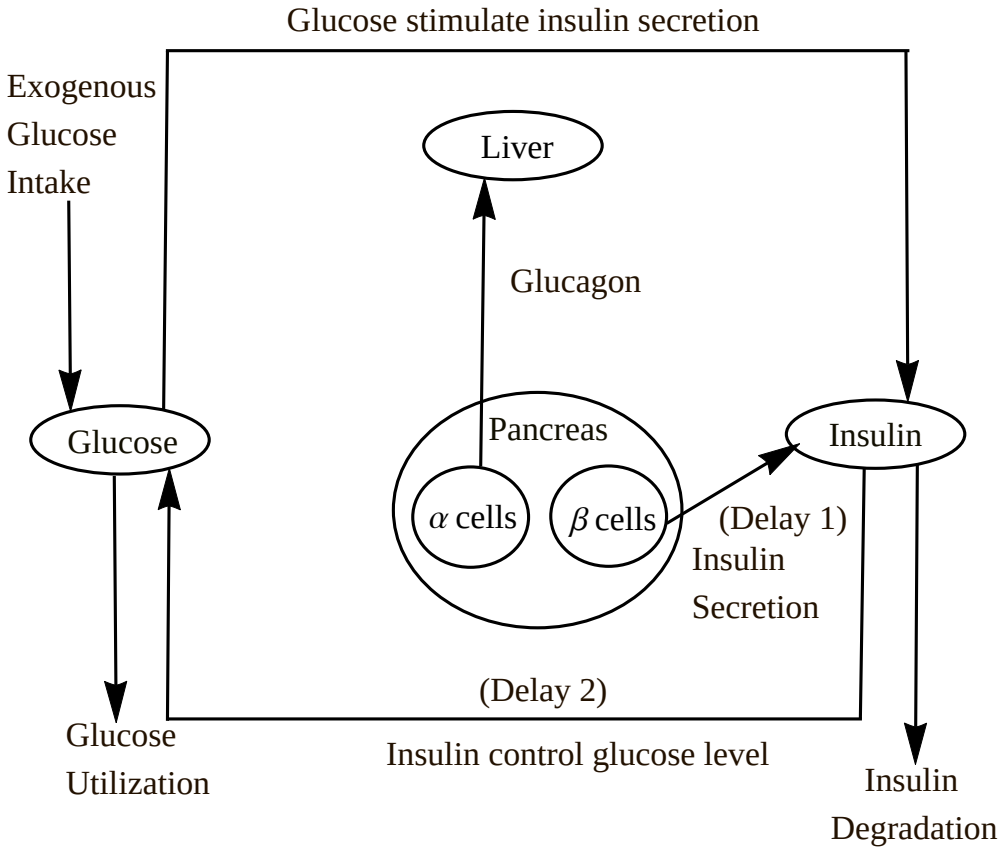


Figure 5.1: Glucose - Insulin dynamics having two delays - delay 1 ($\tau_1$) is observed when insulin is secreted from pancreas and delay 2 ($\tau_2$) is observed in insulin action.

$\infty$ for $x = 0$;

(iii) $f_3(0) = 0,\ f_3(\infty) = \infty,\ f_3^{'}(x) > 0$;

(iv) $f_4(x) = 0 \Leftrightarrow x = 0$.

We assume that the model (5.2.1-5.2.2) possesses a unique equilibrium point ($G^*$,$I^*$) in $R_+^2$.

We define a more general mathematical model for the analysis of glucose - insulin dynamics :

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 G(t) I(t-\tau_2)}{\alpha G(t) + 1} + b_7 \tag{5.2.3}$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 G_t(t-\tau_1) \tag{5.2.4}$$

The initial conditions are : $G(0) = G_b + b_0,\ I(0) = I_b + b_3 b_0,\ G(t) \equiv G_b$ for t $\in$ [-$\tau_1$, 0], $I(t) \equiv I_b$ for t $\in$ [-$\tau_2$, 0] and $G_t(\theta)$= G(t + $\theta$), t $>$ 0, $\theta \in$ [-$\tau_1$, 0]. Also, $H(G_t) = G(t-\tau_1)$ for $\tau_1$ as discrete delay; $H(G_t) = \frac{1}{\tau_1}\int_{-\tau_1}^{0} G(t+\theta)d\theta$ for $\tau_1$ as the distributed delay. $b_0$ $[mg/dl]$ is the increment in plasma glucose concentration over basal glucose concentration at time zero after infusion of intravenous glucose bolus, $b_1$ $[min^{-1}]$ is the rate of glucose degradation, $b_2$ $[min^{-1}]$ is the rate of insulin degradation, $b_3$ $[(mg/dl)^{-1}pM]$ is the first-phase insulin concentration increase per $mg/dl$ increase in the concentration of glucose at time zero due to the injected bolus, $b_4$ $[(pM)^{-1}min^{-1}]$ is the rate of insulin mediated glucose uptake per $pM$ of plasma insulin concentration, $b_6$ $[(mg/dl)^{-1}pMmin^{-1}]$ is the constant amount of second-phase insulin release rate per $mg/dl$ of glucose concentration; $b_7$ $[(mg/dl)min^{-1}]$ is the constant increase in plasma glucose concentration due to hepatic glucose production [48]. The parameters have the same meaning as in the De Gaetano and Arino model [48]. We are taking two delays $\tau_1$ and $\tau_2$ in which $\tau_2$ is discrete delay and $\tau_1$ could be discrete or distributed as defined in the model (5.2.3-5.2.4) and (5.2.5-5.2.6).

For the distributed delay ($\tau_1$), the model becomes

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 G(t) I(t-\tau_2)}{\alpha G(t) + 1} + b_7 \tag{5.2.5}$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{\tau_1}\int_{-\tau_1}^{0} G(t+\theta)d\theta \tag{5.2.6}$$

Both the models (5.2.3-5.2.4) and (5.2.5-5.2.6) possesses a unique equilibrium point ($G^*$, $I^*$) in $R^2_+$. It is also clear that the model (5.2.3-5.2.4) and (5.2.5-5.2.6) are the special cases of model (5.2.1-5.2.2).

At the equilibrium point ($G^*$, $I^*$), we conclude

$$I^* = \frac{b_6}{b_2} G^*$$

$$G^* = (-b_1 + \sqrt{b_1^2 + \frac{4b_4 b_6 b_7}{b_2}})/\frac{2b_4 b_6}{b_2}$$

## 5.3 Positive and bounded solutions of mathematical model

**Proposition 3.** *: The solutions of model (5.2.1-5.2.2) are positive, bounded and exists for all* $t > 0$.

*Proof.* **(i) Solutions ($G(t)$, $I(t)$) are positive.**
Consider the model (5.2.1-5.2.2) and let $(G(t), I(t))$ are the solutions of (5.2.1-5.2.2). For $t_0 > 0$, $G(t_0) = 0$ then $\dot{G}(t_0) \leq 0$.
Following the assumptions for the functions $f_1(0) = f_2(0, y) = 0$, we have

$$\begin{aligned} \dot{G}(t_0) &= -f_1(G(t_0)) - f_2(G(t_0), I(t_0 - \tau_2)) + G_{in} \\ &= G_{in} > 0 \end{aligned}$$

which is a contradiction, hence $G(t) > 0$ for all t.

For $t_0 > 0$, $I(t_0) = 0$ then $\dot{I}(t_0) \leq 0$.
Hence,

$$\begin{aligned} 0 &\geq \dot{I}(t_0) = -f_3(I(t_0)) + f_4 H(G_{t_0}) \\ &= f_4 H(G_{t_0}) > 0 \end{aligned}$$

which is a contradiction, as $G(t_0(\theta)) > 0$ for $\theta \in [-\tau_1, 0)$, hence implies $I(t) > 0$ for all t.

Hence $G(t)$, $I(t)$ are positive for all t.

**(ii) Solutions ($G(t)$, $I(t)$) are bounded.**

Consider the eqn.(5.2.1) of (5.2.1-5.2.2),

$$\begin{aligned} \dot{G(t)} &= -f_1(G(t)) - f_2(G(t), I(t-\tau_2)) + G_{in} \\ &\leq -f_1(G(t)) + G_{in} \end{aligned}$$

which implies $G(t) \leq f_1^{-1}(G_{in})$ .
Hence, $G_b + b_0 \leq G(t) \leq f_1^{-1}(G_{in})$ (by initial condition $G(0) = G_b + b_0$) which implies that $G(t)$ is bounded.

Also from eqn.(5.2.2),

$$\begin{aligned} \dot{I}(t) &= -f_3(I(t)) + f_4 H(G_t) \\ &\leq -f_3(I(t)) + f_4 H f_1^{-1}(G_{in}) \end{aligned}$$

which implies $I(t) \leq f_3^{-1} f_4 H(f_1^{-1}(G_{in}))$.
Hence, $I_b + b_3 b_0 \leq I(t) \leq f_3^{-1} f_4 H(f_1^{-1}(G_{in}))$ (by initial condition $I(0) = I_b + b_3 b_0$) which implies that $I(t)$ is bounded.

Hence $G(t), I(t)$ are bounded for all t.

Hence we conclude that the solutions of (5.2.1-5.2.2) are positive, bounded and exists for all $t > 0$. □

## 5.4 Linearization of the model

We linearize the model (5.2.1-5.2.2) to check the stability of the model whether the oscillatory solution will exists for the defined parameter values.
Consider the model (5.2.1-5.2.2), let $g(t) = G(t) - G^*$ implies $G(t) = g(t) + G^*$, $i(t) = I(t) - I^*$ implies $I(t) = i(t) + I^*$, where $(G^*, I^*)$ are the equilibrium point.
Then the model (5.2.1-5.2.2) is translated to

$$\frac{dg(t)}{dt} = -f_1[g(t) + G^*] - f_2[g(t) + G^*, i(t-\tau_2) + I^*] + G_{in} \tag{5.4.1}$$

$$\frac{di(t)}{dt} = -f_3[i(t) + I^*] + f_4 H(g_t + G^*) \tag{5.4.2}$$

having a unique equilibrium point at (0,0).

The linearized system of (5.4.1-5.4.2) is as follows :

$$\begin{aligned}\frac{dg(t)}{dt} &= -[f_1^{'}(G^*)+f_{2x}(G^*,I^*)]g(t)-f_{2y}(G^*,I^*)i(t-\tau_2)\\ \frac{di(t)}{dt} &= -f_3^{'}(I^*)i(t)+f_4^{'}(G^*)H(g_t)\end{aligned}$$

For convenience, replace $g(t)$ and $i(t)$ by $G(t)$ and $I(t)$.

$$\begin{aligned}\frac{dG(t)}{dt} &= -[f_1^{'}(G^*)+f_{2x}(G^*,I^*)]G(t)-f_{2y}(G^*,I^*)I(t-\tau_2)\\ \frac{dI(t)}{dt} &= -f_3^{'}(I^*)I(t)+f_4^{'}(G^*)H(G_t)\end{aligned}$$

Define A = $f_1^{'}(G^*)+f_{2x}(G^*,I^*)$, B = $f_{2y}(G^*,I^*)$, C = $f_3^{'}(I^*)$, D = $f_4^{'}(G^*)$ .

Hence

$$\frac{dG(t)}{dt} = -AG(t)-BI(t-\tau_2) \tag{5.4.3}$$

$$\frac{dI(t)}{dt} = -CI(t)+DH(G_t) \tag{5.4.4}$$

If $H(G_t)$ takes the discrete delay form, then $H(G_t)=G(t-\tau_1)$, $t>0$ and the characteristic equation is

$$\lambda^2+p\lambda+q+re^{-\lambda(\tau_1+\tau_2)}=0 \tag{5.4.5}$$

where p = A + C, q = AC, r = BD.

If $H(G_t)$ takes the distributed delay form, then $H(G_t)=\frac{1}{\tau_1}\int_{t-\tau_1}^{t}G(\theta)d\theta, t>0$ then the characteristic equation is

$$\lambda^2+p\lambda+q+\frac{re^{-\lambda\tau_2}}{\tau_1}\int_{-\tau_1}^{0}e^{\lambda\theta}d\theta=0 \tag{5.4.6}$$

## 5.5 Delay dependent stability analysis

Case 1 : Discrete delay term

The characteristic equation for discrete delay form is given as :

$$P(\lambda)=\lambda^2+p\lambda+q+re^{-\lambda(\tau_1+\tau_2)}=0 \tag{5.5.1}$$

The trivial solution of (5.5.1) is unstable for all $\tau_1 \geq \tau_0$, $\tau_2 \geq \tau_0$ if there exists $\tau_0 > 0$, then there exists $z > 0$ such that $P(iz) = 0$. The equation becomes

$$z^2 - pzi - q - rcos(\tau_1 + \tau_2)z + irsin(\tau_1 + \tau_2)z = 0$$

implies $z^2 = q + rcos(\tau_1 + \tau_2)z$ and $pz = rsin(\tau_1 + \tau_2)z$.
Since $p, z, r > 0$ therefore, it implies $(\tau_1 + \tau_2) \geq \frac{p}{r}$.

Hence for $H(G_t) = G(t - \tau_1)$, $t > 0$, $\tau_1 > 0$ and $(\tau_1 + \tau_2) < \frac{p}{r}$, the trivial solution of (5.5.1) is globally asymptotically stable.

Case 2 : Distributed delay term
Consider the characteristic equation for distribution delay form

$$P^{'}(\lambda) = \lambda^2 + p\lambda + q + \frac{re^{-\lambda\tau_2}}{\tau_1}\int_{-\tau_1}^{0} e^{\lambda\theta}d\theta \tag{5.5.2}$$

The trivial solution of (5.5.2) is unstable for some $\tau_1 > 0$ and $\tau_2 > 0$, then there exists $\gamma > 0$ and $\beta > 0$ such that $\lambda = \gamma + i\beta$ is a solution of (5.5.2).

$$(\gamma + i\beta)^2 + p(\gamma + i\beta) + q + \frac{re^{-(\gamma+i\beta)\tau_2}}{\tau_1}\int_{-\tau_1}^{0} e^{\gamma\theta}(cos\beta\theta + isin\beta\theta)d\theta = 0$$

$$\gamma^2 - \beta^2 + 2\gamma\beta i + p\gamma + pi\beta + q + \frac{re^{-\gamma\tau_2}(cos\beta\tau_2 - isin\beta\tau_2)}{\tau_1}\int_{-\tau_1}^{0} e^{\gamma\theta}(cos\beta\theta + isin\beta\theta)d\theta = 0$$

comparing the terms, we get

$$\gamma^2 - \beta^2 + p\gamma + q + \frac{re^{-\gamma\tau_2}}{\tau_1}[cos\beta\tau_2\int_{-\tau_1}^{0} e^{\gamma\theta}cos\beta\theta d\theta + sin\beta\tau_2\int_{-\tau_1}^{0} e^{\gamma\theta}sin\beta\theta d\theta] = 0$$

and

$$2\gamma\beta + p\beta + \frac{re^{-\gamma\tau_2}}{\tau_1}[cos\beta\tau_2\int_{-\tau_1}^{0} e^{\gamma\theta}sin\beta\theta d\theta + sin\beta\tau_2\int_{-\tau_1}^{0} e^{\gamma\theta}cos\beta\theta d\theta] = 0$$

$$2\gamma\beta + p\beta = -\frac{re^{-\gamma\tau_2}}{\tau_1}[cos\beta\tau_2\int_{-\tau_1}^{0} e^{\gamma\theta}sin\beta\theta d\theta + sin\beta\tau_2\int_{-\tau_1}^{0} e^{\gamma\theta}cos\beta\theta d\theta] \tag{5.5.3}$$

Since $\beta > 0$,

$$2\gamma + p \leq | \frac{re^{-\gamma\tau_2}}{\tau_1}[cos\beta\tau_2 \int_{-\tau_1}^{0} e^{\gamma\theta}\frac{sin\beta\theta}{\beta}d\theta + sin\beta\tau_2 \int_{-\tau_1}^{0} e^{\gamma\theta}\frac{cos\beta\theta}{\beta}d\theta] |$$

$$2\gamma + p \leq | \frac{re^{-\gamma\tau_2}}{\tau_1} || cos\beta\tau_2 || \int_{-\tau_1}^{0} e^{\gamma\theta}\frac{sin\beta\theta}{\beta}d\theta | + | \frac{re^{-\gamma\tau_2}}{\tau_1} || sin\beta\tau_2 || \int_{-\tau_1}^{0} e^{\gamma\theta}\frac{cos\beta\theta}{\beta}d\theta |$$

$$2\gamma + p \leq \frac{r}{\tau_1}\int_{-\tau_1}^{0} | \theta | d\theta + \frac{r}{\tau_1}\int_{-\tau_1}^{0} | \theta | d\theta = r\tau_1 \tag{5.5.4}$$

This shows $\gamma \leq \frac{1}{2}(r\tau_1 - p)$.

Hence for $H(G_t) = \int_{-\tau_1}^{0} G(t+\theta)d\theta$, $t > 0$, $\tau_1 > 0$ and $\tau_1 < \frac{p}{r}$, the trivial solution of (5.5.2) is globally asymptotically stable.

## 5.6 Numerical simulation and results

Ultradian oscillations are observed in the human body in two different ranges : slow ultradian oscillations (10-15 min) and rapid ultradian oscillations (80-150 min) [184,185]. Often the slow ultradian oscillations are superimposed by rapid ultradian oscillation. Occurrence of ultradian oscillations due to the interaction between insulin and glucose were observed by Sturis et al. [6] in non linear mathematical model comprising six ordinary differential equations. Sustained insulin and glucose oscillations were found numerically to be dependent on time delay by the effect of insulin on glucose production and effect of insulin on glucose utilization [83]. Both "minimal model" and "dynamical model" do not account both the delays and were not constructed for the understanding of insulin oscillations [83].

In 2001, Li et al. [83] found an alternative way of introducing delay term in the dynamical model given by Arino [48] and able to show that the new dynamical model (after incorporating the parameter $\alpha$) possesses unstable steady states and produced oscillatory solutions for very large value of delay term $b_5$ (=550 min). Li et al. showed the periodic oscillations in subjects 6 and 7 (experimental data taken from De Gaetano and Arino [48]) through the graphs by using XPP for windows 98/NT [83].

We extended the model given by Li et al. [83] and presented a new model (5.2.3-5.2.4) for the study of Intravenous glucose tolerance test (IVGTT) which focuses on the metabolism of glucose. The steady state is globally asymptotically stable for all the meaningful values of time delays $\tau_1$ and $\tau_2$ . From our extensive computer simulation using Matlab 2012b, we found that for first subject, periodic solution can be obtained for $\tau_1 = 480$ min, $\tau_2 = 15$ min and $\alpha = 0.01$ and for second subject, periodic solution can be obtained for $\tau_1 = 490$ min, $\tau_2 = 15$ min and $\alpha = 0.05$.

Figure 5.2 illustrate the periodic solutions for discrete delay model (5.2.3-5.2.4) for both subjects using the data given in Table 5.1. It is clearly seen in the Figure 5.2(a) and Figure 5.2(b) that sustained periodic oscillations for both subjects are obtained at time delay of length 480 min and 490 min respectively. Also, it is quite noticeable that since the actual delay length for both the subjects is 23 min [48], hence it is very unlikely to observe sustained periodic oscillations in real life experiments. No sustainable and periodic oscillations are observed for short delays, however it may possible for large enough delays as shown in the Figure 5.2(a) and Figure 5.2(b).

The introduction of $\tau_2 = 15$ min in the model helps to lower down the value of $\tau_1$ from 550 min to 480 min in first subject and $\tau_1$ from 600 min to 490 min in second subject. Also the number of oscillations increased in large time intervals for both subjects. It can be considered as an alternative way to deliver insulin in the body by keeping the two delays in account. Our results also shows that the generalized mathematical model may produce oscillatory solutions even without considering hepatic glucose production.

## 5.7 Conclusion and future scope

The present chapter provides an alternative way of delivering insulin and glucose intake by taking account the necessary delays ($\tau_1$ and $\tau_2$) which occurs in the glucose - insulin dynamics. Numerical results of the model provides the range of time delays which produce periodic solutions and more number of oscillations can be obtained in the same range as compared with the model of Li et al. [83]. One more important delay which occur in the hepatic glucose production influenced by insulin presence can be taken into account for the deep study of glucose - insulin interaction dynamics. No doubt, this will increase the number of equations in the model and make the system complex, but provide a closer approach to understand the metabolism of glucose - insulin interaction dynamics.

| P | $G_b$ | $I_b$ | $b_0$ | $b_1$ | $b_2$ | $b_3$ | $b_4$ | $b_6$ | $b_7$ |
|---|---|---|---|---|---|---|---|---|---|
| U | $mg/dl$ | $pM$ | $mg/dl$ | $min^{-1}$ | $min^{-1}$ | $(mg/dl)^{-1}$ $pM$ | $pM^{-1}min^{-1}$ | $(mg/dl)^{-1}$ $pMmin^{-1}$ | $(mg/dl)$ $min^{-1}$ |
| 1 | 88 | 68.6 | 209 | 0.0002 | 0.4200 | 1.64 | 0.000109 | 0.033 | 0.68 |
| 2 | 87 | 37.9 | 311 | 0.0001 | 0.2196 | 0.64 | 0.000373 | 0.096 | 1.24 |

Table 5.1: The values of parameters for first subject and second subject [48], P stands for parameter, U stands for units, 1 stands for first subject, 2 stands for second subject .

