APPLICATION OF CONTROLLER IN MATHEMATICAL MODELING FOR THE MANAGEMENT OF DIABETES

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DOCTOR OF PHILOSOPHY

in

MATHEMATICS

By

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DECLARATION

I declare that the research work reported in this thesis entitled "**Application of Controller in Mathematical Modeling for the Management 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. and co-supervision of *Dr. Harendra Pal Singh*, Cluster Innovation Centre, University of Delhi.

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.

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CERTIFICATE

This is to certify that the research work embodied in the thesis entitled **"Application of Controller in Mathematical Modeling for the Management of Diabetes "** submitted by **Mr. Ankit Sharma** with enrollment number **2K17/PhD/AM/01** is the result of his original research carried out in the Department of Applied Mathematics, Delhi Technological University, Delhi, for the award of **Doctor of Philosophy** under the supervision of **Dr. Nilam** and co-supervision of **Dr. Harendra Pal Singh**.

It is further certified that this work is original and has not been submitted in part or fully to any other University or Institute for the award of any degree or diploma.

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Date : **(ANKIT SHARMA)**

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Dedicated to My Parents

Mr. Ram Savit Sharma

and

Late Nirmala Sharma

Contents

Abstract

Diabetes Mellitus is a chronic disease that affects millions of people worldwide, with its complications being a leading cause of morbidity and mortality. Despite decades of research, a cure for diabetes remains elusive, and the management of the disease relies heavily on controlling blood sugar levels through a combination of diet, exercise, and medication. Mathematical modelling has proven to be an effective tool in this regard, but the accuracy of the models depends on the effectiveness of the controller used. The aim of the present thesis is to discuss the factors controlling the glucose level through ordinary and delayed mathematical models of glucose insulin system to manage the glucose level. The goal of regulated blood glucose level has been achieved by application of mathematical models and applying controller on these models for the management of both the types of diabetes, Type 1 and Type 2.

The thesis consists of seven chapters, in which first chapter is introductory in nature. Second chapter devotes to the effect of physical activity on blood glucose is introduced through a mathematical model that compares normal, non-insulin dependent and insulin dependent diabetes. The third chapter examines the influence of vitamin D on glucose-insulin dynamics in healthy and diabetic individuals. It investigates the role of vitamin D in maintaining glucose concentration, which is critical but challenging for diabetics. we introduced factors related to the impact of vitamin D into a mathematical model and used numerical simulations to explore how vitamin D affects glucose-insulin regulation in diabetics. Fourth chapter aims to evaluate the effectiveness of diabetes awareness campaigns in prevention. A fuzzy logic controller was designed to lower the diabetic population, with positive and bounded solutions. Fifth chapter focuses on developing a fuzzy logic closed-loop insulin therapy recommendation system for people with type 1 diabetes with delays in insulin production, absorption, and action are addressed with a non-linear delay mechanism in the glucose-insulin model. The controller has been used to regulate glucose concentration in response to changes in delay parameters. The model was tested in four different scenarios includ-

ing skipping a meal, multiple meals, unusual meals, and uncertainty in parameters. Sixth chapter presents a new automatic insulin delivery system called a proportional integral derivative-fuzzy logic controller (PID-FLC) for patients with Type 1 diabetes. Seventh chapter is devoted to describe the conclusion and future work.

Keywords: Diabetes mellitus; Fuzzy logic; Artificial Pancreas; Insulin infusion technique; Ordinary and delay differential equation models

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Chapter 1

Introduction

The primary objective of this chapter is to offer a comprehensive examination of existing and current understanding of the physiological aspects of diabetes and its management through the application of significant mathematical models. The chapter delves into the various forms of diabetes, their global incidence, diagnosis methods, risk factors, symptoms, and treatment options. The purpose of this analysis is to bolster the argument that the biological challenge of regulating blood glucose levels has serious consequences. The ultimate goal of the chapter is to provide an explanation for the motivation behind the research presented in the thesis.

1.1 Diabetes Mellitus

Diabetes mellitus, commonly referred to as diabetes, is a metabolic disorder characterized by high blood sugar levels over an extended period. The increasing number of people with diabetes can be attributed to factors such as population growth, aging, urbanization, rising obesity rates, and physical inactivity. In 2015, the International Diabetes Federation estimated that 41.5 million adults worldwide had diabetes, with 153.2 million in the Western Pacific, 59.8 million in Europe, 44.3 million in North America and the Caribbean, 35.3 million in the Middle East/North Africa, and 14.2 million in Sub-Saharan Africa. The top 10 nations with the most number of people with diabetes are China (109.6 million), India (99.2 million), the United States (29.3 million), Brazil (14.3 million), Russia (12.1 million), Mexico (11.5 million), Indonesia (10 million), Egypt (7.8 million), Japan (7.2 million), and Bangladesh (7.1 million). Despite having the lowest estimation for diabetes prevalence, Sub-Saharan Africa is projected to have the steepest increase (240%) in diabetes [104]. According to the 2020 National Diabetes Report [52], approximately 34.2 million people in the United States have been diagnosed with diabetes, and an additional 7.3 million remain undiagnosed. Globally, it is estimated that 9.3% of the world's population, equivalent to 463 million people, suffered from diabetes in 2019. This number is projected to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. Urban areas exhibit a higher incidence of diabetes (10.8%) compared to rural areas (7.2%) [91]. In 2019, impaired glucose tolerance affected an estimated 7.5% (374 million) of the global population, with projections for this number to rise to 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045 [151]. The highest increase in diabetes will occur in persons over 65 years old in both developed and developing nations, with the most significant increase observed in people aged 45 to 64 years, who are in their most productive period of life. As a result, diabetes represents a significant financial burden, with it consuming anywhere between 5% to 25% of the income of the average impoverished family. The prevalence of diabetes varies based on World Bank