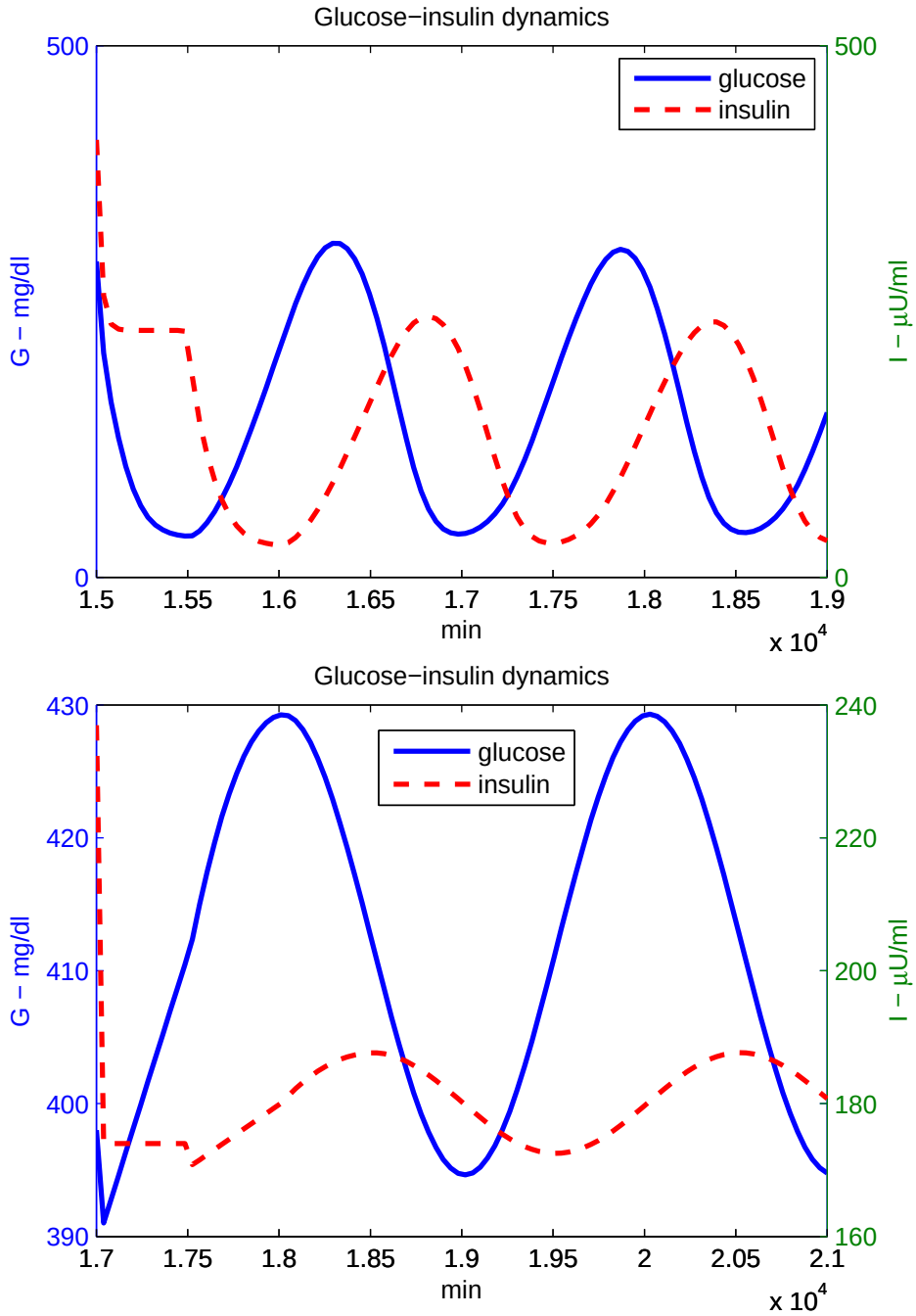


Figure 5.2: Glucose - Insulin dynamics of first subject having $\tau_1$ = 15, $\tau_2$ = 480 shown in first figure and second subject having $\tau_1$ = 15, $\tau_2$ = 490 shown in second figure.

# Chapter 6

# Quantitative analysis of two time delays using artificial pancreas

In this chapter,[1] ranges of time delays in glucose - insulin dynamics of type 1 diabetics using artificial pancreas has been quantified. Time delay in insulin secretion, its absorption and action is a point of consideration in artificial pancreas as it may prove fatal in the extreme situation. The present mathematical model deals with two time delays out of which one occur in insulin secretion and second in its absorption and action. The model assess the change in glucose - insulin dynamics after the induction of different values of these time delays in their respective range. Also, simulation is performed over the model to quantify the amount of two time delays to avoid diabetic comma, which has not been explored much.

[1]The result of this chapter has been published in a research paper entitled "Quantitative analysis of time delays of glucose - insulin dynamics using artificial pancreas" in *Discrete and continuous dynamical system - series b,* **20** (9) (2015) doi:10.3934/dcdsb.2015.20.3115.

## 6.1 Introduction

Type 1 diabetes can occur at any age, but it usually starts in early age. Pancreas of type 1 diabetic people produces almost no insulin and thus such patients have to undergo intensive insulin therapy. The use of insulin pump, also known as Continuous Subcutaneous Insulin Infusion (CSII) therapy, has greatly increased for type 1 diabetes as it also provides a good alternative to insulin injections.

Many endocrine systems show the ultradian rythmetical oscillations. Out of which hormone insulin also shows the same characteristics. Insulin release from the pancreas in human body is a multioscillatory process with rapid pulses of about 10 min and slower oscillation of 50-120 min [12]. For type 1 diabetic people, whole amount of insulin is given from the outer source, so the insulin secretion from the insulin pump is assumed to behave in manner of ultradian oscillation.

The Artificial Pancreas (AP), known as closed - loop control of blood glucose in diabetes, is a system combining a glucose sensor, a control algorithm, and an insulin infusion device [186]. The term Artificial Pancreas was first introduced in 1974 and PID controller was considered to be the best controller until the mechanism was not completely known in application [187].

Hypoglycemia remains a big barrier to the intensification of insulin therapy. Lower levels of glycated hemoglobin are unfortunately associated with an increased risk of hypoglycemia [188]. Continuous glucose monitoring devices measuring ISF (interstitial fluid) glucose exhibit time delays when compared to capillary blood glucose. Short delays exist due to diffusion through glucose membrane, as the process of diffusion often depends upon membrane thickness [189]. Sensors measuring ISF glucose will lag blood glucose by the time, what it takes for glucose to diffuse from the capillary to the interstitial space adjacent to the sensors or sampling device. The relationship between ISF glucose and plasma glucose has been under debate for some time, whether ISF glucose leads plasma glucose or plasma glucose leads ISF glucose. The model [190] assumed the time lag between ISF and plasma glucose concentration is constant. Ward in 2010 [191] established the consistency with rate parameters unaffected by rising and falling glucose levels, which holds time for different insulin concentration. Jiaxu in 2006 [74] compared many models (single and two delays) to find that models which includes two delays are explicitly more robust and more accurate than model which include single delay.

Nowadays, model based control are preferred due to various limitations during their use in subcutaneous systems. These models reflect the physiology of insulin secretion stimulated by raised level of glucose, and glucose absorption controlled by insulin or exogenous insulin given by outer source [73]. The first model containing the delay term for the glucose - insulin dynamics was introduced by Sturis et al. [6] in 1991 for the normal subjects. After that a lot of work has been done by taking the same model to discuss various aspects. In 2006, Li et al. [74] introduced two explicit time delays and proposed a model for better understanding the glucose - insulin regulatory system and ultradian insulin secretary oscillations in normal subjects for the cases of continuous enteral nutrition and constant glucose infusion rate. After that in 2007, Li et al. [75] found the factors which may be responsible for the sustained oscillatory regulation and insulin secretion taking the same model used in [74]. In 2012, Li et al. [76] modified the model by taking single delay and the term denotes the Hepatic glucose production (HGP) as a constant term. He found that HGP is insignificant for type 1 diabetic patients and obtained the results including exogenous insulin injection and the feedback of monitored glucose concentration level for the diabetic people by using artificial pancreas but failed to control the most critical issue of hypoglycemia found in diabetic people.

Time delays that occur in insulin release have been discussed widely in literature but delay happening in insulin absorption and its action has not been paid much attention inspite of being an important factor in maintaining glucose - insulin regulatory system. In this chapter, a model has been developed by considering these two time delays $\tau_s$ (time delay in insulin secretion) and $\tau_a$ (time delay in insulin absorption and action) to discuss the physiological changes in glucose - insulin regulatory system that occur in type 1 diabetic people by using artificial pancreas. The schematic diagram is shown in the Figure 6.1. We tried to quantify the range of time period of both the delays after which glucose level decreases sharply and thus may lead to diabetic comma.

The purpose of this chapter is to use the model of the glucose - insulin regulatory system in order to quantify the amount of two time delays observed during insulin secretion and its absorption and action to avoid diabetic comma.

## 6.2 Mathematical model

The two major factors in the regulatory system model are glucose and insulin. Let G(t) and I(t) represent the glucose and insulin concentration at time $t \geq 0$. The model comprises of : $\frac{dG}{dt}$ = glucose production - glucose utilization and $\frac{dI}{dt}$ = insulin production - insulin utilization.

Glucose production: Glucose is generated from dietary carbohydrate such as starch or sucrose obtained from the food we eat. Glucose is taken through meal ingestion, oral glucose intake, constant glucose infusion which is represented by $G_{in}$ in the first equation of the model [6, 7]. Liver also produce glucose and considered as a source of glucose as glucose is stored mainly in the liver and muscles as glycogen, but in T1DM, working of $\alpha$ cells which are located in the langerhans islets of the pancreas is impaired and so no glucagon is secreted from $\alpha$ cells resulting no glucose production by liver.

Glucose utilization: Glucose utilization is of two types - insulin independent and insulin dependent utilization. Brain is considered as insulin - independent glucose utilizer. The insulin independent glucose utilization is denoted by $f_2(G(t))$ and is of sigmoidal shape [6]. The insulin dependent utilization is mostly due to muscles, fat cells and other tissues which is denoted by the function $f_3(G(t))$ and whole glucose utilization is denoted by $f_3(G(t))\, f_4(I(t))$ in the first equation of the model.

Insulin production: Insulin is produced from $\beta$ cells of the pancreas, mainly in response of elevated glucose concentration in the body. But since we are dealing with type 1 diabetic people and $\beta$ cells are impaired in action, hence insulin is injected from outer source through artificial pancreas. The function $f_1(G(t))$ stands for the insulin production stimulated by glucose concentration and is of sigmoidal shape [6], present in the second equation of the model.

Insulin utilization: In general, insulin is used when the level of glucose raised in the body and is cleared by all insulin sensitive tissues. When insulin is not removed by liver and kidneys, then ultimately it is cleared by muscle cells, adipose cells and other tissues. The aim is to use the inactive insulin in the body and lower the raised glucose level. Experiments have shown that insulin degradation is proportional to insulin concentration [7]. Insulin degradation rate is given by positive constant $d_i \geq 0$.

Two delays: The following feedback loops are present in the system : glucose enhances

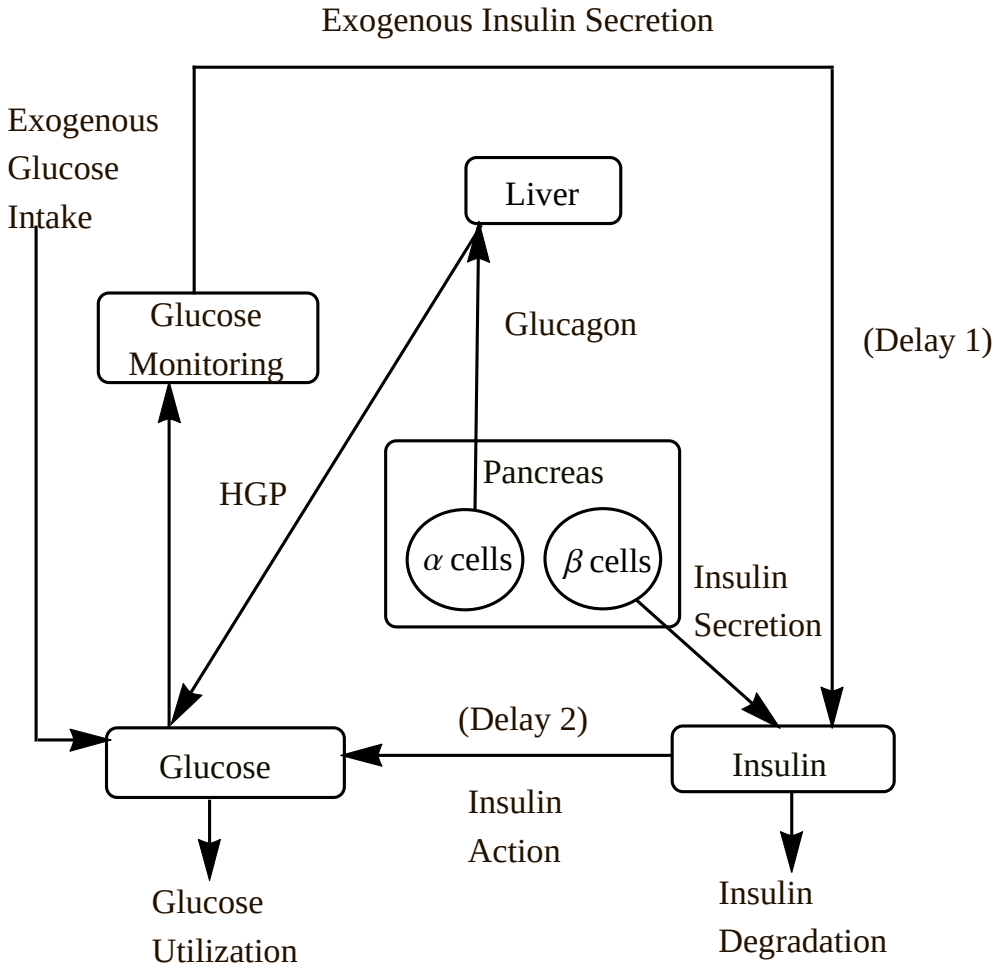


Figure 6.1: Glucose - Insulin dynamics with two time delays - delay 1 ($\tau_s$) indicates the time delay in insulin secretion and delay 2 ($\tau_a$) represents the time delay in insulin action.

its own uptake, glucose stimulates insulin secretion, insulin stimulates glucose uptake. The whole system contains 2 significant delays. When the glucose level rises in the body, glucose sensor becomes activated and directs the insulin pump to inject insulin subcutaneously. In this process, it has been experimentally observed that a delay of (5, 15) min occurs in insulin secretion [186]. $\tau_s$ represents the time delay of the insulin response to the elevated glucose level and time required for the secreted insulin to become remote insulin and is represented by $f_1(G(t-\tau_s))$.

In the model (6.2.1-6.2.2), $\tau_a$ represents the delay of insulin absorption and insulin action in the body to lower the glucose level in its normal range and the range of $\tau_a$ has been observed as (20, 50) min experimentally [186]. This is the delay which will contribute majorly to the situation of diabetic comma that will be discussed in numerical simulation. Since $f_4(I(t))$ is a function of insulin and represents the insulin dependent glucose utilization, hence the delay $\tau_a$ is incorporated in this function and is represented by $f_4(I(t-\tau_a))$ in the model.

The rate of glucose utilization is not uniform in all bodies and it varies according to the different glucose - insulin metabolic regulatory system. Hypoglycemia and hyperglycemia are the most harmful episodes in the insulin therapy treatment (closed loop control system or artificial pancreas) and are caused by unbalanced glucose utilization and insulin production. The objective of the model discussed here is to do the quantitative analysis of two delays in the glucose - insulin metabolic regulatory system for the diabetic people.

According to normal physiology, insulin secretion is controlled by $\beta$ cells of islets of langerhans, which stops secreting insulin as the glucose concentration gets lower than normal range. As a result of which $\alpha$ cells get activated to release glucagon. This glucagon leads to hepatic glucose production and it takes some time for HGP to produce significant effect and a delay in this mechanism is observed [75]. In type 1 diabetes, this whole phenomena does not take place because of insignificant effect of $\alpha$ and $\beta$ cells. Hence, the effect of insulin to control HGP is not significant for diabetic people using artificial pancreas [76]. So effect of HGP is taken as constant (= c) in the model (6.2.1-6.2.2) discussed below.

The proposed model with the time delays $\tau_s$ and $\tau_a$ in the glucose - insulin regulatory

system is given below :

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))\, f_4(I(t-\tau_a)) + c \tag{6.2.1}$$

$$\frac{dI}{dt} = f_1(G(t-\tau_s)) - d_i I(t) \tag{6.2.2}$$

with initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0$, $G(t) \equiv G_0$ for $t \in [-\tau_s, 0]$ and $I(t) \equiv I_0$ for $t \in [-\tau_a, 0]$, $\tau_s, \tau_a \geq 0$. The functions $f_i$, i = 1,2,3,4 are defined in (1.7.13-1.7.16) in chapter 1 and their values are taken from Sturis et al. [6] paper as the shape of the functions are more important than their forms [74] shown in Figure 1.1.

## 6.3 Positive and bounded solutions of mathematical model

To discuss positive and bounded solution of the model (6.2.1-6.2.2), we assume that all the functions $f_i$, i = 1,2,3,4 of model (6.2.1-6.2.2) satisfy the following conditions :

(i) Raised glucose concentration in the body stimulate sensor to release insulin, hence $f_1(x) > 0$ and $f_1'(x) > 0$ for $x > 0$. Since the highly raised glucose concentration saturate the secretion of insulin, hence the amount of insulin secreted by pancreas is finite and so we take $\lim_{x\to\infty} f_1(x) = K_1$ and $f_1'(x) < K_1'$ for $x > 0$. It implies the sigmoidal shape of the function $f_1(x) > 0$ is reasonable. Some amount of insulin can also be secreted by pancreas without the glucose stimulation, hence we assume $f_1(0) = k_1 > 0$.

(ii) The function $f_2(x)$ indicates the insulin - independent glucose utilization, it is clear that $f_2(0) = 0$, $f_2(x) > 0$ and $f_2'(x) > 0$ for $x > 0$. Also as the utilization of glucose is limited, we assume that $\lim_{x\to\infty} f_2(x) = K_2$ and $f_2'(x) < K_2'$ for $x > 0$.

(iii) The insulin - dependent utilization of glucose in the body is represented by the function $f_3(G(t))\, f_4(I(t))$, so it can be written as $f_3(0) = 0$, $f_3'(x) > 0$, $f_4(0) = k_4 > 0$, $f_4(x) > 0$ and $f_4'(x) > 0$ for $x > 0$. From Sturis et al. [6] paper, we assume that there exists constants $k_3 > 0$, $K_4 > 0$ and $K_4' > 0$ such that $0 < f_3(x) \leq k_3 x$, $\lim_{x\to\infty} f_4(x) = K_4$ and $f_4'(x) < K_4'$ for $x > 0$ and so $f_4(x)$ is of sigmoidal shape.

**Lemma 6.3.1.** *[75] Let $f : R \to R$ be a differentiable function. If $l = \lim_{t\to\infty} \inf f(t) < \lim_{t\to\infty} \sup f(t) = L$, then there are sequences $\{t_k\} \uparrow \infty$, $\{s_k\} \uparrow \infty$ such that for all k, $f'(t_k) = f'(s_k) = 0$, $\lim_{k\to\infty} f(t_k) = L$ and $\lim_{k\to\infty} f(s_k) = l$.*

**Proposition 4.** *[75] In model (6.2.1-6.2.2), the following holds:*

*(i) If* $\lim_{x\to\infty} f_3(x) > (G_{in} - K_2 + c)/k_4$*, then model (6.2.1-6.2.2) has unique positive steady state* $(G^*, I^*)$ *with* $I^* = d_i^{-1} f_1(G^*)$*. Also, all solutions exist in* $(0,\infty)$*, and are positive and bounded.*
*(ii) If* $\lim_{x\to\infty} f_3(x) < (G_{in} - K_2)/k_4$*, then* $\lim_{t\to\infty} \sup G(t)$ *tends to* $\infty$*.*

**Remark 1.** Condition (i) indicates that insulin helps the body cells to utilize glucose. If the condition (ii) holds, the glucose concentration level will not be bounded and hence not feasible for the system. Therefore to maintain the feasibility of the system, we assume that condition (i) in Proposition 4 holds throughout this chapter.

*Proof.* **(i)** Let

$$J(x) = G_{in} - f_2(x) - f_3(x) f_4(d_i^{-1} f_1(x)) + c = 0, x \geq 0 \tag{6.3.1}$$

**Uniqueness of solution : Eqn.**(6.3.1) **has unique root in** $(0,\infty)$.
Observe that $f_1^{'}(x) > 0$, $f_2^{'}(x) > 0$, $f_3^{'}(x) > 0$, $f_4^{'}(x) > 0$, we have

$$J^{'}(x) = -f_2^{'}(x) - f_3^{'}(x) f_4(d_i^{-1} f_1(x)) - f_3(x) f_4^{'}(d_i^{-1} f_1(x)) d_i^{-1} f_1(x) < 0$$

Also, $J(0) = G_{in} - f_2(0) - f_3(0) f_4(d_i^{-1} f_1(0)) + c = G_{in} + c > 0$, and

$$\begin{aligned} \lim_{x\to\infty} J(x) &= G_{in} - \lim_{x\to\infty} f_2(x) - \lim_{x\to\infty} f_3(x) f_4(d_i^{-1} \lim_{x\to\infty} f_1(x)) + c \\ &= G_{in} - K_2 - f_4(d_i^{-1} K_1) \lim_{x\to\infty} f_3(x) + c \\ &< G_{in} - K_2 - k_4 \lim_{x\to\infty} f_3(x) + c < 0 \end{aligned}$$

which implies $J(0) > 0$ and $\lim_{x\to\infty} J(x) < 0$.
Hence by Mean Value Theorem, eqn.(6.3.1) has unique root in $(0,\infty)$.

**Solutions (**$G(t)$**,** $I(t)$**) are positive.**
It is clear that $G^*$ is the root of eqn.(6.3.1) and $I^* = d_i^{-1} f_1(G^*)$. Note that $| f_i^{'}(x) |$, $i$ = 1,2,3,4 are bounded, $f_i(x)$, i = 2,3 and $f_j(x_t)$, j = 1,4 are Lipschitzian and completely continuous in $x \geq 0$ and $x_t \in C([-max\{\tau_s, \tau_a\}, 0])$ respectively. Then by theorem 2.1, 2.2 and 2.4 on page 19 and 20 in [192], the solution of model (6.2.1-6.2.2) with given initial condition exists and is unique for all $t \geq 0$. If there exists a $t_0 > 0$ such that $G(t_0) = 0$ and $G(t) > 0$ for $0 < t < t_0$, then $G^{'}(t_0) \leq 0$.

Therefore,

$$\begin{aligned} 0 \geq G^{'}(t_0) &= G_{in} - f_2(G(t_0)) - f_3(G(t_0))\, f_4(I(t_0 - \tau_a)) + c \\ &= G_{in} - f_2(0) - f_3(0)\, f_4(I(t_0) - \tau_a) + c \\ &= G_{in} + c > 0 \end{aligned}$$

this is a contradiction which implies $G(t) > 0$ for all $t > 0$. Hence $G(t)$ is positive.

If there exists $t_0^{'} > 0$ such that $I(t_0^{'}) = 0$ and $I(t) > 0$ for $0 < t < t_0^{'}$, then $I(t_0^{'}) \leq 0$.
Therefore,

$$0 > I(t_0^{'}) = f_1(G(t_0^{'})) - d_i I(t_0^{'} - \tau_s) \geq f_1(G(t_0^{'})) > 0.$$

this is a contradiction which implies $I(t) > 0$ for all $t > 0$. Hence $I(t)$ is positive.

Hence the solution $(G(t), I(t))$ of model (6.2.1-6.2.2) are positive.

**Solutions $(G(t), I(t))$ are bounded.**
If $\lim_{t\to\infty} \sup G(t) = \infty$, then there exist a sequence $\{t_n\}_{n=1}^{\infty} \uparrow \infty$ such that $\lim_{n\to\infty} G(t_n) = \infty$ and $G(t_n^{'}) \geq 0$.
Thus

$$\begin{aligned} 0 < G^{'}(t_n) &= G_{in} - f_2(G(t_n)) - f_3(G(t_n))\, f_4(I(t_n - \tau_s)) + c \\ &\leq G_{in} - f_2(G(t_n)) - k_4 f_3(G(t_n)) + c \end{aligned}$$

and therefore

$$\begin{aligned} 0 \leq \lim_{n\to\infty} G^{'}(t_n) &\leq G_{in} - \lim_{n\to\infty} f_2(G(t_n)) - k_4 \lim_{n\to\infty} f_3(G(t_n)) + c \\ &\leq G_{in} - K_2 - k_4 \lim_{x\to\infty} f_3(x) + c < 0 \end{aligned}$$

This contradiction shows that there exist a $K_G > 0$ such that $G(t) < K_G$ for all $t > 0$ implies $G(t)$ is bounded above.

From second equation of model (6.2.1-6.2.2), since $\mid f_1(x) \mid \leq K_1$, for all $\varepsilon > 0$, $0 < I^{'}(t) \leq$

$f_1(K_G+\varepsilon) - d_i I(t)$ for large $t > 0$ implies $\lim_{t\to\infty} \sup I(t) \leq d_i^{-1} f_1(K_G+\varepsilon)$. For $\varepsilon > 0$, $\lim_{t\to\infty} \sup I(t) \leq d_i^{-1} f_1(K_G) = K_I$. This implies I(t) is bounded above.

Hence the solution $(G(t), I(t))$ of model (6.2.1-6.2.2) are bounded for $t > 0$.

**(ii)** If (ii) is not true, let us suppose $\lim_{t\to\infty} G(t) = K_G < \infty$, then there exists $\{t_n\}_{n=1}^{\infty} \uparrow \infty$ such that $G^{'}(t_n) = 0$, $n$ = 1,2,3,... and $\lim_{n\to\infty} G(t_n) = K_G$.
Thus

$$\begin{aligned} G^{'}(t_n) &= G_{in} - f_2(G(t_n)) - f_3(G(t_n)) f_4(I(t_n - \tau_a)) + c & (6.3.2) \\ \Rightarrow 0 &\geq G_{in} - f_2(G(t_n)) - k_4 f_3(G(t_n)) & (6.3.3) \end{aligned}$$

Now, after taking $\lim_{n\to\infty}(0 \geq G_{in} - f_2(G(t_n)) - k_4 f_3(G(t_n)))$, eqn.(6.3.3) implies $f_3(K_G) \geq (G_{in} - f_2(K_G))/k_4$. While from part (ii) of Proposition1, $f_3(K_G) \leq \lim_{x\to\infty} f_3(x) < (G_{in} - K_2)/k_4 \leq (G_{in} - f_2(K_G))/k_4$, which is a contradiction, hence (ii) is true.

When $\lim_{x\to\infty} f_3(x) \leq (G_{in} - K_2 + c)/k_4$, a continuous decrement in glucose utilization occur which results into continuous increment in glucose concentration till $\lim_{x\to\infty} f_3(x) = (G_{in} - K_2)/k_4$ and $\lim_{t\to\infty} \sup G(t)$ tends to $\infty$ when $\lim_{x\to\infty} f_3(x) < (G_{in} - K_2)/k_4$, as discussed in (ii). This situation is in contradiction with the human physiology. Since the steady state is unique for any system which is discussed in condition (i), therefore condition (ii) and inequality $(G_{in} - K_2)/k_4 \leq \lim_{x\to\infty} f_3(x) \leq (G_{in} - K_2 + c)/k_4$ become infeasible. □

## 6.4 Stability analysis of mathematical model

The linearized system of model (6.2.1-6.2.2) about the steady point $(G^*, I^*)$ is given by :

$$\begin{aligned} \frac{dG}{dt} &= -PG(t) - QI(t - \tau_a) & (6.4.1) \\ \frac{dI}{dt} &= RG(t - \tau_s) - d_i I(t) & (6.4.2) \end{aligned}$$

where
$\mathrm{P} = f_2^{'}(G^*) + f_3^{'}(G^*) f_4(I^*) > 0$, $\mathrm{Q} = f_3(G^*) f_4^{'}(I^*) > 0$, $\mathrm{R} = f_1^{'}(G^*) > 0$

The characteristic equation is given as

$$\lambda^2 + (P + d_i)\lambda + Pd_i + QRe^{-\lambda(\tau_s+\tau_a)} = 0 \tag{6.4.3}$$

For $\lambda = 0$, characteristic equation reduces to $Pd_i + QR > 0$, hence $\lambda = 0$ is not a solution of (6.4.3).

To analyze the stability of model we define a lemma.

**Lemma 6.4.1.** *[192] Consider the following delay differential equation :*

$$x''(t) + px'(t) + qx(t) + rx(t-\tau) = 0, \tau \geq 0 \tag{6.4.4}$$

*and assume p,q,r* $> 0$*, then the number of pairs of pure imaginary roots of the characteristic equation*

$$\lambda^2 + p\lambda + q + r\exp^{-\lambda\tau} = 0, \tau \geq 0 \tag{6.4.5}$$

*can be zero, one, or two only.*

*(i) For* $q > r$, $2q - p^2 < 0$ *and* $2q - p^2 < 2\sqrt{q^2 - r^2}$*, there are no such roots exist for* $\tau > 0$ *and the trivial (zero) solution of eqn.*(6.4.5) *is stable for all* $\tau > 0$ *.*

*(ii) For* $q < r$ *and* $2q - p^2 > 0$*, then there are one such root exists for* $\tau > 0$ *and the trivial (zero) solution of eqn.*(6.4.5) *is uniformly asymptotically stable for* $\tau < \tau_0$*, and unstable for* $\tau > \tau_0$*, where* $\tau_0 > 0$ *is a constant.*

*(iii) For* $q > r$, $2q - p^2 > 0$ *and* $2q - p^2 > 2\sqrt{q^2 - r^2}$*, there are two such roots for* $\tau > 0$ *and the stability of the trivial (zero) solution of eqn.*(6.4.5) *can change a finite number of times as* $\tau$ *is increased, and eventually it becomes unstable.*

A theorem is given below in which stability of the mathematical model (6.2.1-6.2.2) has been analyzed in four cases.

**Theorem 6.4.2.** *Consider the model (6.2.1-6.2.2), then we have*

*(1) If* $\tau_s = 0$ *and* $\tau_a = 0$*, then* $(G^*, I^*)$ *is stable.*

*Proof.* : $\tau_s = \tau_a = 0$

The characteristic equation is given by :

$$\lambda^2 + (P + d_i)\lambda + Pd_i + QR = 0 \tag{6.4.6}$$

and $P + d_i > 0$, $Pd_i + QR > 0$ implies $(G^*, I^*)$ is stable. □

(2) For $\tau_s > 0$ and $\tau_a = 0$, and

(2.a) if $Pd_i > QR$, then $(G^*, I^*)$ is stable.

*Proof.* $\tau_s > 0$, $\tau_a = 0$

The characteristic equation is

$$\lambda^2 + (P + d_i)\lambda + Pd_i + QRe^{-\lambda\tau_s} = 0 \tag{6.4.7}$$

Here, $2q - p^2 = -P^2 - d_i^2 < 0$, then $Pd_i > QR$ implies that the trivial solution of linearized model (6.4.1-6.4.2) is always stable for $\tau_s > 0$ (By Lemma 6.4.1(i)).

□

(2.b) if $Pd_i < QR$, then $\exists\ \tau_{s,0} > 0$ such that $(G^*, I^*)$ is stable when $\tau_s \in (0, \tau_{s,0})$ and unstable when $\tau_s \geq \tau_{s,0}$.

*Proof.* From the Lemma 6.4.1(ii), we can see that the trivial solution of the linearized system (6.4.1-6.4.2) is stable when $\tau_s \in (0, \tau_{s,0})$ and unstable when $\tau_s \geq \tau_{s,0}$. Now we need to find $\tau_{s,0}$ and $\tau_{a,0}$ for the sustained oscillations if exists for the model (6.2.1-6.2.2).

Put $\lambda = iz$, $z > 0$ be an eigenvalue of eqn.(6.4.5), we have

$$-z^2 + (P + d_i)iz + Pd_i + QR(cos\tau_s z - isin\tau_s z) = 0 \tag{6.4.8}$$

That is,

$$-z^2 + Pd_i + QRcos\tau_s z = 0$$
$$(P + d_i)z - QRsin\tau_s z = 0$$

This leads to

$$z^4 + (P^2 + d_i^2)z^2 + P^2 d_i^2 = Q^2 R^2 \tag{6.4.9}$$

Now the roots are given by :

$$z_{1+}^2 = \frac{1}{2}\{-(P^2 + d_i^2) + [(P^2 - d_i^2)^2 + Q^2 R^2]^{1/2}\} \tag{6.4.10}$$

$$z_{2+}^2 = \frac{1}{2}\{-(P^2 + d_i^2) - [(P^2 - d_i^2)^2 + Q^2 R^2]^{1/2}\} \tag{6.4.11}$$

Based on the arguments (3.12) - (3.17) from [ [192], pg 74 - 77], From eqn.(6.4.9), we get

$$\begin{aligned} \tau_{s,0} &= \frac{\theta_1}{z_{1+}} \\ \tau_{a,0} &= \frac{\theta_2}{z_{2+}} \end{aligned}$$

where $z_{1+}$ and $z_{2+}$ are the roots of eqn.(6.4.5).
For $0 \leq \theta_1 \leq 2\pi$, we have

$$\begin{aligned} cos\tau_s z_{1+} &= \frac{z_{1+}^2 - Pd_i}{QR} \\ sin\tau_s z_{1+} &= \frac{(P + d_i)z_{1+}}{QR} \end{aligned}$$

and for $0 \leq \theta_2 \leq 2\pi$, we have

$$\begin{aligned} cos\tau_a z_{2+} &= \frac{z_{2+}^2 - Pd_i}{QR} \\ sin\tau_a z_{2+} &= \frac{(P + d_i)z_{2+}}{QR} \end{aligned}$$

It is found from computational results that for $\tau_a = 0$, sustained oscillations exist for $\tau_s \in (40, 48)$ min and no sustained oscillations exists if $\tau_s \geq 48$ min.

Hence the system $(G^*, I^*)$ is stable when $\tau_s \in (40, 48)$ min and unstable when $\tau_s \geq 48$ min. □

(3) For $\tau_s = 0$ and $\tau_a > 0$, and

(3.a) if $Pd_i > QR$, then $(G^*, I^*)$ is stable.

(3.b) if $Pd_i < QR$, then $\exists\ \tau_{a,0} > 0$ such that $(G^*, I^*)$ is stable when $\tau_a \in (0, \tau_{a,0})$ and unstable when $\tau_a \geq \tau_{a,0}$.

*Proof.* Proof of (3.a) is same as proof of (2.a) which is discussed above. For (3.b), computational result shows that sustained oscillations occurred for $\tau_a \in (43, 48)$ min and no sustained oscillations exists if $\tau_a \geq 48$ min at $\tau_s = 0$.

Hence the system $(G^*, I^*)$ is stable when $\tau_a \in (43, 48)$ min and unstable when $\tau_a \geq 48$ min. □

(4) If $\tau_s > 0$ and $\tau_a > 0$, then $(G^*, I^*)$ is stable..

*Proof.* $\tau_s > 0$, $\tau_a > 0$

Let $\lambda = iz$, $z > 0$ be an eigenvalue of eqn.(6.4.5), then we have,

$$-z^2 + (P + d_i)iz + Pd_i + QR(cos(\tau_s + \tau_a)z - isin(\tau_s + \tau_a)z) = 0 \tag{6.4.12}$$

That is, we have

$$-z^2 + Pd_i + QRcos(\tau_s + \tau_a)z = 0 \tag{6.4.13}$$

$$(P + d_i)z - QRsin(\tau_s + \tau_a)z = 0 \tag{6.4.14}$$

This leads to

$$z^4 + (P^2 + d_i^2)z^2 + P^2 d_i^2 = Q^2 R^2 \tag{6.4.15}$$

The above equation is not possible for $Pd_i >$ QR i.e. q > r therefore, the steady state ($G^*$, $I^*$) is stable. □

From the analysis of all four cases, we conclude that eqn.(6.4.15) is a biquadratic equation and is stable for all values of $z$. Also, since it is not possible to bifurcate the equation by varying any of the parameters, it does not create any type of chaos which may disturb the stability of the system. It confirms that the given model with two explicit delays is more stable than other predefined models. The numerical results and simulation of the model discussed in the next section also supports the same.

## 6.5 Numerical simulation and results

Numerical Simulation has been carried out by using matlab 2012b [193] to simulate the model consisting of two time delays. Insulin secretion in the glucose - insulin dynamics occurs in an oscillatory manner over a range of (50 - 150) min and is usually referred to as ultradian oscillations in the normal people. The ultradian oscillations of insulin secretion are assumed to result from an instability in the glucose - insulin endocrine dynamical system [6]. We observed the same ultradian oscillation of insulin secretion over a range of (50 - 200) min in type 1 diabetic people, which is shown through the graphs. The focus of this simulation therefore is to find the range of two time delays for which the sustained and ultradian oscillations occurred for people having type 1 diabetes using artificial pancreas. The significant impact of two time delays in generating ultradian oscillation of insulin secretion is also explained and discussed below.

The values of parameter used in the simulation are taken from [6, 7] which were experimentally estimated. Units of glucose and insulin are converted into glucose and insulin concentration to plot the graphs. As already mentioned in Section 6.2 of the chapter, the effect of insulin to control HGP is not significant for diabetic people, hence effect of HGP is taken as constant (c = 150) in the first equation of the model (6.2.1-6.2.2). The value of glucose infusion rate ($G_{in} = 0.54$) and insulin degradation rate ($d_i = 0.06$) are fixed throughout the simulation.

The differences in glucose - insulin concentration for different values of time delays in their respective ranges are discussed below :

Case 1: $\tau_s = 0$ and $\tau_a \geq 0$ i.e there is no delay in insulin secretion and presence of delay in insulin absorption and action.

Fixing $\tau_s = 0$ and varying $\tau_a$ from 0 to 43 min, glucose concentration oscillate between (79 - 129) mg/dl and may be considered to be in the physiological range for the diabetic people. Sturis et al. [6] and Tolic et al. [7] reported that the system will have sustained oscillations at large delay. Our simulation shows that the system attained sustained oscillations when $\tau_a \geq 43$ min and $\tau_a \leq 48$ min as seen in Figure 6.2(a) and Figure 6.2(b) which confirms the observation of Sturis et al. [6] and Tolic et al. [7].

Case 2 : $\tau_s \geq 0$ and $\tau_a = 0$ i.e presence of delay in insulin secretion and no delay in insulin absorption and action.

Fixing $\tau_a = 0$ and varying $\tau_s$ from 0 to 15 min, damped oscillations are attained which confirms the finding of Sturis et al. [6] and Tolic et al. [7] according to which the oscillations become damped if the delay is very short. When $\tau_s$ is between 0 to 15 min, glucose concentration is slightly below of physiological reasonable range discussed in [74] as shown in Figure 6.3(a), so we have to increase the time delay to get the physiological glucose concentration range for the diabetic people. The system attained sustained oscillation when $\tau_s \geq 40$ and $\tau_s \leq 48$ as shown in Figure 6.3(b) and Figure 6.3(c). The value of this delay is very large here compared to its range (5, 15) min, the reason behind it is that it is the total time that includes the time of insulin secretion and insulin action to lower the glucose level since insulin does not start working instantly even in a normal person.

Case 3 : $\tau_s \geq 0$ and $\tau_a \geq 0$ i.e presence of delay in both insulin secretion and insulin absorption and action.

We carried out simulation for various values of $\tau_s$ and $\tau_a$ and found that at $\tau_s = 5$ min (minimum value) and $\tau_a \in (31, 35)$ min, ultradian oscillations are observed for glucose and insulin concentration each of time period 182 min after ignoring the first oscillation of time period 166 min. For $\tau_a \in (36, 39)$ min, ultradian oscillation with time period of 197 min after ignoring the first oscillation of 182 min are observed as shown in Figure 6.4. For $\tau_s = 5$ min and $\tau_a = 43$ min, the glucose level oscillates between (68 - 135) mg/dl which is normal range of glucose concentration for diabetic people.

For $\tau_s = 10$ min and $\tau_a \in (26, 30)$ min, ultradian oscillations of glucose and insulin concentration, each of time period 182 min after ignoring the time period of first oscillation which is 166 min, is observed. For $\tau_a \in (31, 35)$ min, ultradian oscillation with time period of 197 min are observed after ignoring the first oscillation of 182 min as shown in Figure 6.5. For $\tau_s = 10$ min and $\tau_a = 38$ min, the glucose level oscillates between (68 - 135) mg/dl. The range of ultradian oscillations for normal people is (50 - 150) min and we conclude that maximum value in the range of ultradian oscillation increases for diabetic people.

One of the most important findings of this study is that delay of more than 43 min in the insulin action (when $\tau_s = 5$ min) and a delay of more than 38 min in the insulin action (when $\tau_s = 10$ min) bring disturbances in the physiological range of glucose concentration,

which may lead to diabetic comma shown in Figure 6.4(d) and Figure 6.5(d). The reason behind it is that in the absence of insulin, glucose will not be converted into glycogen which force cells to starve [194]. Prolonged cell starvation in the body creates critical condition in which inspite of hyperglycemic condition, diabetic people feel hungry. This situation is more dangerous than hyperglycemic condition and has been reported as a reason behind diabetic comma.

Simulations show that glucose concentration peak leads the insulin concentration by 14 min. This validates the statement of Sturis et al. [6] "advance of glucose oscillations compared with insulin oscillation". The reason behind is that raised glucose concentration stimulates insulin secretion. It is also observed that amplitude of oscillations are larger with higher rates of glucose infusion and their frequency remains constant which is also verified from Sturis et al. [6] and the number of oscillations also decreases during the same time period for either of the value of $\tau_s$ and $\tau_a$ increases.