Income Group, with high-income countries having a higher prevalence (10.4%) than middle-income countries (9.5%) and low-income countries (4.0%) [128]. By 2045, the estimated prevalence of diabetes in high, middle, and low-income countries is 11.9%, 11.8%, and 4.7% respectively[108].

The financial impact of diabetes is substantial, consuming anywhere from 5% to 25% of a typical low-income family's budget [5]. On March 22, 2018, the American Diabetes Association (ADA) released updated data revealing a rise in the overall cost of diagnosed diabetes from $245 billion in 2012 to $327 billion in 2017, a 26% increase over a five-year span [65]. The largest expenses come from hospital inpatient treatment (30%), followed by prescriptions for diabetes complications (30%), anti-diabetic drugs and supplies (15%), and doctor visits (20%) [5]. On average, medical expenses for those with diabetes are $16,752, with $9,601 attributed directly to the disease [129]. This is typically 2.3 times higher than for those without diabetes. This estimate shows the considerable cost that diabetes imposes on society. However, it does not take into account intangible factors such as pain and suffering, the resources provided by unpaid caregivers, and the burden of undiagnosed diabetes.

Since, Diabetes is a global health issue that affects millions of people worldwide, research into the causes and management of diabetes is critical in improving the quality of life for those affected by this disease. By studying the biological, environmental, and social factors that influence diabetes, researchers can develop better treatments and preventive strategies for managing this condition. Additionally, research into diabetes can help to identify new risk factors and develop novel therapies to reduce its prevalence in our society. Therefore, research in diabetes is an essential part of our public health efforts to improve the lives of those affected by this disease [185].

1.1.1 Diabetes is epidemic

Diabetes has become such a widespread issue that the number of people affected has risen dramatically over the past three decades. Designating it as an epidemic highlights the urgency for public health strategies to address it. Currently, efforts to

control the disease include monitoring, assessing risk, implementing risk reduction treatments, identifying patients, and tracking outcomes. These methods have been successful in controlling infectious diseases. However, the management of diabetes differs from traditional communicable diseases, as it also requires the philosophy of “finding and treating" patients. If preventive and treatment measures are not implemented, the diabetes epidemic is expected to escalate rapidly [192].

1.1.2 History of diabetes

Antiquity saw efforts by Arabs, Chinese, Indians, and Egyptians to understand the signs and symptoms of diabetes mellitus. However, only a few notable individuals have made a significant impact on the diagnosis and treatment of the disease, as well as paved the way for further research and the development of diabetology as a medical sub-specialty. The Ebers Papyrus from 1500 BC mentions people with excessive thirst and urination who were treated with plant extracts, but this depiction of diabetes is considered inadequate and potentially inaccurate according to Egyptian endocrinologist and medical historian Paul Ghaliongui [119]. Indian surgeon Sushruta used the term “Madhumeha”, meaning honey-like urine, to describe diabetes in his work Samhita, noting not only its sweet taste, but also its sticky texture and ability to attract ants. He demonstrated a remarkable insight by drawing a connection between diabetes and the opulent dietary habits of the affluent classes, characterized by a proclivity for rice, cereal, and sugary treats. Meanwhile, the renowned Chinese physician Chang Chung-Ching, hailed as the "Chinese Hippocrates," astutely identified the triad of polyuria, polydipsia, and weight loss as hallmarks of a distinct disease. Notably, Chen Chuan, a 7th-century AD scholar, exhibited an impressive diagnostic acumen by identifying the presence of saccharine urine in diabetes, which he christened as Hsiao Kho ping, and accurately delineating its classic symptoms of insatiable thirst, copious drinking, and the production of voluminous amounts of sweet-tasting urine. Since the 18th century, doctors have observed that people with diabetes are more prone to eye problems, skin diseases like furuncles, and rat ulcers [56]. Arab

physician Avicenna in the 11th century, author of the Canon of Medicine, characterized diabetes and its complications such as gangrene and sexual dysfunction. Moises Maimonides, a medieval scholar, later detailed diabetes in great detail, including its symptoms of acidosis.