Another interesting finding is that while earlier it was understood that the delay due to hepatic glucose production was the reason of oscillations of insulin secretion [6], our simulations showed that $\tau_a$ may possibly be the reason for such type of oscillations in absence of HGP delay. If there is a delay in insulin secretion and insulin action, then glucose - insulin dynamics will be affected in a substantial manner and an increment in these delays will lead to the condition of diabetic comma. Our model has taken this condition into account. From the Figure 6.2(b) and 6.3(c) it can be shown that after $\tau_a > 48$ min ($\tau_s = 0$) or $\tau_s > 48$ min ($\tau_a = 0$), diabetic comma may occur as glucose level is reducibly below than basal glucose level. Therefore, it is concluded that to avoid diabetic comma, total time delay in insulin release and action should not be more than 48 min.

From the simulation and hence figures, it is also found that the sum of both the delays responsible for the situation of diabetic comma is always constant and delay $\tau_a$ depends upon the occurrence of delay $\tau_s$ which can be explained physiologically as insulin action depends upon insulin secretion.

## 6.6 Conclusion and future scope

In this chapter, we have discussed the effects and quantification of time delays in glucose - insulin regulatory system for type 1 diabetic people using artificial pancreas. We also studied the model analytically and numerically. For the first time, delay in insulin action

has been dealt with mathematically to discuss the situation of diabetes. Our results reveal that the second delay incorporated in the model may be the cause of ultradian oscillations of the insulin secretion stimulated by elevated glucose concentration and are critical for ensuring sustained oscillation of the insulin secretion. The information of the approximate time after which glucose level decreases and leading to diabetic comma is the most important factor for the clinical therapy as it proved very useful for the smooth working of glucose monitoring system. An attempt has been made to quantify two time delays for the proper functioning of artificial pancreas. The present model can be extended further to incorporate the delay occurred in insulin absorption and action separately for the better functioning of artificial pancreas.

| Parameters | Units | Values | Parameters | Units | Values |
|---|---|---|---|---|---|
| $R_m$ | $mUmin^{-1}$ | 210 | $V_p$ | $l$ | 3 |
| $R_g$ | $mgmin^{-1}$ | 180 | $V_i$ | $l$ | 11 |
| $U_m$ | $mgmin^{-1}$ | 940 | $V_g$ | $l$ | 10 |
| $U_0$ | $mgmin^{-1}$ | 40 | $t_p$ | min | 6 |
| $U_b$ | $mgmin^{-1}$ | 72 | $t_i$ | min | 100 |
| $C_1$ | $mgl^{-1}$ | 2000 | $t_d$ | min | 36 |
| $C_2$ | $mgl^{-1}$ | 140 | E | $lmin^{-1}$ | 0.2 |
| $C_3$ | $mgl^{-1}$ | 1000 | $a_1$ | $mgl^{-1}$ | 300 |
| $C_4$ | $mUl^{-1}$ | 80 | $\alpha$ | $lmin^{-1}$ | 0.29 |
| $C_5$ | $mUl^{-1}$ | 26 | $\beta$ | | 1.77 |

Table 6.1: The values of the parameters.

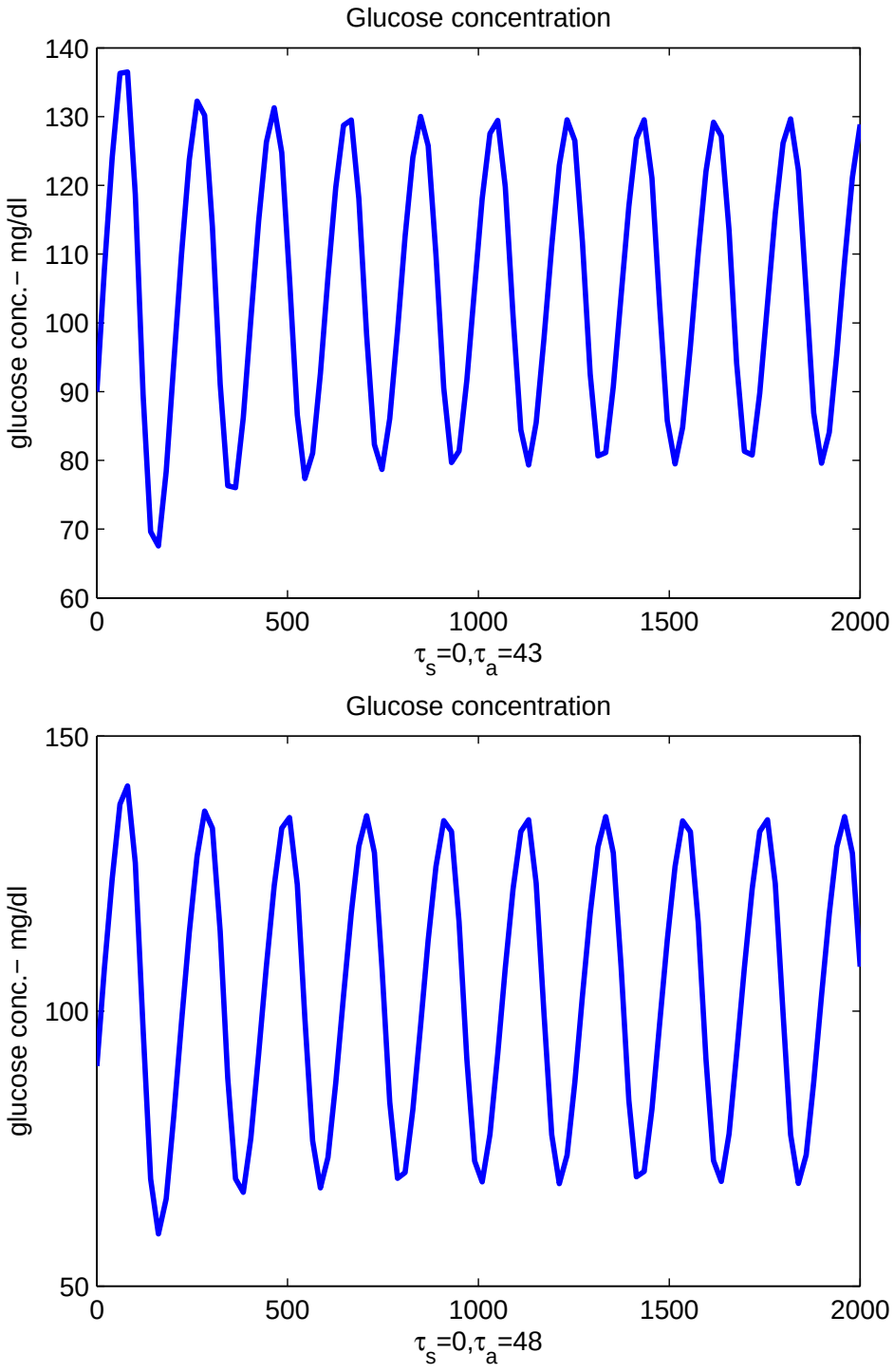


Figure 6.2: Glucose concentration curve produced by model and the system attained sustained oscillation when $\tau_a \geq 43$ and $\tau_a \leq 48$ for $\tau_s = 0$.

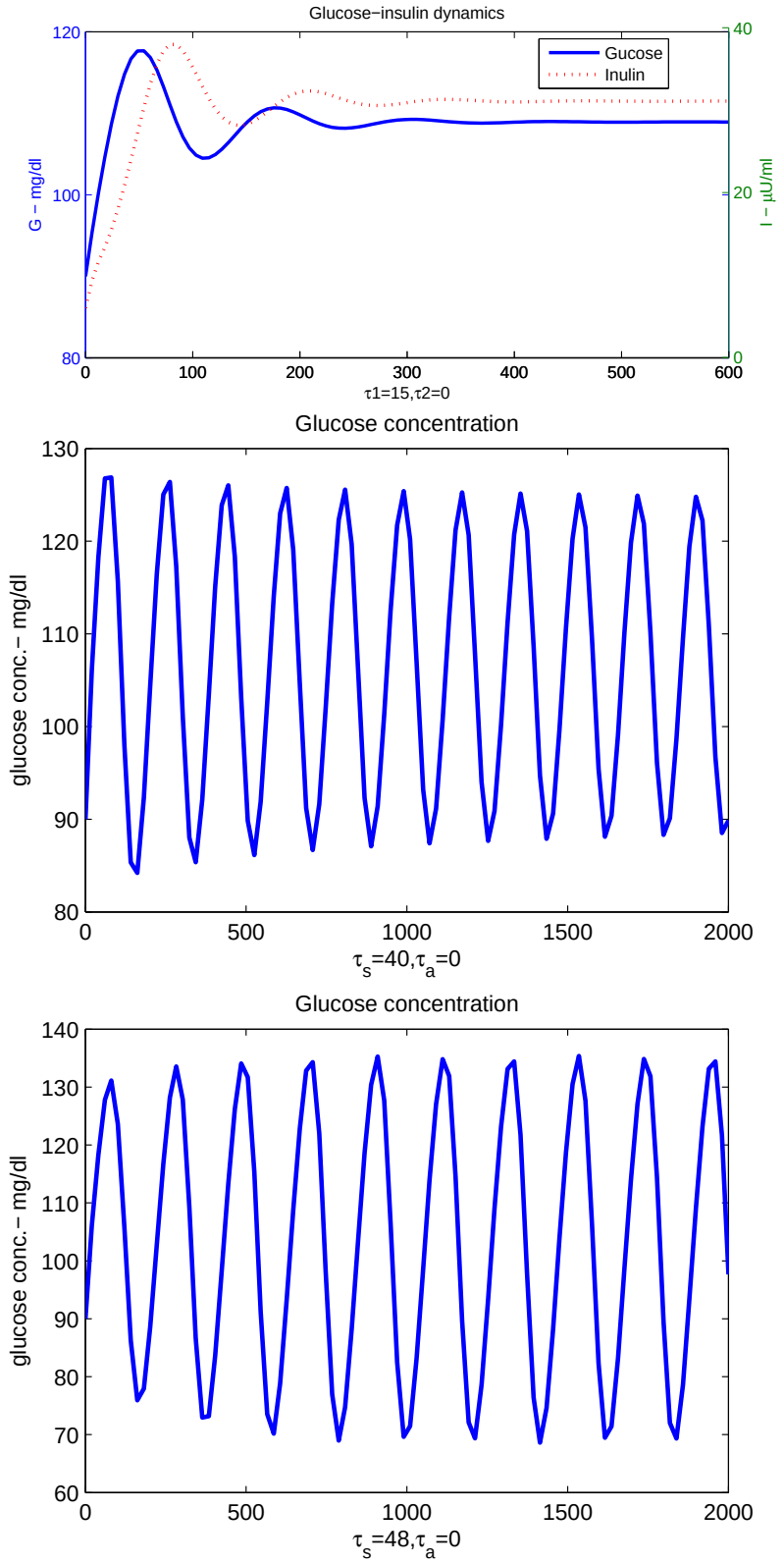


Figure 6.3: Glucose concentration curve produced by model and the system attained sustained oscillation when $\tau_s \geq 40$, $\tau_s \leq 48$ for $\tau_a = 0$ in second and third graph.

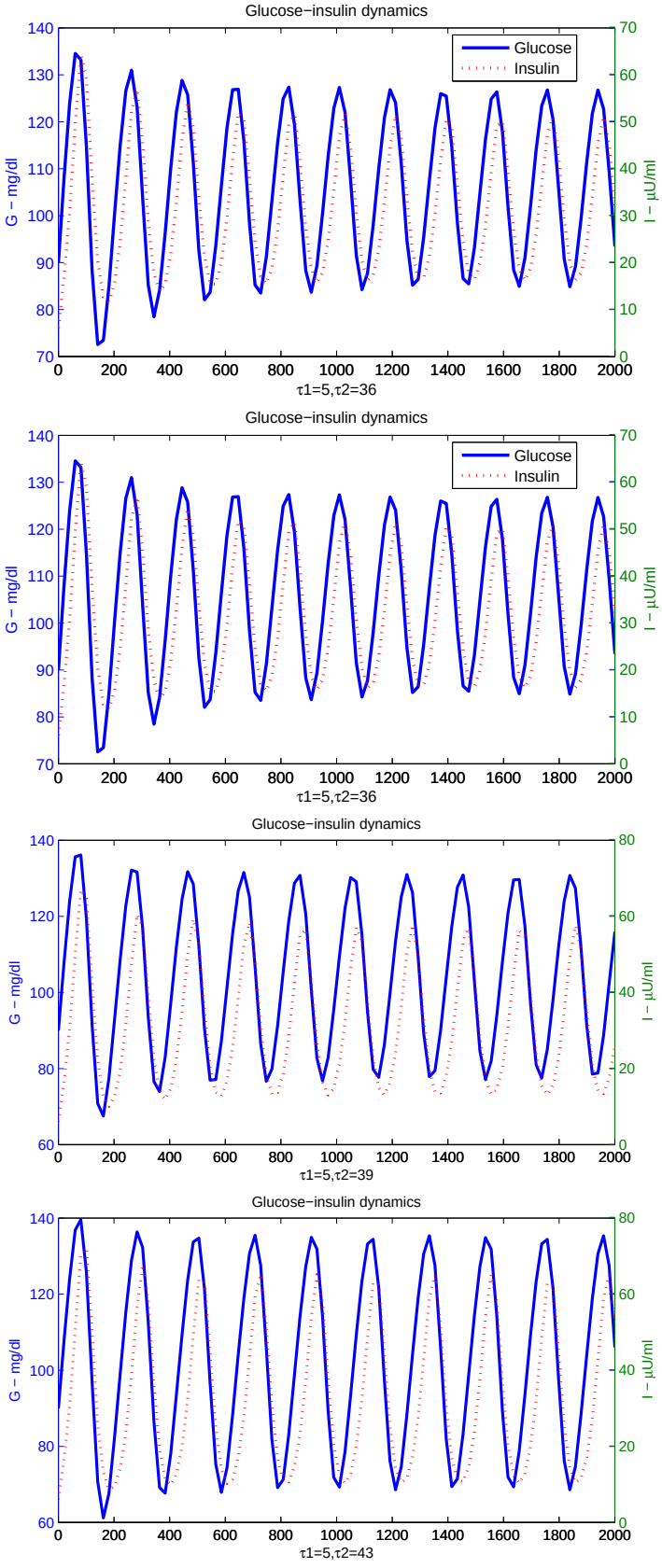


Figure 6.4: Glucose and insulin concentration curves are shown for fixed $\tau_s = 5$ and varies $\tau_a$ from 31 to 43 min.

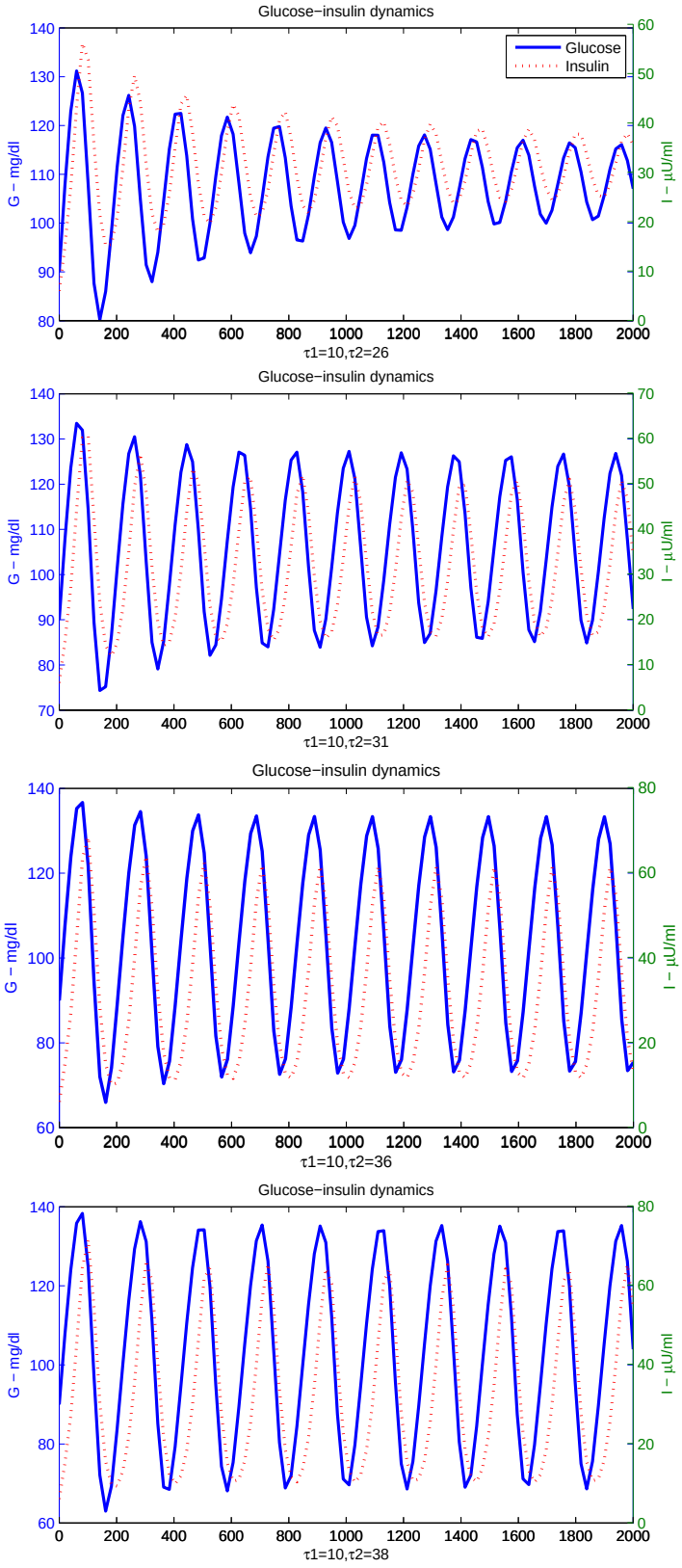


Figure 6.5: Glucose and insulin concentration curves are shown for fixed $\tau_s = 10$ and varies $\tau_a$ from 26 to 38 min.

# Chapter 7

# Quantitative analysis of three time delays using artificial pancreas

In this chapter,[1] we continue our attempt to better understand the glucose - insulin regulatory system via a mathematical model of delay differential equations with three time delays. With these three time delays, the model is more realistic in physiology, more accurate in mathematics, and more robust in applications. Several time delays exist in the glucose - insulin regulatory system, out of which we are considering in the present study are delay in insulin secretion, delay in inhibition in hepatic glucose production stimulated by insulin and delay in time taken by insulin to reach interstitial compartment to lower glucose level (i.e. glucose utilization delay or insulin action delay). None of the time delay is negligible. Our analytical and numerical results shows that periodic and sustained oscillations of glucose and insulin concentration exists for type 1 diabetic people and delay in insulin secretion may be one of the major possible reason behind the occurrence of ultradian oscillations. We have also found out more practical range of all three time delays from the simulation of present model, which may be proved very useful in better designing and improved functioning of artificial pancreas.

[1]The results of this chapter has been communicated in a research paper entitled "Quantitative and stability analysis of three time delays in glucose and insulin oscillations profile using artificial pancreas".

## 7.1 Introduction

The goal of this study is to model three time delays for the advancement of artificial pancreas and to avoid the hypoglycemic condition. Hypoglycemia remains a big barrier to the intensifications of insulin therapy [187] and timely attempts have been made to deal with this episode of hypoglycemia. Many mathematical models have been proposed for artificial pancreas [11, 17, 195–200] and proved useful in improving the designing and functioning of artificial pancreas to maintain the glucose level in normal range.

According to the literature available, there exists three physiological time delays in the glucose - insulin regulatory system [6, 46, 48, 77, 83]. The first is delay in insulin secretion, second is delay in inhibition in hepatic glucose production stimulated by insulin and third is delay in time taken by insulin to reach interstitial compartment to lower glucose level. A delay in insulin action to lower glucose concentration was observed by Bergman et al. [46]. Delay in insulin secretion and insulin action is discussed by Cobelli et al. [186]. Sturis et al. [6] noticed the delay in inhibition in hepatic glucose production by insulin. De Gaetano and Arino in 2000 [48] and Li et al. in 2001 [83] modeled IVGTT protocol by using single delay. Li and his colleagues [73–75] modeled the glucose - insulin regulatory system by using two explicit time delays.

We formulate a DDE model for closed - loop control by taking three time delays terms in account, which are given as : $\tau_s$ - delay in insulin secretion from insulin pump, $\tau_h$ - delay in inhibition in hepatic glucose production stimulated by insulin and $\tau_a$ - delay in time taken by insulin to reach interstitial compartment to lower glucose level as shown in Figure 7.1. Three time delay terms are incorporated simultaneously in mathematical model to analyse the behavior of oscillations of insulin secretion and glucose concentration level. The analytical and numerical analysis of the model will provide more insightful information in the development of artificial pancreas.

## 7.2 Mathematical model

Glucose and insulin are the two major factors in the glucose - insulin regulatory system. Let G(t) and I(t) represent the glucose and insulin concentration at time $t \geq 0$. The mathematical model comprises of $\frac{dG}{dt}$ = glucose production - glucose utilization and $\frac{dI}{dt}$ = insulin production - insulin utilization.