1.1.3 What is diabetes

Diabetes, often known as diabetes mellitus, is defined as having sweet urine. Diabetes is a disorder that is developed when our blood sugar levels are continuously too high. Hyperglycemia in diabetic individuals is brought on by the liver's lackness or inadequate synthesis of insulin. Chronic hyperglycemia caused by inadequate insulin production and/or activity is a hallmark of the diabetes syndrome. It may also be described as a disorder developed depending upon the way our bodies utilize digested food for energy and growth-their metabolism-of carbohydrates, proteins, and fats [185].

1.2 Glucose-Insulin Endocrine Metabolic Regulatory System

A person is said to have hyperglycemia if their blood glucose level exceeds the normal physiological range, which is generally believed to be between 70 and 110 mg/dl. A key factor in controlling the glucose-insulin metabolic pathway is the pancreatic endocrine hormones glucagon and insulin [166].
The body's elevated plasma glucose concentration causes the processes listed below to happen:

- In response to increased plasma glucose levels, the pancreas releases insulin from β-cells.

- The insulin receptors on cells are where insulin (both serum and freshly produced insulin) interacts.

- Glucose transporters (GLUT4) carry plasma glucose into cells as a result of insulin receptors retaining the insulin (muscles and adipose cells).
- The cells ingest it and use it to produce energy at appropriate time.

Low levels of plasma glucose will result in the following process:

- The α-cells of the pancreas began to release glucagon in response to low glucose levels.
- The liver receives the secreted glucagon.
- Glucagon is converted to glucose by the liver.

The procedure raises the plasma glucose concentration level. Unused glucose is then stored in the liver, where it may be converted back to glucose if the plasma glucose concentration falls. Meal consumption, oral glucose intake, and continuous everlasting nourishment are the produces which raise the levels of glucose. The pancreas and liver is crucial in keeping blood glucose levels within the normal physiological range.

1.3 Disease Pathophysiology

Diabetes Mellitus is a metabolic disorder where the body struggles to produce or use insulin effectively, resulting in imbalanced glucose levels (3.9-6.9 mmol/L). In the process of carbohydrate metabolism, carbohydrates are broken down into soluble sugars that are absorbed into the bloodstream through the intestinal wall. This leads to an increase in blood sugar levels, causing the pancreas to release insulin and glucagon hormones to maintain a balanced level. Insulin, produced by β-cells, helps lower blood sugar levels by facilitating glucose absorption into cells. When blood glucose levels remain persistently high, it is known as hyperglycemia ($>$6.9 mmol/L) due to irregularities in either insulin secretion or action. Glucagon, a peptide hormone produced by α-cells, helps raise blood glucose levels by triggering the liver to convert stored Glycogen into glucose, which is then released into the bloodstream. If blood

glucose levels remain persistently low, it is known as hypoglycemia ($<$3.9 mmol/L) [166].

1.4 Several Fundamental Terminology and Definitions

There are several fundamental terms and definitions related to diabetes, including

- Glucose: In living things, glucose is the most prevalent aldohexose. The body uses it as its primary source of energy. In both plants and animals, glucose is stored in a polymer known as starch or glycogen.
- Glycogen: A multi-branched glucose polymer known as glycogen is a source of energy. The liver and muscles' cells store glycogen, which is kept hydrated with three to four parts water. Granules of glycogen are located in the cytoplasm of cells and are crucial components of the glucose cycle.
- Endocrine system: It is composed of glands that produce and release hormones into the bloodstream or nearby tissues. It encompasses various organs, such as the pituitary gland, thyroid, parathyroid, adrenal gland, pancreas, ovaries, and testes.
- Liver : It is a large, complex organ that plays a vital role in the body, including the regulation of metabolism, the production of bile, and the detoxification of harmful substances.
- Pancreas: It is an endocrine gland that creates a variety of vital hormones that circulate in the blood and serve a variety of purposes, including insulin, glucagon, somatostatin, and others. Additionally, the pancreas secretes a variety of pancreatic juices that are rich in digestive enzymes that aid in small intestine nutrition absorption and digestion.
- Peptide hormones: It is composed of shorter chains of amino acids compared to protein hormones, are substances released into circulation or surrounding tissues by cells.

- α - cell: The pancreatic islets' alpha cells, which are endocrine cells, release the peptide hormone glucagon.

- Glucagon: A peptide hormone called glucagon is generated by pancreatic α-cells and increases the level of glucose in the blood. It functions in direct opposition to the insulin hormone, which reduces blood glucose levels. The pancreas releases glucagon when the blood's level of glucose drops.

- β - cell: It make about 65 to 80 percent of the cells of the pancreatic islets, which are where they may be located. In order to store and release insulin, β-cells are mostly used.

- Insulin: It is a peptide hormone produced by the pancreatic β-cells. By encouraging the absorption of glucose from the blood to skeletal muscles and adipose tissue, it controls the metabolism of carbohydrates and lipids. Insulin also prevents the liver from producing glucose.

- Insulin sensitivity (S_I): It is a measure of how easily and efficiently body cells respond to insulin's signal to take up glucose. A body that exhibits high insulin sensitivity requires a lower amount of insulin to lower blood sugar levels compared to a body with low sensitivity.