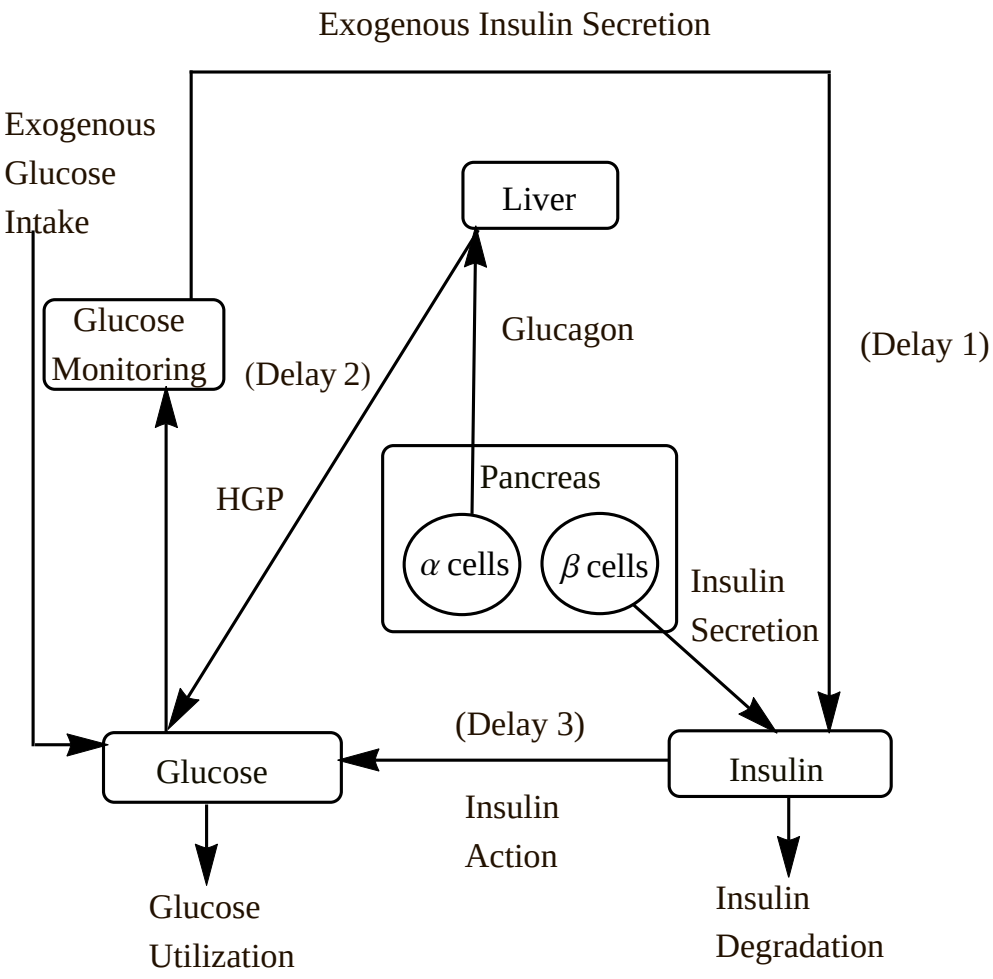


Figure 7.1: Glucose - Insulin dynamics with three time delays : Delay 1 (delay in insulin secretion), Delay 2 (delay in inhibition in hepatic glucose production) and Delay 3 (delay in insulin action to lower glucose level).

The following feedback loops are present in the system : glucose level raised in the body (either by oral meal infusion or by hepatic production), which stimulates insulin secretion, and insulin stimulates glucose uptake. In the whole dynamical system three significant delays are observed. Glucose is produced by meal ingestion, oral glucose intake or by constant glucose infusion. Glucose is also stored in the liver in glucagon form which further convert into glucose when body required. In this conversion process a delay is observed in hepatic glucose production known as $\tau_h$ and is presented by $f_5(I(t-\tau_h))$ in the first equation of model. When glucose level rises in the body, glucose sensor becomes activated and directs the insulin pump to inject insulin subcutaneously. In this process, a second delay is occurred in insulin secretion [186] known as $\tau_s$ and is represented by $f_1(G(t-\tau_s))$ in the second equation of model. $\tau_a$ represents the delay in insulin absorption and insulin action in the body to lower the glucose level in its normal range [186]. Since $f_4(I(t))$ represents the insulin dependent glucose utilization, hence the delay $\tau_a$ is incorporated in this function and is represented by $f_4(I(t-\tau_a))$ in the model.

Closed loop control system requires a perfect algorithm to predict accurate dose and precise timing of insulin delivery to avoid the most critical episodes of hyperglycemia and hypoglycemia. Hypoglycemia due to overdose of insulin and hyperglycemia, due to under dose of insulin, are the two critical episodes occurred in therapies of insulin infusion [77]. To avoid these two harmful episode, a physiological model is much required which calculate the exact length of time delays. Our focus here is to find the feasible range of all time delays so that accurate dose of insulin and exact timing of insulin delivery can be figured out in the closed loop control system. The length of time delays if known will helps in proper designing of artificial pancreas and for other clinical applications. Here, we presented mathematical model by incorporating three time delays : $\tau_s$, $\tau_h$ and $\tau_a$ to study the behavior of glucose-insulin regulatory system.

The extended mathematical models of glucose - insulin regulatory system containing three time delays are given as :

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))\, f_4(I(t-\tau_a)) + f_5(I(t-\tau_h)) \tag{7.2.1}$$

$$\frac{dI}{dt} = f_1(G(t-\tau_s)) - d_i I(t) \tag{7.2.2}$$

with initial conditions: $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G(t) \equiv G_0$ and $I(t) \equiv I_0$ for $t \in [-\tau, 0]$, where $\tau = \max\{\tau_s, \tau_a, \tau_h\}$ and $\tau_s, \tau_a, \tau_h \geq 0$. The time delays are defined as $\tau_s$ - delay

in insulin secretion, $\tau_h$ - delay in inhibition in hepatic glucose production stimulated by insulin and $\tau_a$ - delay in time taken by insulin to reach interstitial compartment to lower glucose level.

The functions $f_i$, i = 1,2,3,4,5 are defined in (1.7.13-1.7.17) in chapter 1 and their values are taken from [6] as shape of the functions are more important than their forms [74]. The values of the parameters are taken from [74] and given in Table 6.1.

## 7.3 Positive and bounded solutions of mathematical model

In this section, we will show the solutions of mathematical model (7.2.1-7.2.2) are positive and bounded. To discuss the positive and bounded solution of the model (7.2.1-7.2.2), we assume that all functions $f_i$, i = 1,2,3,4,5 of model (7.2.1-7.2.2) satisfy the following conditions :

(i) $f_1(x) > 0,\ f_1(0) = k_1 \geq 0,\ f_1'(x) > 0,\ f_1'(x) < K_1'$ for $x > 0$ and $\lim_{x\to\infty} f_1(x) = K_1$.

(ii) $f_2(x) > 0,\ f_2(0) = 0,\ f_2'(x) > 0,\ f_2'(x) < K_2'$ for $x > 0$ and $\lim_{x\to\infty} f_2(x) = K_2$.

(iii) $f_3(x) > 0,\ f_3(0) = 0,\ f_4(x) > 0,\ f_4(0) = k_4 > 0$ for $x > 0$. Also $0 < k_3' < f_3'(x) < K_3'$ and $f_4'(x) < K_4'$ for $x > 0$, $\lim_{x\to\infty} f_3(x) = K_3$ and $\lim_{x\to\infty} f_4(x) = K_4$

(iv) $f_5(x) \geq 0,\ f_5(0) = K_5,\ f_5'(x) < 0,\ f_5'(x) > -K_5'$ for $x > 0$ and $\lim_{x\to\infty} f_5(x) = 0$.

**Proposition 5.** *: Let $(G(t), I(t))$ is a solution of system (7.2.1-7.2.2) with $G(t) = G_0 > 0$, $I(t) = I_0 > 0$ for all $t \in [-\tau, 0]$, $\tau = max\{\tau_s, \tau_a, \tau_h\}$ then $G(t) > 0$, $I(t) > 0$ for all $t > 0$.*

*Proof.* **(i) $G(t)$ is non-negative.**

Let if possible $G(t)$ is not non-negative, then there exist $t > 0$ such that $G(t) < 0$.

Let $t_1 = \inf\{t : G(t) < 0\}$, then $G(t_1) = 0$, $\dot{G}(t_1) < 0$.

From eqn.(7.2.1), we have

$$\dot{G}(t_1) = G_{in}(t_1) + f_5(I(t_1 - \tau_h))$$

If $I(t) > 0$ for all $t > 0$, then $I(t_1 - \tau_h) \geq 0$ implies $f_5(I(t_1 - \tau_h)) \geq 0$ and hence $\dot{G}(t_1) > 0$, which is a contradiction.

Hence $G(t) \geq 0$ for all $t \geq 0$ i.e $G(t)$ is non-negative.

**(ii) $I(t)$ is non-negative.**

Let if possible $I(t)$ is not nonnegative, then there exist $t > 0$ such that $I(t) < 0$.

Let $t_2$ = inf $\{t : I(t) < 0\}$, then $I(t_2) = 0$, $\lim_{t \to t_2^-} \dot{I}(t_1) < 0$.
From eqn.(7.2.2) of the system (7.2.1-7.2.2), we have

$$\lim_{t \to t_2^-} \dot{I}(t) = f_1(G(t_2 - \tau_s))$$

Now 2 cases arises : when $t_1 \leq t_2$, then $t_1 - \tau_h < t_2$, $I(t_1 - \tau_h) \geq 0$ and $f_5(I(t_1 - \tau_h)) \geq 0$ and hence $\dot{G}(t_1) > 0$, which is a contradiction.
When $t_1 > t_2$, then $t_2 - \tau_s < t_1$, $G(t_2 - \tau_s) \geq 0$, also $f_1(G(t_2 - \tau_s)) \geq 0$ implies $\lim_{t \to t_2^-} \dot{I}(t) \geq 0$, which is again a contradiction.

Hence $I(t) \geq 0$ for all $t > 0$ i.e $I(t)$ is non-negative.

Since $\dot{G}(t) > 0$ when $G(t) = 0$ and $\dot{I}(t) > 0$ when $I(t) = 0$. We have $G(t) = G_0 > 0, I(t) = I_0 > 0$ for all $t \in [-\tau, 0]$. □

**Proposition 6.** *: The solution $(G(t), I(t))$ of the system (7.2.1-7.2.2) are bounded (below and above by some constant).*

*Proof.* **(i) Solutions ($G(t)$, $I(t)$) are bounded above.**

From eqn.(7.2.1) of the system (7.2.1-7.2.2), we have

$$\begin{aligned} \frac{dG}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))\, f_4(I(t - \tau_a)) + f_5(I(t - \tau_h)) \\ &\leq Sup_{t \in [0,k]} G_{in} - k_3 k_4 + K_5 \\ &\leq Sup_{t \in [0,k]} G_{in} + K_5 = M_1(say) \end{aligned}$$

then $G(t) \leq M_1$ (a positive constant) for all $t \geq 0$ i.e $G(t)$ is bounded above by $M_1$.
From eqn.(7.2.1), we have

$$\begin{aligned} \frac{dI}{dt} &= f_1(G(t - \tau_s)) - d_i I(t) \\ &\leq K_1 - d_i I(t) \\ &\leq K_1 = M_2(say) \end{aligned}$$

then $I(t) \leq M_2$, for all $t \geq 0$ i.e $I(t)$ is bounded above by $M_2$.

Hence $G(t)$ and $I(t)$ are bounded above by some positive number.

**(ii) Solutions ($G(t)$, $I(t)$) are bounded below.**

From eqn.(7.2.1) of the system (7.2.1-7.2.2),

$$\frac{dG}{dt} \geq inf_{t\in[0,k]}G_{in}(t) - K_2G(t) - K_3K_4G(t)$$

$$\frac{dG}{dt} + (K_2 + K_3K_4)G(t) \geq inf_{t\in[0,k]}G_{in}(t)$$

which implies

$$G(t) \geq \frac{inf_{t\in[0,k]}G_{in}(t)}{K_2+K_3K_4} + (G_0 - \frac{inf_{t\in[0,k]}G_{in}(t)}{K_2+K_3K_4})e^{-(K_2+K_3K_4)t} = M_3(say)$$

Hence $G(t) \geq M_3$ i.e $G(t)$ is bounded below by $M_3$.
From eqn.(7.2.2) of the system (7.2.1-7.2.2), we have

$$\begin{aligned}\frac{dI}{dt} &= f_1(G(t-\tau_s)) - d_iI(t)\\ &\geq k_1 - d_iI(t)\end{aligned}$$

which implies

$$I(t) \geq \frac{k_1}{d_i} + \left(I_0 - \frac{k_1}{d_i}\right)e^{-d_it} = M_4$$

then $I(t) \geq M_4$ i.e $I(t)$ is bounded below by $M_4$.

Hence we can conclude from (i) and (ii) that the solution $(G(t), I(t))$ of the system is bounded. □

## 7.4 Stability analysis of mathematical model

In this section, stability analysis of the system (7.2.1-7.2.2) has been discussed.

**Lemma 7.4.1.** *Let p be a real number and g be a non negative function defined and integrable on $[p,\infty)$ and is uniformly continuous on $[p,\infty)$, then $lim_{t\to\infty}g(t) = 0$ [77].*

**Lemma 7.4.2.** *Let $f(x)$ be a continuous function on [a, b] and $F^{'}(x) = f(x)$, then there exists a point $c \in (a,b)$ such that $\frac{F(b)-F(a)}{b-a} = F^{'}(c)$.*

For T1DM, almost all $\beta$ - cells secreted by pancreas are not functional and secrete no insulin. Diabetics rely on exogenous supply of insulin. So we assume the function $f_1 = 0$ to prove the stability of system (7.2.1-7.2.2). We will show the system is globally asymptotically stable by using lemma 7.4.1 and 7.4.2.

**Theorem 7.4.3.** *For $f_1 \equiv 0$, the positive solution $(G(t), I(t))$ of the system (7.2.1-7.2.2) is unique and globally asymptotically stable.*

*Proof.* For $f_1 = 0$, consider an eqn.(7.2.2) of the system (7.2.1-7.2.2),

$$\begin{aligned} \frac{dI}{dt} &= -d_i I(t) \\ I(t) &= I_0 e^{-d_i t} \end{aligned}$$

Let

$$\begin{aligned} P_1(t) &= \frac{1}{2}(I(t) - I^*(t))^2 = \frac{1}{2}(I_0 e^{-d_i t} - I_0^* e^{-d_i t})^2 \\ &= \frac{1}{2}(I_0 - I_0^*)^2 e^{-2d_i t} \\ &= P_1(0) e^{-2d_i t}, \end{aligned}$$

where, $P_1(0) = \frac{1}{2}(I_0 - I_0^*)^2$

and $\dot{P_1}(t) = -2d_i P_1(0) e^{-2d_i t} = -2d_i P_1(t)$ for $t > 0$.
Consider

$$\begin{aligned} P(t) &= \alpha P_1(0) e^{-2d_i t} + \frac{1}{2}(G(t) - G^*(t))^2 \\ &= \alpha P_1(t) + \frac{1}{2}(G(t) - G^*(t))^2 \end{aligned}$$

where $\alpha$ is a constant.

Differentiate both sides, we get

$$\begin{aligned}
\dot{P}(t) &= -2\alpha d_i P_1(0)e^{-2d_i t} + (G(t)-G^*(t))(\dot{G}(t)-\dot{G}^*(t)) \\
&= -2\alpha d_i P_1(0)e^{-2d_i t} + (G(t)-G^*(t))[-f_2(G(t)) - f_3(G(t))\,f_4(I(t-\tau_a)) + f_5(I(t-\tau_h)) \\
&+ f_2(G^*(t)) + f_3(G^*(t))\,f_4(I^*(t-\tau_a)) - f_5(I^*(t-\tau_h))] \\
&= -2\alpha d_i P_1(0)e^{-2d_i t} - (G(t)-G^*(t))[\{f_2(G(t)) - f_2(G^*(t))\} + \{f_3(G(t))\,f_4(I(t-\tau_a)) \\
&- f_3(G^*(t))\,f_4(I^*(t-\tau_a))\} - \{f_5(I(t-\tau_h)) - f_5(I^*(t-\tau_h))\}]
\end{aligned}$$

By using Lemma 7.4.2, we have

$$\begin{aligned}
\dot{P}(t) &= -2\alpha d_i P_1(0)e^{-2d_i t} - (G(t)-G^*(t))^2\{f_2^{'}(\beta_2) + f_3^{'}(\beta_3)\,f_4(I(t-\tau_a))\} \\
&- (G(t)-G^*(t))\,f_3(G^*(t))\,f_4^{'}(\beta_4)\{I(t-\tau_a) - I^*(t-\tau_a)\} \\
&+ (G(t)-G^*(t))\,f_5^{'}(\beta_5)\{I(t-\tau_h) - I^*(t-\tau_h)\}
\end{aligned}$$

By using the inequality $2ab < \gamma a^2 + \frac{b^2}{\gamma}$, we have

$$\begin{aligned}
\dot{P}(t) &\leq -2\alpha d_i P_1(0)e^{-2d_i t} - (G(t)-G^*(t))^2\{f_2^{'}(\beta_2) + f_3^{'}(\beta_3)\,f_4(I(t-\tau_a))\} \\
&+ \frac{\gamma_1}{2}(G(t)-G^*(t))^2 f_3(G^*(t))\,f_4^{'}(\beta_4) + \frac{1}{2\gamma_1}(I(t-\tau_a) - I^*(t-\tau_a))^2 f_3(G^*(t))\,f_4^{'}(\beta_4) \\
&+ \frac{\gamma_2}{2}(G(t)-G^*(t))^2 f_5^{'}(\beta_5) + \frac{1}{2\gamma_2}(I(t-\tau_h) - I^*(t-\tau_h))^2 f_5^{'}(\beta_5)
\end{aligned}$$

$$\begin{aligned}
&= -(G(t)-G^*(t))^2\Big\{f_2^{'}(\beta_2) + f_3^{'}(\beta_3)\,f_4 I(t-\tau_a) - \frac{\gamma_1}{2}f_3(G^*(t))\,f_4^{'}(\beta_4) - \frac{\gamma_2}{2}f_5^{'}(\beta_5)\Big\} \\
&- 2\alpha d_i P_1(0)e^{-2d_i t} + \frac{e^{-2d_i(t-\tau_a)}}{\gamma_1}P_1(0)\,f_3(G^*(t))\,f_4^{'}(\beta_4) + \frac{e^{-2d_i(t-\tau_h)}}{\gamma_2}P_1(0)\,f_5^{'}(\beta_5)
\end{aligned}$$

$$\begin{aligned}
&= -(G(t)-G^*(t))^2\Big\{f_2^{'}(\beta_2) + f_3^{'}(\beta_3)\,f_4 I(t-\tau_a) - \frac{\gamma_1}{2}f_3(G^*(t))\,f_4^{'}(\beta_4) - \frac{\gamma_2}{2}f_5^{'}(\beta_5)\Big\} \\
&+ P_1(0)e^{-2d_i t}\Big\{-2\alpha d_i t + \frac{e^{2d_i\tau_a}}{\gamma_1}f_3(G^*(t))\,f_4^{'}(\beta_4) + \frac{e^{2d_i\tau_h}}{\gamma_2}f_5^{'}(\beta_5)\Big\}
\end{aligned}$$

where $\beta_2$, $\beta_3$ lie between $G(t)$ and $G^*(t)$, $\beta_4$ lies between $I(t-\tau_a)$ and $I^*(t-\tau_a)$ and $\beta_5$ lies between $I(t-\tau_h)$ and $I^*(t-\tau_h)$. Let $\gamma_1 > 0$, $\gamma_2 > 0$ are arbitrary constants. Choose $\gamma_1 > 0$,

$\gamma_2 > 0$ very small such that

$$f_2^{'}(\gamma_2) + f_3^{'}(\beta_3) f_4(I(t-\tau_a)) - \frac{\gamma_1}{2} f_3(G^*(t)) f_4^{'}(\beta_4) - \frac{\gamma_2}{2} f_5^{'}(\beta_5) > \delta > 0$$

where $\delta$ is very small enough positive constant. For given $\gamma_1$, $\gamma_2$, choose $\delta > 0$ large enough such that

$$-2\alpha d_i + \frac{e^{2d_i\tau_a}}{\gamma_1} f_3(G^*(t)) f_4^{'}(\beta_4) + \frac{e^{2d_i\tau_h}}{\gamma_2} f_5^{'}(\beta_5) < -\delta < 0$$

hence we have

$$\dot{P}(t) \quad < \quad -\delta(G(t) - G^*(t))^2 - \delta P_1(0) e^{-2d_i t}$$

implies $\dot{P}(t) < 0$. Hence $P(t)$ is decreasing.

Integrating both sides from 0 to $t$, we get

$$\begin{aligned} P(t) - P(0) &< -\delta \int_0^t (G(x) - G^*(x))^2 dx - \delta \int_0^t P_1(0) e^{-2d_i x} dx \\ P(t) &+ \delta \int_0^t (G(x) - G^*(x))^2 dx + \delta P_1(0) \int_0^t e^{-2d_i x} dx \leq P(0) \end{aligned}$$

Hence, we get $(G(t) - G^*(t))^2 \in L^1(0,\infty)$. $(G(t) - G^*(t))^2$ and its derivative are both bounded on $[0,\infty)$. Hence $(G(t) - G^*(t))^2$ is uniformly continuous on $[0,\infty)$. By lemma 7.4.1, we have $\lim_{t\to\infty}(G(t) - G^*(t))^2 = 0$.