- Insulin Resistance: It is a condition where the body's cells do not respond normally to insulin, leading to higher insulin levels and increased risk of developing type 2 diabetes.

- Disposition index (D_I): It is a measure of insulin secretion and sensitivity that predicts the likelihood of developing Type 2 Diabetes and assesses the health of the beta cells in the pancreas.

- Hyperglycemia: This is a condition where the concentration of glucose in the body rises due to the pancreas not secreting enough insulin or the insulin produced not allowing muscle and liver cells to take up glucose.

- Hypoglycemia: A state in which the pancreas secretes more insulin than is normally necessary to keep glucose levels within the normal physiological range.
- Glucose transporter type 4 (GLUT4): It is a protein that is responsible for transporting glucose in response to insulin signaling. This protein is encoded by the GLUT4 gene in humans and is primarily found in adipose tissues and muscles.
- Effectiveness of glucose: The capacity of glucose to accelerate its own disappearance without the assistance of insulin.
- Acute insulin response (AIR) glucose: It is a rapid increase in insulin secretion in response to rising blood glucose levels, crucial for regulating glucose homeostasis.
- Ultradian oscillations: It is a periodic cycle that occurs continuously during a 24-hour day.
- Gluconeogenesis: It is a metabolic process that involves the creation of glucose from non-carbohydrate sources, such as amino acids and fatty acids. This process is the reverse of glycolysis and is used by the body to maintain a constant supply of glucose in the blood, particularly during periods of low carbohydrate intake or increased energy demand.
- Lipogenesis: It is process that involves turning acetyl-Coenzyme into a fatty acids.
- Continuous glucose monitoring (CGM): Continuous glucose monitoring automatically tracks blood sugar levels both day and night, allowing patients to view the glucose level at a glance and monitor fluctuations over time. Real-time glucose monitoring helps diabetics adjust their diet, exercise, and medication for better management throughout the day.
- Continuous subcutaneous insulin infusion (CSII): Continuous Subcutaneous Insulin Infusion (CSII), also known as insulin pump therapy, is a method of delivering insulin to people with diabetes. In CSII, a small device, known as an

insulin pump, is worn outside the body and is connected to a catheter that is inserted under the skin. The insulin pump continuously delivers small amounts of insulin into the body, mimicking the body's natural secretion of insulin. This method provides more flexibility and better glucose control compared to multiple daily injections, as it allows for adjustments in insulin delivery to accommodate for changing insulin needs, physical activity, and meals. The infusion set can be placed in various positions on the body, depending on how it's being used and what kind of clothing is being worn.

- Insulin Pump: It is a compact, portable electronic device that continuously infuses subcutaneous insulin at according to requirement dosages throughout the day in order to manage the body's elevated glucose content (CSII).

- Basal rate: The quantity of insulin constantly supplied to the body to maintain normal function is known as the basal rate.

- Bolus dose: The extra insulin that can be given to the body to keep the level of glucose stable.

- Artificial pancreas: By acting as a healthy pancreatic substitute, it helps diabetics manage their blood glucose levels. The failure of the pancreatic β-cells to operate properly is what drives scientists to create insulin alternatives. The artificial pancreas aims to enhance insulin replacement treatment and simplify insulin therapy for persons with type 1 diabetes.

- Time delays: There are some documented delays in the whole glucose-insulin regulation mechanism. These lags include:

  i) A lag in the release of insulin, whether it is released from the pancreas or an insulin pump.

  ii) A lag in the suppression of hepatic glucose synthesis.

  iii) A delay in the insulin's ability to reduce blood glucose levels.

1.5 Type of Diabetes

Diabetes can be broadly divided into two categories: Type 1 diabetes and Type 2 diabetes.

1.5.1 Type 1 diabetes mellitus (T1DM)

Type 1 diabetes, previously known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, is an autoimmune disorder where the immune system attacks and destroys the pancreatic β-cells responsible for producing insulin. This leads to a complete insulin deficiency and the presence of anti-insulin or anti-islet cell antibodies in the blood. The onset of the illness can be rapid and occur over a matter of days to weeks, but the destruction of the pancreatic islets and lymphocyte infiltration can take longer. People with type 1 diabetes typically require insulin therapy and oral insulin-stimulating medications are usually not effective. It represents 5 to 10 percent of all diagnosed cases of diabetes.

Symptoms of Diabetes

- Extreme Hunger
- Frequent urination
- Bed-wetting in youngsters
- Weight Loss
- Irritability
- Exhaustion and weakness
- Blurred Vision
- A vaginal yeast infection in females

Risk factors of Type 1 Diabetes

- History of the Family
- Inadequate Exercise
- Nutritionally Poor
- Overeating
- Pancreatic Illnesses

1.5.2 Type 2 diabetes mellitus (T2DM)

Type 2 diabetes is characterized by the body's insensitivity to insulin, leading to decreased insulin production, resistance to insulin, and eventual decline in the function of pancreatic β-cells. This results in decreased transport of glucose into the liver, muscle, and fat cells. The peripheral insulin resistance, which is linked to β-cell depletion, prevents low blood sugar levels even if blood insulin levels are high, due to modifications to the insulin receptors responsible for insulin activity. Obesity is a major cause of insulin resistance, while genetics and lifestyle factors, such as lack of physical activity, smoking, excessive alcohol consumption, and sedentary habits, also play a role. Approximately 55% of type 2 diabetes cases are attributed to obesity. The increase in juvenile obesity over the past few decades has contributed to the rise in type 2 diabetes in children and adolescents. The recent increase in rates of type 2 diabetes may also be due to environmental toxins.