Also we have $\lim_{t\to\infty}(I(t) - I^*(t))^2 = \lim_{t\to\infty} 2P_1(t) = \lim_{t\to\infty} 2P_1(0)e^{-2d_i t} = 0$.
Hence, the periodic solutions $(G^*(t), I^*(t))$ of the system (7.2.1-7.2.2) are globally asymptotically stable and unique. □

## 7.5 Numerical simulation and results

In this section, numerical analysis of the model (7.2.1-7.2.2) is discussed using Matlab 2012b. In glucose - insulin dynamics, the possibilities of three types of time delays have been discussed in literature [6, 7, 77]. Therefore to understand the dynamics more deeply and for proper designing and functioning of artificial pancreas we have incorporated all three time delays in the mathematical model (7.2.1-7.2.2) which occurs in the metabolism, first in insulin secretion, second in inhibition in hepatic glucose production and third in

insulin action.

Raised blood glucose concentration in the body reglated in three stages : 1) $\beta$ cells of the pancreas triggered by raised glucose concentration to secrete insulin (or by artificial pancreas in case of T1DM and severe T2DM) 2) Hepatic glucose production is inhibited by secreted insulin 3) Insulin helps the muscles cells and adipose tissues in glucose utilization. Since all three stages are interlinked, therefore delay in one stage will effect the functioning of other two stages.

The range of time delays in all three stages have been reported in the literature [6,73,74] as (5-15) min for delay in insulin secretion, (25-50) min for delay in inhibition in hepatic glucose production, (43-48) min for delay in insulin action [17]. The main drawback in the above reported ranges of the delays is that they have been calculated by either considering one delay or two delays instead of all three delays simultaneously because of which the range is comes out to be very large and hence infeasible for the human body. Therefore, to overcome this problem we are considering three time delays simultaneously to find out more feasible range of time delays at which sustained and ultradian oscillations of glucose and insulin concentration may be obtained.

Hence the goal of numerical simulation is to find the range of all time delays which will not only feasible for body but support sustained oscillations also. The range of ultradian oscillations for normal people is (50, 150) min [17]. We will discuss seven cases in which different feasible values of time delays will be explored numerically.

Case 1 : $\tau_s = 0$, $\tau_h \geq 0$ and $\tau_a \geq 0$ i.e. no delay in insulin secretion but delays will occur in inhibition in hepatic glucose production and insulin action.

For $\tau_s = 0$ and $\tau_h \in (25, 50)$ min, ultradian and sustained oscillations occurred for glucose and insulin concentration at $\tau_a \in (14, 21)$ min each of time period 125 min. The system will not attain sustained oscillations for $\tau_a \leq 14$ min and $\tau_a \geq 21$ min as shown in Figure 7.2.

Case 2: $\tau_h = 0$, $\tau_s \geq 0$ and $\tau_a \geq 0$ i.e. no delay occur in inhibition in hepatic glucose production and delays will occur in insulin secretion and insulin action.

For $\tau_h = 0$ and $\tau_s \in (5, 14)$ min, no oscillations obtained for any positive value of $\tau_a$. While for $\tau_s = 15$ min, ultradian and sustained oscillations will be obtained for glucose and insulin concentration at $\tau_a \in (20, 36)$ min. The system will not attain sustained os-

cillations for $\tau_s \leq 20$ min and $\tau_a \geq 36$ min as shown in the Figure 7.3.

Case 3: $\tau_a = 0$, $\tau_s \geq 0$ and $\tau_h \geq 0$ i.e. no delay in insulin action and delays will occur in inhibition in hepatic glucose production and insulin secretion.

For $\tau_a = 0$ and $\tau_s \in (5, 15)$ min, we noticed from numerical simulation that no oscillation occurred for $\tau_s \in (5, 14)$ min whatever the positive value of $\tau_h$ is considered. For $\tau_s = 15$ min and $\tau_h \in (25, 50)$ min, ultradian and sustained oscillations of glucose and insulin concentration will occurred. It also confirms the observation observed by Sturis et al. [6] and Tolic et al. [7] that delay in inhibition in hepatic glucose production belongs to range $(25, 50)$ min and may be the major possible reason for ultradian oscillations as seen in Figure 7.4.

Case 4: $\tau_s = 0$, $\tau_h = 0$ and $\tau_a \geq 0$ i.e. no delay in insulin secretion and inhibition in hepatic glucose production but a delay will occur in insulin action.

For $\tau_s = 0$ and $\tau_h = 0$, no ultradian and sustained oscillations of glucose and insulin concentration will be observed for any positive value of $\tau_a$. The result also implies that delay in insulin action is not solely responsible for the oscillations of glucose and insulin concentration.

Case 5: $\tau_s = 0$, $\tau_a = 0$ and $\tau_h \geq 0$ i.e. no delay occur in insulin secretion and insulin action and a delay will occur in inhibition in hepatic glucose production.

For $\tau_s = 0$ and $\tau_a = 0$ in the simulation of the system (7.2.1-7.2.2), we observed that no oscillations of glucose and insulin concentration will be occurred for any positive value of $\tau_h$. It also implies that delay in hepatic glucose production is not solely responsible for the occurrence of oscillations of the glucose and insulin concentration.

Case 6: $\tau_h = 0$, $\tau_a = 0$ and $\tau_s \geq 0$ i.e. no delay occur in inhibition in hepatic glucose production and insulin action but a delay will occur in insulin secretion.

In this case, fixing $\tau_h = 0$ and $\tau_a = 0$, ultradian and sustained oscillations of glucose and insulin concentration at $\tau_s \in (22, 25)$ min will be obtained. No sustained oscillations will be attained for $\tau_s \leq 22$ min and $\tau_s \geq 25$ min which can be seen in Figure 7.5. It can also be concluded from this case that delay in insulin secretion may be one of the major possible reason behind the occurrence of ultardian oscillations of glucose and insulin

concentration in absence of other two delays.

Case 7: $\tau_a \geq 0$, $\tau_s \geq 0$ and $\tau_h \geq 0$ i.e. there is some delay in insulin action, inhibition in hepatic glucose production and insulin action.

Fixing $\tau_s = 5$ min and $\tau_h \in (25, 50)$ min, we observed that ultradian and sustained oscillations of glucose and insulin concentration at $\tau_a = 10$ min are obtained as shown in the Figure 7.6.

Fixing $\tau_s = 10$ min and $\tau_h \in (25, 50)$ min, we observed that ultradian and sustained oscillations of glucose and insulin concentration at $\tau_a = 5$ min are obtained as shown in the Figure 7.7. A delay of more than 5 min in insulin action (for $\tau_s = 10$ min) and a delay of more than 10 min in insulin action (for $\tau_s = 5$ min) makes the glucose concentration level high and long persistence of raised glucose concentration level may leads to diabetes.

Periodic and sustained oscillations of glucose and insulin concentration were observed by many researchers by incorporating one or two time delays term in the mathematical model [17,73,74]. More number of periodic and sustained oscillations are observed in the same time intervals if above ranges of three time delays are considered simultaneously as compared to one or two time delays terms. Also, glucose concentration peak in every figure leads the insulin concentration by approximately 25 min which validate the statement of Sturis et al. [6] that there is advancement in occurrence of glucose concentration peak than insulin concentration peak. The reason behind the statement is that insulin secretion is stimulated by raised glucose concentration level.

Previously it was reported that delay in inhibition in hepatic glucose production was the reason for ultradian oscillations [6,73,74]. Later delay in insulin action was reported as the reason for ultradian oscillations of glucose and insulin concentration when two delays were considered together [17]. Numerical simulation (by considering all the above 7 cases) of the present mathematical model suggests that together with many possible metabolic and physiological reasons, delay in insulin secretion may be one of the major possible reasons for the occurrence of ultradian and sustained oscillations. Since insufficient amount or no secretion of insulin is the main reason behind the occurrence of diabetes, therefore this finding seems to be more close to real situation.

To the time it was observed and assumed that damped oscillations are attained if the

delays are short and sustained oscillations were observed only for large delays [6, 7, 17]. Ultradian oscillations were obtained at $\tau_a \in (43, 48)$ min [17] and for $\tau_h \geq 46$ min or $\tau_s \geq 18$ min [74]. From the present study it can be concluded that if three delays are considered together then the ultradian and sustained oscillations will be attained for short delays also ($\tau_s \in (5, 15)$ min, $\tau_h \in (25, 50)$ min and $\tau_a \in (5, 15)$ min).

A delay of more than 10 min in $\tau_a$ (when $\tau_s = 5$ min and $\tau_h \in (25, 50)$ min) and a delay of more than 5 min in $\tau_a$ (when $\tau_s = 10$ min and $\tau_h \in (25, 50)$ min) raised the glucose concentration level in the body and which further leads to diabetes if persists for long duration in the body.

It is also interesting to note from case 7 that the total time delay i.e. delay in insulin secretion ($\tau_s$) and delay in insulin action ($\tau_a$) to lower glucose concentration is constant i.e. approximately 15 min. Since both the delays $\tau_s$ and $\tau_a$ are interlinked as insulin action depends upon the time taken by insulin pump (for T1DM and severe T2DM people) or pancreas (for normal people) to secrete insulin, hence delay in one process affect the second process. If time delay in insulin secretion is more than 15 min then there should be no delay occur in the insulin action to maintain the normal glucose level and vice versa.

## 7.6 Conclusion and future scope

In this chapter, we studied the glucose - insulin regulatory system for the case of closed loop delivery system by considering three time delays simultaneously as observed in the body. The analytical studies of the system (7.2.1-7.2.2) ensures the positive and bounded (below and above) solutions. The system possesses globally asymptotically stability for the case of T1DM, where $f_1 = 0$. The range of time delay in insulin action ($\tau_a$) was quantified as approximately 48 min [17] by incorporating two time delays ($\tau_a$ i.e. delay in insulin action and $\tau_s$ i.e. delay in insulin secretion) in the system. Simulation of present model reveals that range of $\tau_a$ has been reduced and new range is more feasible according to the physiology of human body. In fact we are able to find the range of $\tau_a$ as (5, 10) min which is very less as compared to (43, 48) min [17] for $\tau_s \in (5, 10)$ min and $\tau_h \in (25, 50)$ min. Here, we are able to approximate the exact time duration of all the necessary time delays which will be proved very useful for smooth working of glucose monitoring system as exact amount of insulin and precise timing of delivery of insulin can be figured out. An

attempt has been made to provide more feasible ranges of three time delays occurred in glucose - insulin dynamics which can provide a deep insight into the better management of artificial pancreas.

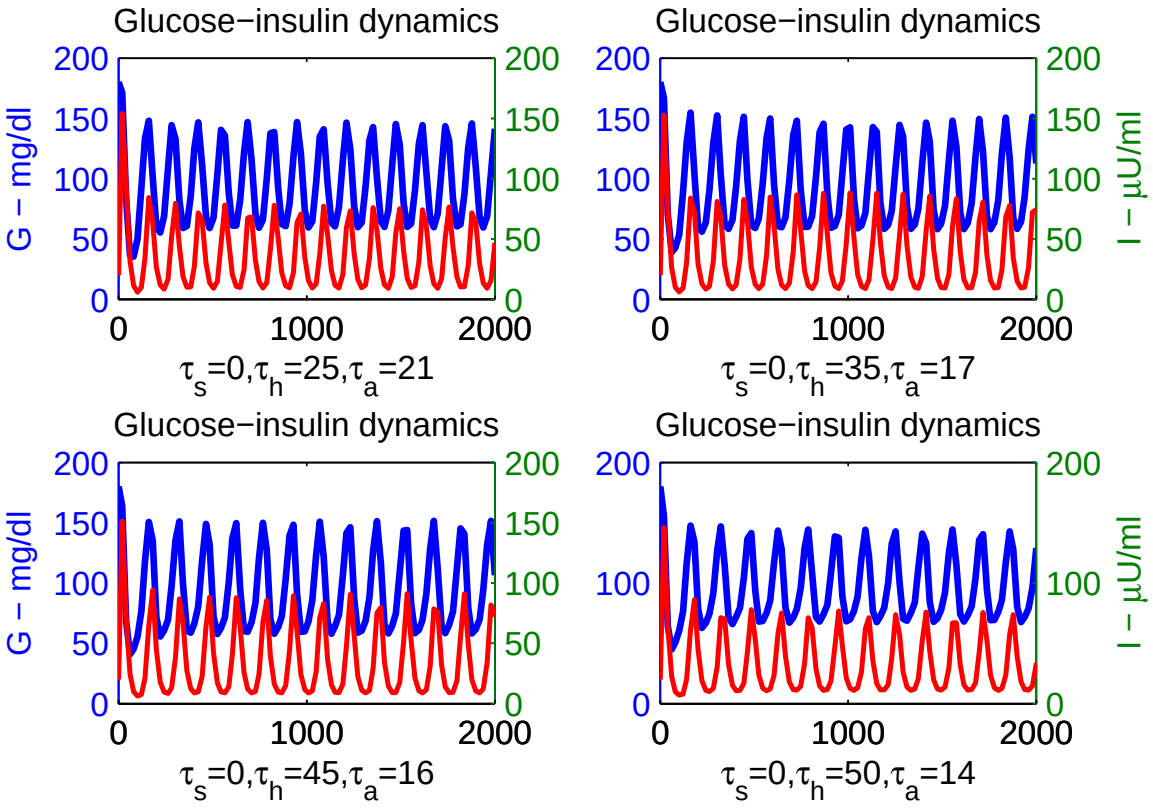


Figure 7.2: Case1 : Profile of glucose and insulin oscillations for $\tau_s = 0$, $\tau_h \in (25, 50)$ and $\tau_a \in (14, 21)$.

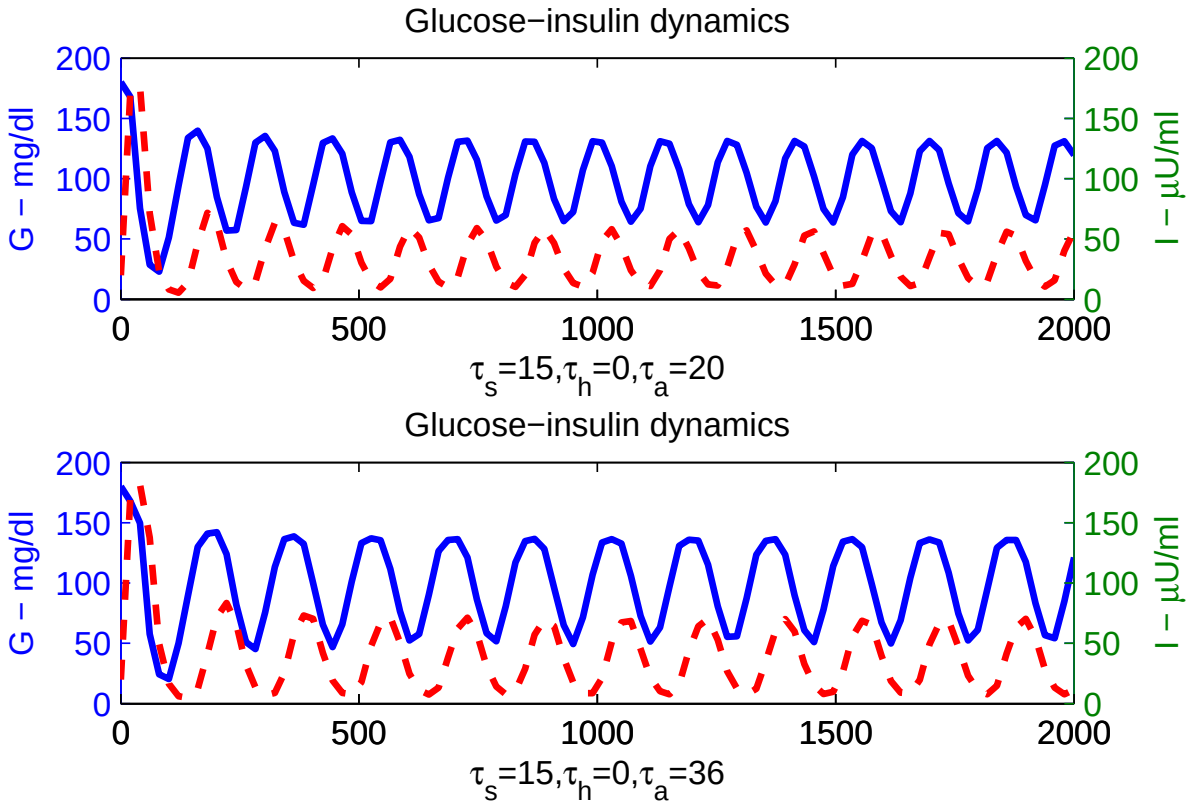


Figure 7.3: Case 2 : Profile of glucose and insulin oscillations for $\tau_s = 15$, $\tau_h = 0$ and $\tau_a \in (20, 36)$.

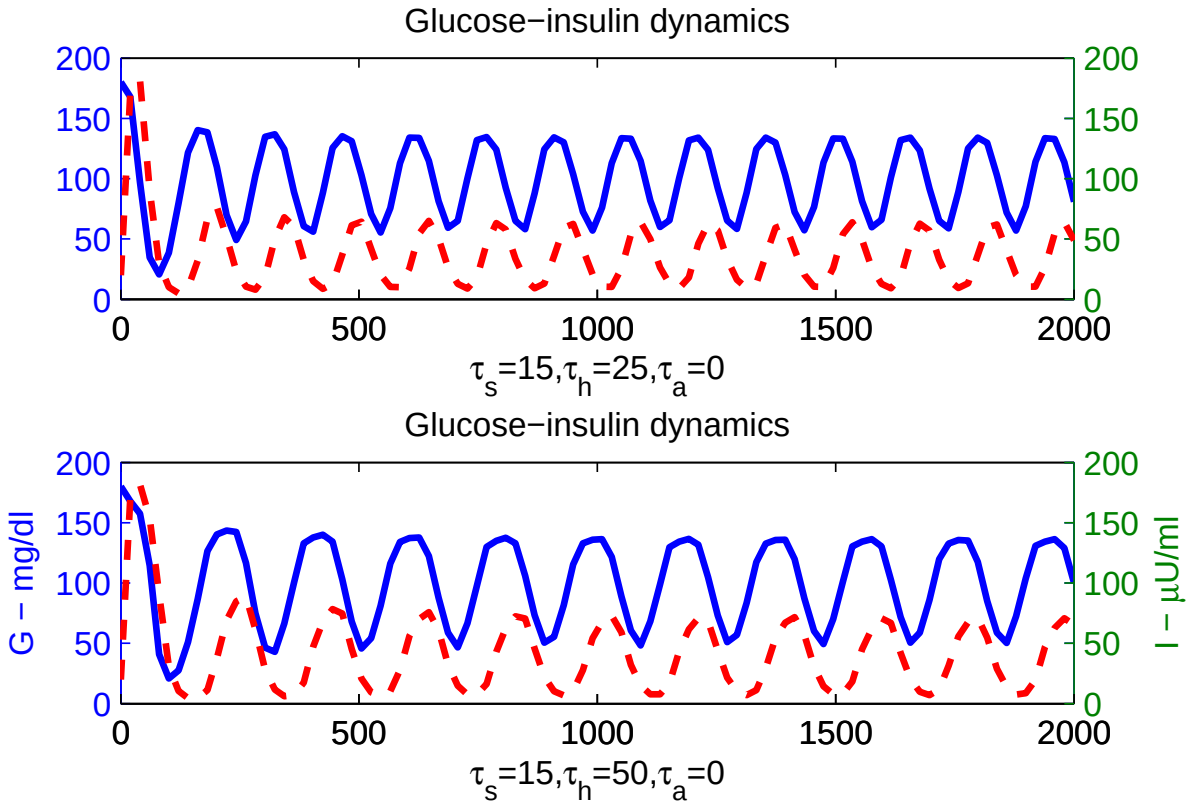


Figure 7.4: Case 3 : Profile of glucose and insulin oscillations for $\tau_s = 15$, $\tau_a = 0$ and $\tau_h \in (25, 50)$.

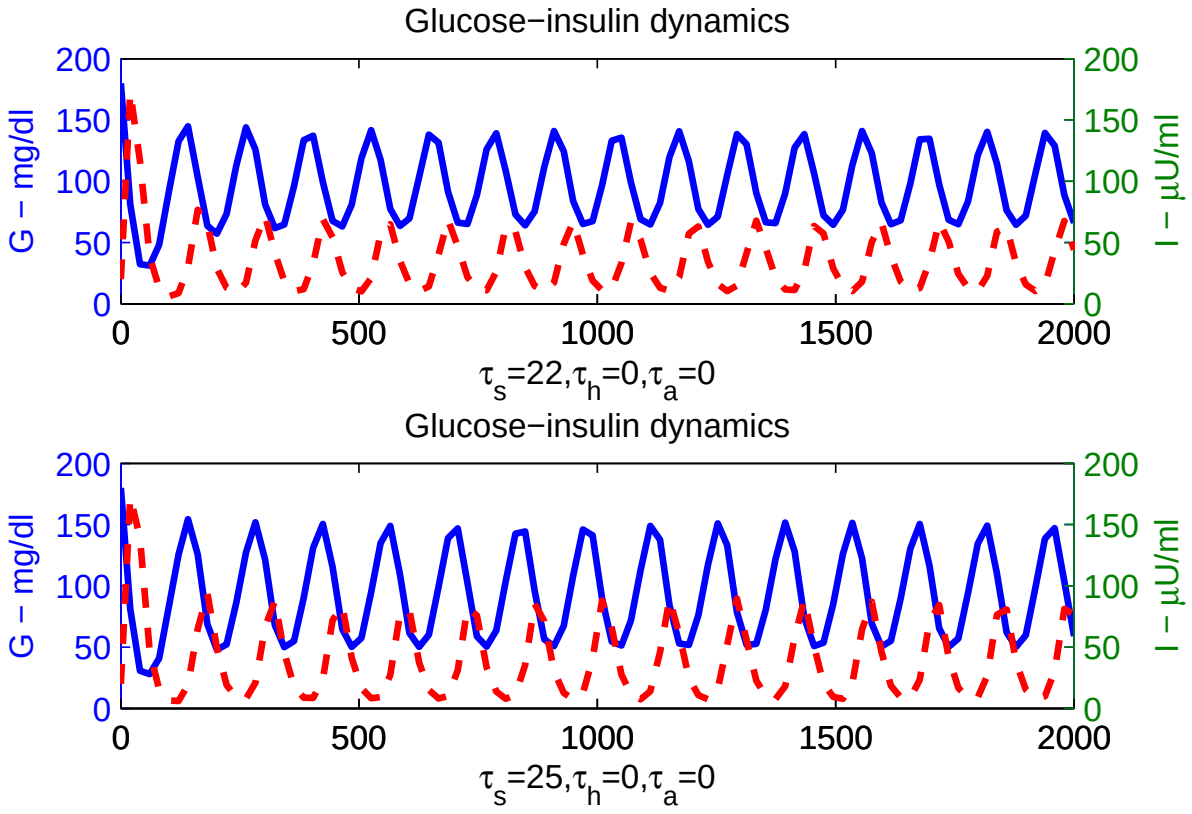


Figure 7.5: Case 6 : Profile of glucose and insulin oscillations for $\tau_h = 0$, $\tau_a = 0$ and $\tau_s \in (22, 25)$.

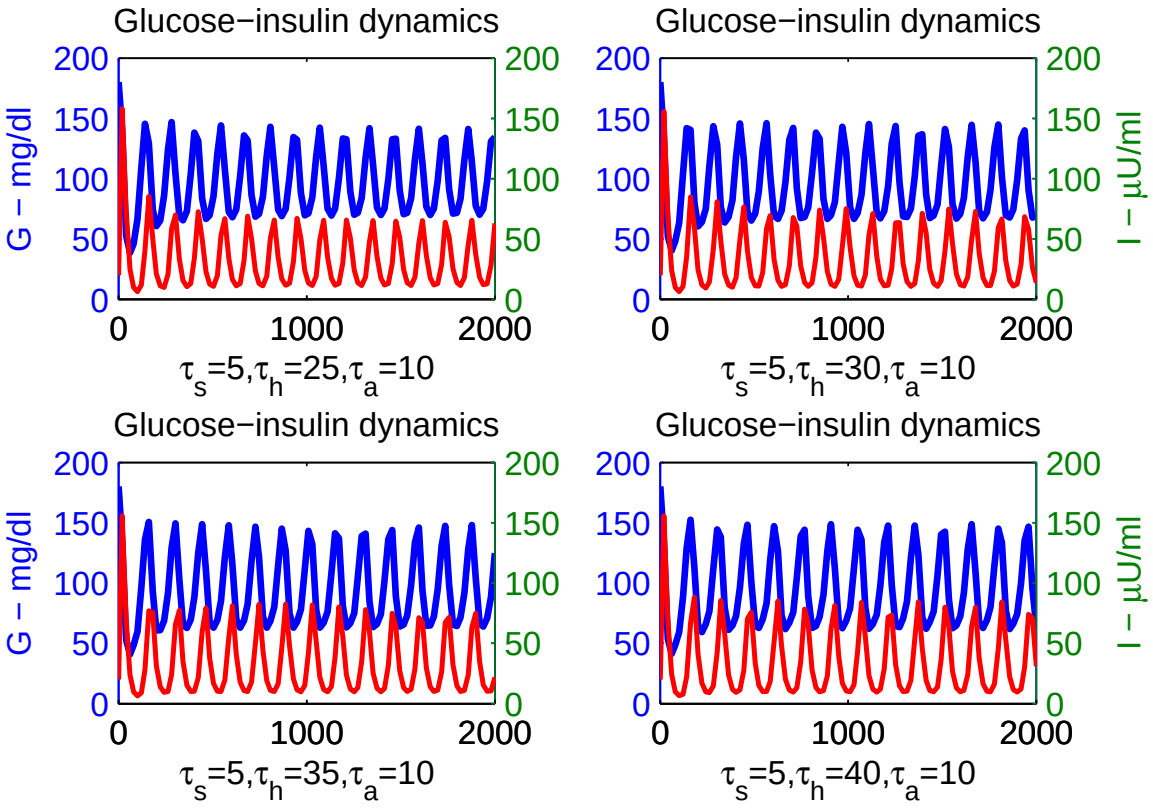


Figure 7.6: Case 7 : Profile of glucose and insulin oscillations for $\tau_s = 5$, $\tau_a = 10$ and $\tau_h \in (25, 50)$.

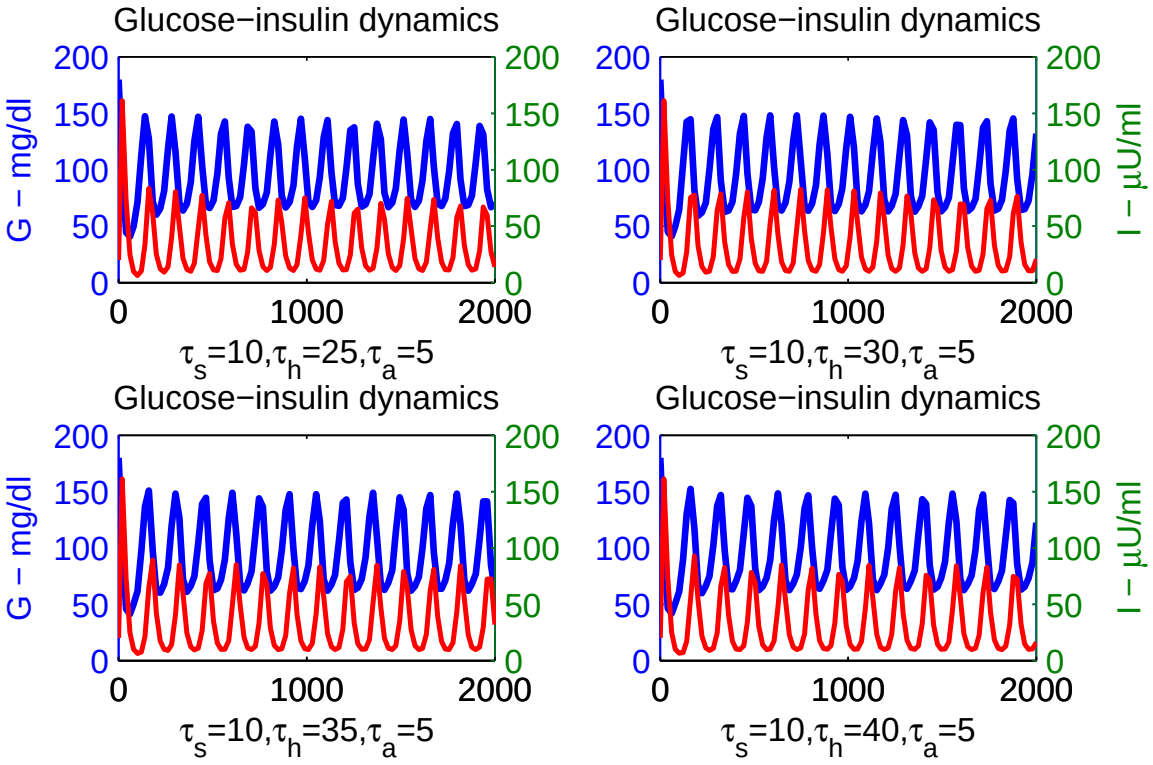


Figure 7.7: Case 7 : Profile of glucose and insulin oscillations for $\tau_s = 10$, $\tau_a = 5$ and $\tau_h \in (25, 50)$.

# Chapter 8

# Dynamics of insulin analogues using two explicit time delays

Management of type 1 diabetes and severe type 2 diabetes rely on exogenous insulin or insulin analogues to control raised blood glucose concentration. Insulin lispro and insulin aspart are rapid acting insulin analogue which have a shortened delay of onset and are easily absorbed in the bloodstream. Insulin analogue exists in hexameric, dimeric and monomeric states and hexameric form dissociates into dimeric and monomeric form which can penetrate the capillary membrane and can be absorbed into plasma. For different insulin analogues the transformation of hexameric state into dimeric and monomeric state takes different time which will be considered as first time delay in the present study. More the time it will take in this transformation, utilization of insulin in the body will be delayed which will be termed as second time delay in this chapter [1]. Therefore, an attempt has been made to find the ranges of these two time delays for the concoction of better rapid acting insulin analogues for better management of glucose and insulin concentration in diabetics through DDE model. The profile of plasma insulin concentration level obtained from simulation of the model are in good agreement with previously observed results for the quantified range of both time delays.

[1]The results of this chapter has been communicated in a research paper entitled "Modeling the dynamics of insulin analogues in type 1 diabetes using two explicit time delays".

## 8.1 Introduction

The absorption kinetics of subcutaneously injected insulin has been widely studied by many researchers [201–205]. The absorption of insulin from the subcutaneous tissues is a very complex process and many factors are suppose to influence its absorption rate i.e. exercise [206–208], rate of injection [209, 210], technique of delivering injection [211], hot water baths, local massage, temperature of the body and smoking [212]. Absorption rate also depends on injection volume [204] and concentration [209, 211]. Inspite of many theoretical and experimental research, the mechanism behind the subcutaneous absorption of insulin are still unknown.

In 1989, Mosekilde et al. [201] proposed a partial differential equation (PDE) mathematical model of the absorption process for soluble insulin by considering some suitable assumptions. It has been assumed that injected soluble insulin is present in the subcutaneous tissue in hexameric and dimeric form. Binder [213] assumed in his study that only dimeric form can penetrate the capillary membrane. The hypothesis was further supported by Brange et al. [214] and Kang et al. [215] in their studies. Inspite of considerable assumption, the mathematical model was not able to find widespread clinical application. Later in 1993, Trajanoski et al. [206] modified the model of Mosekilde et al. [201] for monomeric insulin analogues and estimated the parametric form, the time course of plasma insulin following subcutaneous insulin injection.

Normally insulin is secreted from $\beta$ cells of the pancreas in two time scales in an oscillatory manner : pulsatile oscillations accounting for the basal insulin and ultradian oscillations controlled by plasma glucose concentration levels [6, 7, 9, 12, 42, 74]. Several different types of insulin analogues have been produced and used in clinical practices [216–219]. Basal dose and bolus dose are the two types of insulin doses which simulate the insulin pulsatile secretion and ultradian secretion in an oscillatory manner, respectively. The doses are given to the patients according to their daily physical activities and can be adjusted manually [42]. Insulin analogue exists in hexameric, dimeric and monomeric states and hexameric form is the predominant state after the subcutaneous injection of soluble insulin. The hexameric form dissociates into dimeric and monomeric form which can penetrate the capillary membrane and can be absorbed into plasma [110]. The conversion of hexameric into dimeric and monomeric state is shown in Figure 8.1.

Insulin lispro is a rapid acting insulin analogue and it was the first insulin analogue to

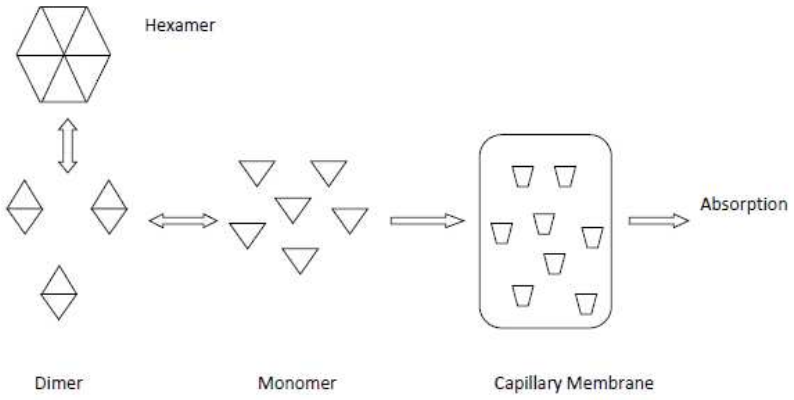


Figure 8.1: Conversion of hexamer to dimeric and monomeric state.

enter in the market in 1996 [42]. Insulin lispro has a shortened delay of onset. Insulin aspart is also a rapid acting insulin analog and is manufactured from the human insulin by changing a single amino acid. This helps the rapid acting insulin analog to absorb into bloodstream. Insulin glargine developed by rDNA technology in 2002 is a long acting basal insulin analogue, given once daily to help in controlling the raised blood glucose level. Insulin monomers are the functional and physiologically active unit of insulin. To mimic the normal physiological insulin secretion in type 1 diabetes, the best way is to use lispro or aspart as the bolus insulin and glargine as the basal insulin for pulsatile secretion of insulin stimulated by elevated plasma glucose concentration level [42].

This is clearly seen that insulin analogue are desirable to simulate the physiological pulsatile insulin secretion that observed in normal subjects [217,218]. Several mathematical models have been proposed to understand the dynamics of insulin analogues from the subcutaneous injection to absorption [42, 201, 206, 220–223].

Here, our motive is to model the profile of plasma insulin concentration level by incorporating two time delay terms in the previously developed insulin analogues model [42,201]. To the time, no one has considered the explicit time delays in model which are very necessary as delays are observed in the whole process from delivery of insulin injection to

insulin absorption. The first delay is observed in conversion of insulin analogues from hexameric state to dimeric and monomeric state and second delay is observed in utilization of plasma insulin concentration.

## 8.2 Mathematical model

In 2009, Li et al. [42] proposed an ODE mathematical model to stimulate the dynamics of rapid acting insulin analogue of the whole metabolic system. In 2009, Li and Johnson [111] considered the explicit delay $\tau > 0$ for transformation of hexameric to dimeric form. They demonstrate the plasma insulin concentration profile and compared with the experimental data but the range of the delay term was not figured out in the paper. Here, we will modify the existing mathematical model proposed by Li et al. [42] by incorporating two explicit time delay terms in the mathematical ODE model.

$\tau_t$ is the time delay observed in the transformation of hexameric state to dimeric state and is incorporated in eqn.(8.2.2) of the model. $\tau_u$ is the time delay observed in the utilization of plasma insulin concentration and is incorporated in eqn.(8.2.3) of the model. We will observe the change in plasma insulin concentration level due to the presence of these two time delay terms in the model.

The DDE mathematical model containing two explicit delay terms for the insulin analogues is :

$$\frac{dH}{dt} = -pH(t) + pqD^3(t) \tag{8.2.1}$$

$$\frac{dD}{dt} = pH(t-\tau_t) - pqD^3(t) - \frac{bD(t)}{1+I(t)} \tag{8.2.2}$$

$$\frac{dI}{dt} = \frac{rbD(t)}{1+I(t)} - d_iI(t-\tau_u) \tag{8.2.3}$$

with initial conditions: $H(0) = H_0 > 0,\ D(0) = 0,\ I(0) = I_0 \geq 0,\ \tau_t \geq 0,\ \tau_u \geq 0$, where $H(t)(U/ml)$ represents the insulin analogue concentration in hexameric form, $D(t)(U/ml)$ represents the insulin analogue concentration in dimeric form, $I(t)(U/ml)$ represents the plasma insulin concentration at time $t \geq 0$, $p$ $(min^{-1})$ is the transform rate from one hexameric molecule to three dimeric molecules [223], $q$ $(ml^2/U^2)$ represents chemical equilibrium constant [223], $pq$ is the transform rate from three dimeric molecules to one hexameric molecule, $b$ $(U/min)$ is a constant parameter [201, 222, 223], $r$ is the rate at

which fractional molecules became plasma insulin [222], $d_i(min^{-1})$ is the insulin degradation rate.

Rate of dimers penetrating the capillary is inversely proportional to the plasma insulin concentration and is depicted by the term $bD(t)/(1+I(t))$ in eqn.(8.2.2) and the term $rbD(t)/(1+I(t))$ in eqn.(8.2.3) of the model (8.2.1-8.2.3).

## 8.3 Stability analysis of mathematical model

We will analyse the model mathematically and prove the analytical results of model.

It can be clearly seen from the model that (0,0,0) is the unique equilibrium.

**Proposition 7.** *The solutions of model (8.2.1-8.2.3) with initial conditions* $H(0) = H_0 > 0$, $D(0) = 0$ *and* $I(0) = I_0 \geq 0$ *are positive and bounded.*

*Proof.* **(i) All solutions** $H(t)$**,** $D(t)$ **and** $I(t)$ **are positive for all** $t > 0$.
Let us assume that $H(t)$ or $D(t)$ is not always positive for $t > 0$. Then there exists $t_1 > 0$ such that $H(t_1) = 0$, $D(t_1) = 0$ and $H(t) > 0$ and $D(t) > 0$ for $0 < t < t_1$.
Let

$$\begin{aligned} H^{'}(t) &= -pH(t) + pqD^3(t) \\ &\geq -pH(t) \end{aligned}$$

which implies $H(t) \geq H_0 e^{-pt}$ for $0 < t < t_1$.

Also $H(t_1) \geq H_0 e^{-pt_1} > 0$ which implies $H(t) > 0$ for all $t > 0$, $D(t) > 0$ for all $\tau_t > 0$.

Also if there exists $t_2 > 0$ such that $I(t_2) = 0$, $I(t_2 - \tau_u) = 0$ and $I(t) > 0$ for $\tau_u > 0$ and $0 < t < t_2$, then $0 \geq I(t_2) = rbD(t_2) > 0$, this is a contradiction which implies that $I(t) > 0$ for all $t > 0$.

Hence all solutions $H(t), D(t)$ and $I(t)$ are positive and bounded below for all $t > 0$.

**(ii) All solutions** $H(t), D(t)$ **and** $I(t)$ **are bounded.**
Let

$$G(t) = rH(t) + rD(t) + I(t), for t > 0 \tag{8.3.1}$$

and

$$\begin{aligned} G^{'}(t) &= rH^{'}(t)+rD^{'}(t)+I^{'}(t) \\ &= -d_iI(t)<0 \end{aligned}$$

Also

$$G^{'}(t) = -pr(H(t)-H(t-\tau_t)-d_iI(t-\tau_u)<0$$

for all $\tau_t > 0$, $\tau_u > 0$.

Hence there exists a constant say $C_1 \geq 0$ such that $lim_{t\to\infty}G(t) = C_1 \geq 0$ which implies $H(t)$, $D(t)$ and $I(t)$ are bounded uniformly for all $t > 0$. □

**Lemma 8.3.1.** *: Let $f : R \to R$ be a differential function. If $l = lim\,inf_{t\to\infty} f(t) < lim\,sup_{t\to\infty} f(t) = L$, then there exists sequences $\{s_n\} \uparrow \infty$, $\{r_n\} \uparrow \infty$ such that for all n, $f^{'}(s_n) = f^{'}(r_n) = 0$, $lim_{n\to\infty} f(s_n) = L$ and $lim_{n\to\infty} f(r_n) = l$ [224].*

**Theorem 8.3.2.** *The origin (0,0,0) of model (8.2.1-8.2.3) is a global attractor.*

*Proof.* To prove the theorem we have to show $C_1 = 0$.
Let

$$P(t) = rH(t)+rD(t), for t > 0 \tag{8.3.2}$$

Then,

$$\begin{aligned} P^{'}(t) &= rH^{'}(t)+rD^{'}(t) \\ &= -pr(H(t)-H(t-\tau_t))-\frac{-rbD(t)}{1+H(t)}<0 \end{aligned}$$

Hence there exists a constant say $C_2 \geq 0$ such that $lim_{t\to\infty}P(t) = C_2 \geq 0$. Thus from eqn.(8.3.1) and eqn.(8.3.2) we can say that $I(t) = G(t)-P(t) \to C_1-C_2$ as $t \to \infty$. Hence for any sequence $\{s_k\} \to \infty$, $I(s_k) \to C_1-C_2$ as $k \to \infty$.

Now consider

$$\overline{H} = lim_{t\to\infty} supH(t), \underline{H} = lim_{t\to\infty} inf H(t),$$

$$\overline{D} = lim_{t\to\infty} supD(t), \text{ and } \underline{D} = lim_{t\to\infty} inf D(t).$$

From Lemma 8.3.1, there exists a sequence $r_k \to \infty$ such that $D^{'}(r_k) = 0$ for every k and $lim_{k\to\infty} D(r_k) = \overline{D}$.