Symptoms of type 2 diabetes mellitus

- Increased urination rate and push
- Increased appetite
- Loss of weight
- Fatigue
- Distorted vision

- Repeated infections
- Darkened skin spots

Risk factrors of type 2 diabetes mellitus

- Family diabetes history
- Overeating
- Unhealthy diet
- Active inactivity
- Increasing age
- Elevated blood pressure
- Gestational diabetes in the past
- An inadequate diet during pregnancy
- Insulin sensitivity
- Very little of Very Dense HDL cholesterol in the lipoprotein form and high triglyceride levels (TG)
- Sedentary kind of life
- Ovarian poly cystic syndrome

Graphical explanation of both the types of diabetes is shown in Fig 1.1

1.6 Treatments for Diabetes: Diagnosis and Testing

Despite the fact that diabetes affects many people, each person must get individualized care and treatment. The medical treatments and methods for managing the condition should be made available to people with diabetes and their families.

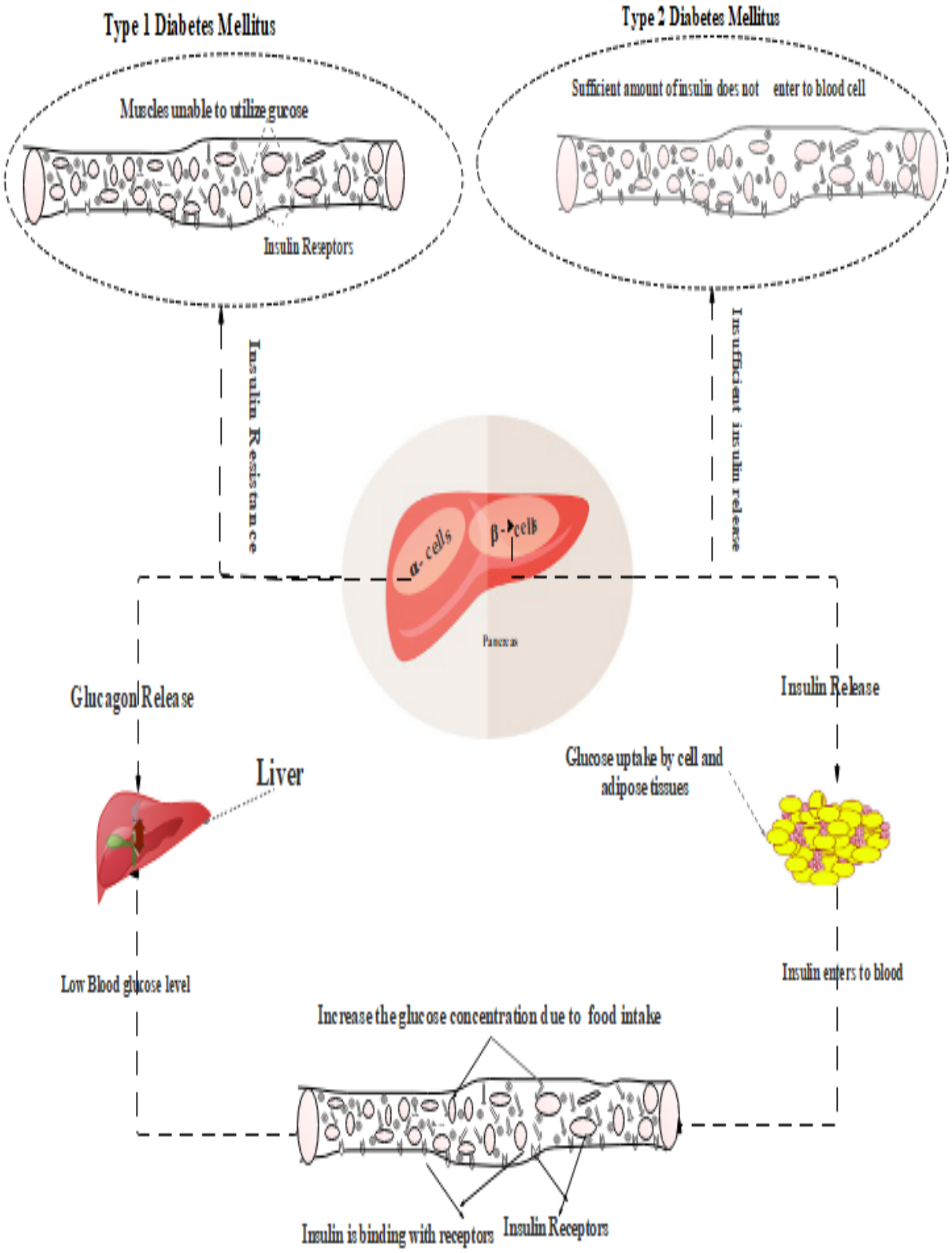

Figure 1.1: The Biological framework of Type 1 and Type 2 diabetes

1.6.1 Diagnosis of illness with glucose tolerance tests

Over the years, several glucose tolerance tests have been developed and used in clinical studies. A glucose tolerance test can be used to determine whether or not a

person has diabetes.

HbA1c

It is a blood test that reveals details about a person's average blood glucose, commonly known as blood sugar, levels during the previous three months. The A1C test is also known as the hemoglobin A1c, HbA1c, or glyco-hemoglobin test.

Fasting Sampled Intravenous Glucose Tolerance Test (FSIGTT)

A test to check blood sugar levels in which nothing is provided for 8 to 12 hours prior to the test (including food and drink). If the glucose level is more than 126 mg/dl over a long period of time than diabetes is more likely to develop.

Oral Glucose Tolerance Test (OGTT)

Blood samples are taken over a 2-hour period after the participant is given a glass of glucose liquid (75 mg). When the blood glucose level is above 200 mg/dl, then it is considered as hyperglycemia which may cause diabetes if persists for long duration.

Intravenous Glucose Tolerance Test (IVGTT)

It involves injecting glucose intravenously and then taking blood samples. IVGTT and FSIGTT measure how responsive or sensitive insulin is to elevated plasma glucose levels. In these tests, many samples of plasma glucose and serum insulin are taken, and the subject must fast for 8 to 10 hours prior to the test. It takes around 2.5 minutes to inject a bolus of 0.33 g/kg body weight into an antecubital vein.

1.6.2 Treatment therapies of diabetes

Diabetes is a chronic condition that can be managed with insulin therapy or by leading a sedentary lifestyle, or with a combination of both.

Lifestyle

- Eat healthy

- Exercise
- Get checkups
- Manage stress
- Stop smoking

Oral medication

Oral medication in diabetes management refers to drugs that are taken orally to help control blood glucose levels in individuals with type 2 diabetes. These medications work by increasing insulin sensitivity, decreasing glucose production, or stimulating insulin release, among other mechanisms. Examples of oral medications for diabetes management include alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, meglitinides, and others. The specific type of medication and dosage prescribed will depend on the individual's unique medical history and current health status.

Insulin therapy

Insulin therapy is a treatment for people with diabetes that involves taking insulin injections or using an insulin pump. The goal of insulin therapy is to maintain blood glucose levels within a target range and to prevent the development of long-term complications. Insulin therapy can be tailored to an individual's needs and can be adjusted based on various factors, such as food intake, physical activity, and blood glucose levels. There are several different types of insulin, including rapid-acting, short-acting, intermediate-acting, and long-acting.

- **Short-acting** : regular (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).

Each type has a different onset and duration of action and can be used in different ways to achieve optimal blood glucose control. It is mainly used for people with type 1 diabetes, but some people with type 2 diabetes who require intensive insulin therapy may also benefit from it.

Delivery of insulin

Traditional treatments for managing blood glucose levels in both Type 1 and Type 2 diabetes typically involve administering multiple daily insulin doses or continuous subcutaneous insulin infusion, with or without a continuous glucose monitor. Despite their widespread use, these approaches often fail to maintain glucose homeostasis, as patients are required to manually calculate their insulin doses throughout the day based on blood glucose test strip measurements. This manual process can be challenging. To determine the appropriate insulin levels to maintain glucose homeostasis, past and current glucose values are taken into account. Insulin delivery methods can be broadly classified into open-loop and closed-loop strategies, which is discussed below.

- **Open loop strategy**: The subcutaneous insulin injection method is a typical example of an open-loop control. Patients typically inject insulin before meals to cover their basal insulin needs. The insulin passes from the subcutaneous layer into the bloodstream, but some of the infused insulin degrades in the subcutaneous tissue and not all of it is utilized by the body. In the 1970s, researchers began working on an electronic device based on an open-loop control strategy: the insulin pump. An insulin pump is a small, battery-operated device attached to a small plastic tube that's placed under the skin and taped in place. Unlike the pancreas, insulin pumps don't automatically deliver the right amount of insulin. Patients, with the help of their healthcare team, program the insulin doses themselves in the insulin pump, allowing them to closely monitor their glycemia and calculate the glucose intake to adjust insulin doses delivered. The benefit

of an insulin pump is that it reduces the burden of self-managing insulin doses, increases patient convenience, and eliminates the need for multiple injections or external devices. However, it also has disadvantages such as the risk of hypoglycemia from over-infusing insulin, a higher risk of developing diabetic ketoacidosis, and a higher cost compared to syringes.