Eqn.(8.2.2) of model (8.2.1-8.2.3) implies

$$0 \quad = \quad D^{'}(r_k) = pH(r_k) - pqD^3(r_k) - \frac{bD(r_k)}{1+I(r_k)} \tag{8.3.3}$$

For $\varepsilon > 0$, there exists $T > 0$ such that $H(t) \leq \overline{H} + \varepsilon$ when $t \geq T$. Then for sufficiently large k, $H(r_k) \leq \overline{H} + \varepsilon$ and eqn.(8.3.3) becomes

$$0 \leq p(\overline{H} + \varepsilon - qD^3(r_k)) - \frac{bD(r_k)}{1+I(r_k)}$$

Let $k \to \infty$

$$0 \leq p(\overline{H} + \varepsilon - q\overline{D}^3) - \frac{b\overline{D}}{1+C_1-C_2}$$

which is true for all $\varepsilon > 0$, hence

$$0 \leq p(\overline{H} - q\overline{D}^3) - \frac{b\overline{D}}{1+C_1-C_2}$$

or

$$q\overline{D}^3 + \frac{b\overline{D}}{p(1+C_1-C_2)} \leq \overline{H} \tag{8.3.4}$$

Similarly, there exists a sequence $r_k^{'} \to \infty$ such that $H^{'}(r_k^{'}) = 0$ for every k and $lim_{k\to\infty} H(r_k^{'}) = \overline{H}$. Hence eqn.(8.2.1) implies

$$0 = H^{'}(r_k^{'}) = -pH(r_k^{'}) + pqD^3(r_k^{'})$$

For $\varepsilon > 0$, there exists $T^{'} > 0$ such that $D(t) \leq \overline{D} + \varepsilon$ for all $t \geq T^{'}$. For sufficiently large value of k, $D(r_k^{'}) \leq \overline{D} + \varepsilon$ and hence

$$0 \leq -pH(r_k^{'}) + pq(\overline{D} + \varepsilon)^3$$

Let $k \to \infty$

$$0 \leq -p\overline{H} + pq(\overline{D} + \varepsilon)^3$$

which is true for all $\varepsilon > 0$, hence

$$0 \leq -p\overline{H} + pq\overline{D}^3$$

or

$$\overline{H} \leq q\overline{D}^3 \tag{8.3.5}$$

From eqn.(8.3.4) and eqn.(8.3.5), we conclude that

$$q\overline{D}^3(r_k) + \frac{b\overline{D}}{p(1 + C_1 - C_2)} \leq q\overline{D}^3$$

implies $\overline{D} = 0$ and $\overline{H} = 0$ i.e $lim_{t\to\infty}D(t) = 0$ and $lim_{t\to\infty}H(t) = 0$, since $D(t)$ and $H(t)$ are positive for all $t > 0$. From eqn.(8.2.3), we can say that $lim_{t\to\infty}I(t) = 0$.
Hence eqn.(8.3.1) implies,

$$lim_{t\to\infty}G(t) = rlim_{t\to\infty}H(t) + rlim_{t\to\infty}D(t) + lim_{t\to\infty}I(t) = 0$$

i.e

$$C_1 = 0.$$

Hence the origin (0,0,0) of the model (8.2.1-8.2.3) is a global attractor. □

## 8.4 Numerical simulation and results

In this section, we perform numerical simulation using parameters identified in the literature. Table 8.1 lists the values of all parameters used in model (8.2.1-8.2.3) and the related references from which parameter values are determined.

We consider the delay differential equations (DDE) mathematical model to model the profile of plasma insulin concentration. The calculation is simplified by using Matlab

2012b. Bolus injection of insulin is the most commonly used in diabetics, but the continuous subcutaneous injection is more effective region for insulin delivery. Insulin is secreted from the pancreas in two oscillatory manners. Pulsatile oscillations having small amplitude and short period of (5, 15) min and ultradian oscillations having large amplitude and long period of (50, 150) min [6, 7, 17, 42].

We compare the profile of plasma insulin concentration obtained from the numerical simulation of the model (8.2.1-8.2.3) with the results obtained by Li et al. [42] and found that after incorporating the necessary time delay terms in the model, the profile of plasma insulin concentration is compatible with the previous obtained results. Plasma insulin concentration is considered as a variable in simulation of both the models. The dynamics of plasma insulin concentration is in agreement with measured data [225, 226].

Insulin lispro and insulin aspart were injected subcutaneously in the experiments performed in [225], while the plasma volume was assumed to be 45 ml/kg [222]. Hence the initial value of $H(0) = H_0 = 0.0029$ U/ml $= 2900\ \mu$ U/ml, $D(0) = D_0 = 0$ and $I(0) = I_0 = 0.000006$ U/ml $= 6\ \mu$ U/ml [227] are considered to model the profile of plasma insulin concentration.

The values of the parameters used are same as the value taken in [42]. The values of $b = 0.0060$, $d_i = 0.0775$ are considered for simulating insulin lispro and values of $b = 0.0068$, $d_i = 0.0081$ are considered for simulating insulin aspart [42]. The range of values of $b$ and $d_i$ are selected from range discussed in the best model 9 and model 10 proposed in [217] from Table III(a). Model is proposed for bolus injection only hence we compare the plasma insulin concentration of our model with the Li et al. [42] model.

We also quantify the range of two time delays in 3 cases at which the good profile of plasma insulin concentration is obtained.
Case 1 : $\tau_t > 0$, $\tau_u = 0$ i.e delay in transformation of hexameric state to dimeric state but no delay in insulin utilization.

For $\tau_t = 15$ min, $\tau_u = 0$ we observe that $I(t) = 10$ U/ml. In Figure 8.2 plasma insulin concentration level are plotted for aspart and lispro insulin which is also compatible to the profile obtained by previous models [42, 111, 225].

Case 2 : $\tau_t > 0$, $\tau_u > 0$ i.e delay in transformation of hexameric state to dimeric state and delay in insulin utilization.

For $\tau_t = 15$ min, $\tau_u = 425$ min, we observe that $I(t) = 12$ U/ml. In Figure 8.3 plasma insulin concentration level are plotted for aspart and lispro insulin which is also compatible to the profile obtained by previous models [42, 111, 225].

Case 3 : $\tau_t = 0$, $\tau_u > 0$ i.e delay in transformation of hexameric state to dimeric state and delay in insulin utilization.

For $\tau_t = 0$, $\tau_u = 440$ min, we observe that $I(t) = 6$ U/ml. Plasma insulin concentration level are plotted for aspart and lispro insulin which is again compatible to the profile obtained by previous models [42, 111, 225] as seen in Figure 8.4.

In Figure 8.5, comparison of the simulated plasma insulin concentration produced for lispro having $\tau_t = 15$ min, $\tau_u = 0$ and Li et al. [42] model is shown. In Figure 8.6, comparison of the simulated plasma insulin concentration produced for aspart having $\tau_t = 15$ min, $\tau_u = 0$ and Li et al. [42] model is shown.

Relationship of hexamer, dimer and plasma insulin concentration ($\tau_t = 15$ min, $\tau_u = 425$ min) can be seen in Figure 8.7.

Figures demonstrate the plasma insulin concentration after incorporating both the delays in model. It can be seen clearly in figures that plasma insulin concentration profile given by DDE model is compatible with the profile of the previous models [42, 111].

## 8.5 Conclusion and future scope

To maintain the normal blood glucose level in the body, regulation of glucose insulin endocrine system should work continuously. Lispro and aspart as the bolus insulin are the best form of insulin for the normal physiological secretion stimulated by elevated blood glucose concentration in type 1 diabetic patients while glargin as the basal insulin is considered to be the best [42]. To maintain the glucose concentration in physiological range, the exact timing and doses of subcutaneous insulin injection is required. Here our purpose is to solve the above problem by discussing the model with the help of two explicit time delays.

The profile of plasma insulin concentration are modeled by many researchers time to time but no one has considered the time delays in the previous models. Here, we tried to make an attempt to model the plasma insulin concentration by incorporating necessary time delays and the obtained results are compatible with the results obtained by previous

models.

The only limitation we can observe here is that the value of second delay ($\tau_u$) is very large and sounds impractical in life. The obtained results also reveals the fact that there must be some hidden time delays which should also be considered and incorporated in the model so that more physiological results can be obtained. So in our future study we tried to deal with more number of time delays so that the range of all delays lies in physiological range.

The above discussed model having necessary time delay ($\tau_t$ and $\tau_u$) can form a foundation of an artificial pancreas if integrated with continuous glucose monitoring system. The above model is simple in nature and can be proved helpful in clinical practices. Information obtained from the simulation of model may be useful in designing and development of artificial pancreas.

| Parameters | Explanantion | Units | Values | References |
|---|---|---|---|---|
| $p$ | transfer rate of one hexameric molecule to three dimeric molecules | $min^{-1}$ | 0.5 | [206] |
| $q$ | chemical equilibrium constant | $ml^2U^{-2}$ | 0.13 | [223] |
| $r$ | rate at which fractional molecules became plasma insulin | | 0.2143 | [222] |
| $d_i$ | insulin degradation rate | $min^{-1}$ | 0.081 (lispro) | [217] |
| $d_i$ | insulin degradation rate | $min^{-1}$ | 0.0775 (aspart) | [217] |
| $b$ | constant parameter | $min^{-1}$ | 0.0068 (lispro) | [217] |
| $b$ | constant parameter | $min^{-1}$ | 0.0060 (aspart) | [217] |
| $H_0$ | insulin concentration in hexameric form at t=0 | $Uml^{-1}$ | 0.0029 | [225] |
| $D_0$ | insulin concentration in dimeric form at t=0 | $Uml^{-1}$ | 0 | [42] |
| $I_0$ | plasma insulin concentration at t=0 | $Uml^{-1}$ | 0.000006 | [225] |

Table 8.1: Parameters used in the mathematical model.

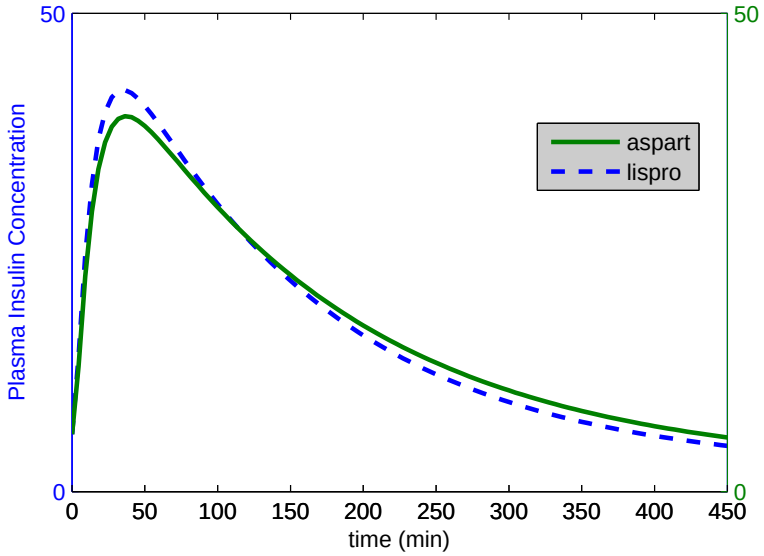


Figure 8.2: Plasma insulin concentration level having p=0.5, q=0.13, r=0.2143, $d_i$=0.0081, b=0.0068 $\tau_t = 15$, $\tau_u = 0$ for lispro (dashed line) and p=0.5, q=0.13, r=0.2143, $d_i$=0.0775, b=0.0060, $\tau_t = 15$, $\tau_u = 0$ for aspart (solid line).

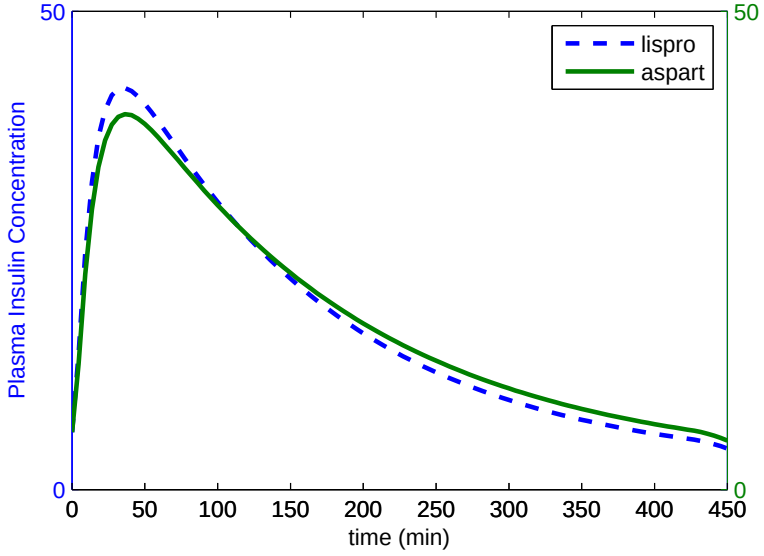


Figure 8.3: Plasma insulin concentration level having p=0.5, q=0.13, r=0.2143, $d_i$=0.0081, b=0.0068 $\tau_t = 15$, $\tau_u = 425$ for lispro (dashed line) and p=0.5, q=0.13, r=0.2143, $d_i$=0.0775, b=0.0060, $\tau_t = 15$, $\tau_u = 425$ for aspart (solid line).

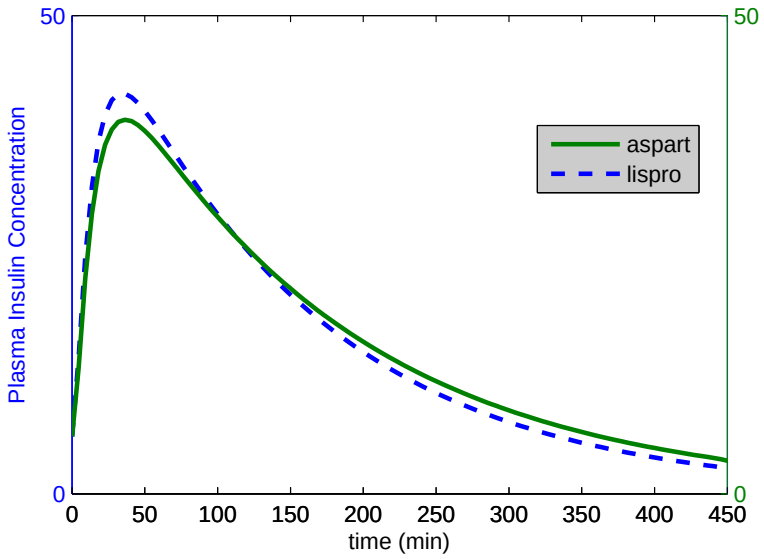


Figure 8.4: Plasma insulin concentration level having p=0.5, q=0.13, r=0.2143, $d_i$=0.0081, b=0.0068, $\tau_t = 0$, $\tau_u = 440$ for lispro (dashed line) and p=0.5, q=0.13, r=0.2143, $d_i$=0.0775, b=0.0060, $\tau_t = 0$, $\tau_u = 440$ for aspart (solid line).

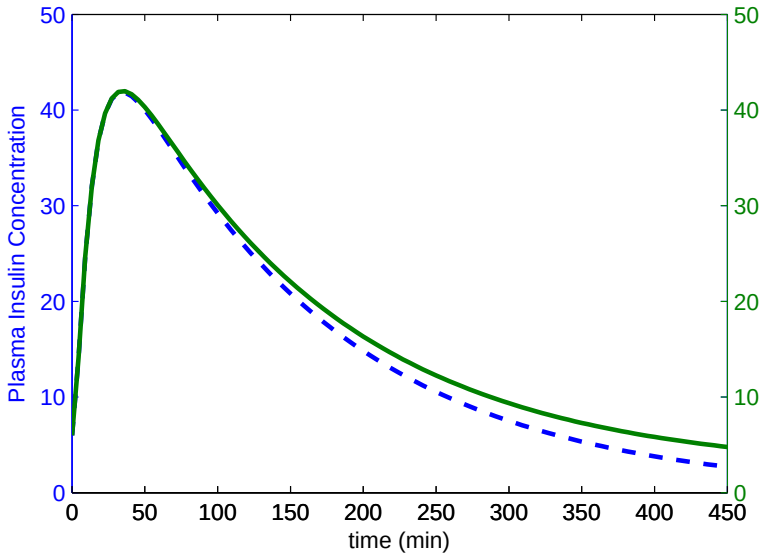


Figure 8.5: Comparison of the simulated plasma insulin concentration (solid line) for lispro having $\tau_t = 15$, $\tau_u = 0$ and dashed line is the simulation by model [42].

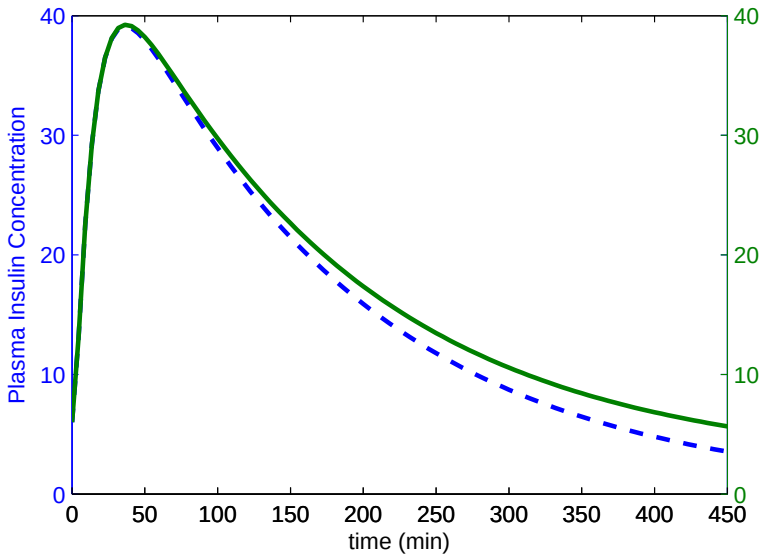


Figure 8.6: Comparison of the simulated plasma insulin concentration (solid line) for aspart having $\tau_t = 15$, $\tau_u = 0$ and dashed line is the simulation by model [42].

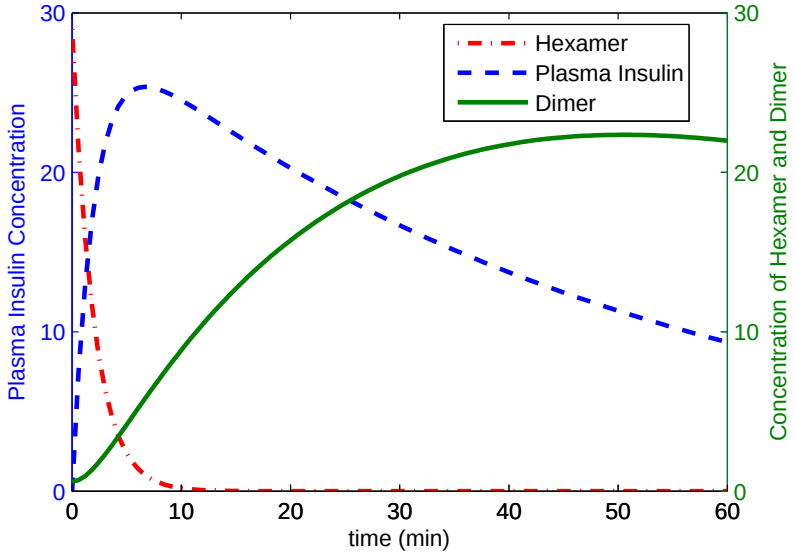


Figure 8.7: Dynamics of hexamer, dimer and plasma insulin concentration ($\tau_t = 15$, $\tau_u = 425$).

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# List of Publications

1. **Saloni Rathee** and Nilam; Quantitative analysis of time delays of glucose - insulin dynamics using artificial pancreas, *Discrete and continuous dynamical systems-series B,* **20***, 9, doi:10.3934/dcdsb.2015.20.3115 (2015) (AIMS).*

2. **Saloni Rathee** *and Nilam;* ODE models for the Management of diabetes : A review, *International journal of Diabetes in developing countries, DOI 10.1007/s13410-016-0475-8 (2016) (Springer).*

3. **Saloni Rathee** *and Nilam;* Dynamical system for glucose - insulin space in different organs of diabetes, *Communication in Mathematical Biology and Neuroscience* **9** *(2016) ISSN: 2052-2541.*

4. **Saloni Rathee** *and Nilam;* Study of the effects of FFA and obesity on diabetes through numerical simulation of the mathematical model, *Journal of Mathematics and System Science* **5***, doi: 10.17265/2159-5291/2015.06.004 (2015) (David Publishing).*

5. **Saloni Rathee** *and Nilam;* Dynamics and control of glucose - insulin regulatory system in diabetics using vitamin D.

6. **Saloni Rathee** *and Nilam;* Quantitative and stability analysis of three time delays in glucose and insulin oscillations profile using artificial pancreas.

7. **Saloni Rathee** *and Nilam;* Study of two time delays in IVGTT glucose - insulin dynamical system.

8. **Saloni Rathee** *and Nilam;* Modeling the dynamics of insulin analogues in type 1 diabetes using two explicit time delays.

# Papers in Conferences

1. Paper entitled "Application of I - HDMR in glucose insulin dynamics", published in International Conference on Mathematical Sciences (ICMS-2014) held in Sathyabama University, Chennai, Tamil Nadu during 17-19 July, 2014 (Elsevier).

2. Paper entitled "Maintenance of glucose level in diabetes using vitamin D : A mathematical model", presented in International Congress of Mathematicians (ICM-2014) held in Seoul, Coex, South Korea during 13-21 August, 2014.

3. Paper entitled "Dynamical system for glucose - insulin space for heart in diabetics", presented in 2nd Cardiovascular Outcome Trial Summit held in Munich, Germany during 20-21 October, 2016.

4. Paper entitled "Study of three time delays in glucose and insulin oscillations profile", presented in 2nd Cardiovascular Outcome Trial Summit held in Munich, Germany during 20-21 October, 2016.