- **Closed loop strategy**: An efficient alternative to traditional insulin delivery methods for diabetic patients can be achieved through the use of a closed-loop strategy. This reduces the burden on the patient and determines the insulin amount in real-time, making it effective in any situation. A well-known example of this approach is the artificial pancreas. Since the introduction of capillary blood glucose meters in the 1950s [117], advancements in diabetes technology have played a crucial role in improving diabetes management. The use of insulin pump therapy, which became a widely used treatment modality, particularly in pediatric populations, in the 1970s [117], paved the way for the development of the artificial pancreas. The artificial pancreas is designed to maintain the physiological range of blood glucose levels accurately, providing greater flexibility to patients. The continuous glucose monitor measures the blood glucose levels in real-time, and the insulin pump delivers insulin as needed. The artificial pancreas system automatically adjusts insulin delivery to keep blood glucose levels within a target range, reducing the risk of high or low blood sugar. This technology aims to provide better glycemic control and improve the quality of life for people with diabetes.

  The concept of an “artificial pancreas” dates back to the early 20th century when doctors and scientists first began to experiment with insulin as a treatment for diabetes. The idea of creating an artificial device to mimic the functions of the pancreas was first proposed in the 1920s [117], soon after the discovery of insulin. The first artificial pancreas was created by Dr. John Langer at the University of Toronto in 1966 [117]. Over the following decades, advances in medical technology and understanding of diabetes paved the way for the development

of various insulin delivery systems, including insulin pumps and continuous glucose monitoring (CGM) devices. In the 1980s and 1990s, research into closed-loop insulin delivery systems began, with the goal of creating a fully automated artificial pancreas. The first prototypes of closed-loop insulin delivery systems were developed in the early 2000s and were tested in clinical trials. The first commercially available artificial pancreas was approved for use in 2016 [179]. Despite ongoing efforts by researchers and companies to improve artificial pancreas systems, there is currently no fully functional artificial pancreas system available in the market [179].

Working of artificial pancreas

The four components of the artificial pancreas are necessary for its operation.

- It continually monitors blood glucose levels using a glucose sensor and a transmitter that checks the levels every minute..
- The system uses an algorithm to determine the appropriate insulin delivery based on the blood glucose level and the user's insulin requirements.
- Insulin is then delivered into the body through an insulin pump, which is worn on the body.
- The glucose sensor, insulin pump, and algorithm work together to maintain normal blood glucose levels, reducing the risk of both high and low blood sugar episodes.

Challenges in designing of artificial pancreas

Developing an artificial pancreas is challenging due to the complexity and dynamic nature of the human body. Designing a control strategy that can accurately regulate blood glucose levels through a closed-loop system requires an adaptable and responsive algorithm that can adjust to changes in the patient's physiology. This includes changes in insulin sensitivity caused by physical activity, stress, or illness, as well as individual patient characteristics such as age, weight, and medication use.

Another challenge is accurately predicting glucose levels by accounting for factors like meal consumption, insulin absorption rates, and glucose clearance rates, while also considering individual variability. Some of the challenges in designing an artificial pancreas include:

- Accuracy and reliability: The artificial pancreas system must be able to accurately and reliably monitor blood glucose levels and deliver the correct amount of insulin to keep blood glucose within a target range. Any errors or malfunctions in the system can result in dangerous fluctuations in blood glucose levels.
- Response time: The system must respond quickly to changes in blood glucose levels to prevent hyperglycemia or hypoglycemia. This requires real-time monitoring of glucose levels and rapid adjustment of insulin delivery.
- Integration with the human body: The artificial pancreas system must be designed to work in harmony with the human body. This means ensuring that the system is bio compatible, minimally invasive, and does not cause any adverse reactions.
- Power source: The system must have a reliable and long-lasting power source. Battery life is particularly important for wearable artificial pancreas systems that must be worn continuously.
- Regulatory approval: The artificial pancreas system must meet regulatory standards for safety and effectiveness before it can be approved for clinical use.

1.7 Mathematical model for Glucose-Insulin Dynamics

Mathematical modeling of Glucose insulin system is an important tool in the management of diabetes. It helps to understand the dynamics of glucose metabolism and insulin action, and to predict the response to changes in diet, lifestyle or activity. The model can be used to design better treatments for diabetes, and to individualize therapy for each patient. Blood glucose level and blood insulin level, denoted by $G(t)$

and $I(t)$ respectively at $t \geq 0$, are the two primary variables that make up the human body's glucose-insulin regulatory system and that can be measured or manipulated in a therapeutic procedure. The model comprises of:

$$\frac{dG(t)}{dt} = \text{glucose production - glucose utilization and}$$

$$\frac{dI(t)}{dt} = \text{insulin production - insulin utilization}$$

Glucose production: When blood glucose levels fall below the baseline level G_b, the liver releases glucose or it is administered orally. We get glucose from our diet in the form of starch or sucrose. Additionally, glucose is consumed orally, with meals, and through glucose infusion. Hence,

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

Glucose utilization: Insulin promotes the metabolism of sugar, leading to a decrease in blood sugar levels. A higher level of either insulin or blood sugar results in faster utilization of glucose, so the product of these two levels serves as a good indicator of glucose utilization.

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

Therefore, the rate of change in glucose concentration can be modeled as:

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

where the glucose gradient's sensitivity to low blood sugar levels and the presence of insulin are represented by the letters a and b, respectively.

Insulin production : The pancreas β-cells secrete insulin if the blood sugar level rises beyond the fasting level, or in the case of diabetics, an external source (an

insulin pump or artificial pancreas). Hence

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

Insulin utilization : Insulin itself degrades by separate biochemical process, which can be express mathematically as

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

Therefore, the rate of variation in insulin concentration can be expressed as:

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

where c and e represent the insulin gradient's sensitivity to high glucose and insulin levels, respectively. The basic mathematical model for glucose - insulin dynamics may be modeled as :

$$\left.\begin{aligned} \frac{dG(t)}{dt} &= a(G(t) - G_b) - bG(t)I(t) \\ \frac{dI(t)}{dt} &= c(G(t) - G_b)^+ - eI(t) \end{aligned}\right\} \tag{1.7.7}$$

The next two subsection will explain the previous research towards the development of various mathematical models of glucose homeostasis. Important aspects of these models are to a realistic representation of the long-term physiological behaviour, prediction of diabetes and its prevention, and evaluating disease maintaining therapies

1.7.1 Ordinary differential equation mathematical models

A simple model was developed by Bolie [25] to assess the coefficients of healthy blood glucose regulation. The two compartmental differential equations for the insulin-

glucose regulation system are expressed as:

$$\left.\begin{aligned}\frac{dx(t)}{dt} &= p - \alpha x + \beta y \\ \frac{dy(t)}{dt} &= q - \gamma x - \delta y\end{aligned}\right\} \tag{1.7.8}$$

where, p is the rate of insulin injection divided by the extracellular compartment value, and q is the changing the rate of glucose level divided by the extracellular compartment value. The deviation of insulin concentration from its mean physiological value is represented by x, and the deviation of glucose concentration from its mean physiological value is represented by y.The combined response of liver glycogen storage and tissue glucose utilization to an increase in insulin concentration is denoted by the symbol γ, whereas the symbol δ represents the combined response of liver glycogen storage and tissue glucose utilization to an increase in glucose concentration. The sensitivity of insulinase activity to elevated insulin concentration is represented by α, the sensitivity of pancreatic insulin to elevated glucose concentration is represented by β.

Ackerman et al. [3] developed a model in 1965 that simulates the behaviour of the human regulating system in order to forecast the blood glucose level. To control the blood glucose and blood insulin concentration, they compared the predictions produced during the OGTT. Segre et al. [153] examined a 2-compartment model in 1973 and used it to analyse the mechanisms of glucose and insulin control in 26 healthy, 16 diabetic, and 8 obese people. By injecting glucose (0.5 gm/min for approximately 300 min), the blood glucose levels for all three groups were measured. In 1978, Ruby et al. [138] discussed a model to show how both glucagon and insulin function as blood glucose controllers. The simulation's findings imply that insulin is the hormone that is most crucial to controlling hyperglycemia, whereas glucagon serves as a key regulator when blood sugar levels dip below 50 mg/dl. In the early 1980s, Bergman et al. [21] introduced the minimal model of glucose-insulin dynamics to explain the levels of glucose and insulin. The mathematical representation of the three-compartment

minimal model is as follows:

$$\left.\begin{aligned} \frac{dG(t)}{dt} &= -[p_1 + X(t)]G(t) + p_1 G_b \\ \frac{dX(t)}{dt} &= -p_2 X(t) + p_3[I(t) - I_b] \\ \frac{dI(t)}{dt} &= p_4[G(t) - p_5]^+ - p_6 \end{aligned}\right\} \tag{1.7.9}$$

with initial value $G(0) = p_0$, $X(0) = 0$, and $I(0) = b_7 + I_b$. The variables in the equation are defined as follows: $G(t)$ and $I(t)$ represents the concentration of glucose and insulin at time t in minutes, respectively. $X(t)$ represents an auxiliary variable proportional to insulin concentration in minutes^{-1}. G_b is the baseline value of glycemia in mg/dl. I_b ($\mu U/ml$) is the baseline value of insulinemia. p_0 is the initial glycemia concentration after a glucose bolus intake in mg/dl. p_1 is the constant rate of glucose uptake by insulin-independent tissue in minutes^{-1}. p_2 represents the decrease rate of tissue glucose uptake ability in minutes^{-1}. p_3 represents the increasing rate of insulin-dependent tissue glucose uptake ability in min $^{-2}(\mu U/ml)^{-1}$. p_4 represents the pancreatic insulin rate after a glucose bolus intake per unit of glucose concentration above the target glycemia in $(\mu U/ml)(mg/dl)^{-1}(min)^{-1}$. p_5 is the pancreatic target glycemia in mg/dl. p_6 represents the decay rate of plasma insulin in $\mu U/ml$. p_7 is the initial plasma insulin concentration above the basal insulinemia in $\mu U/ml$.

In 1980, The simplest model for insulin kinetics was put forth by Toffolo et al. [173]. They considered six mathematical models to study the kinetics of insulin and discovered that the proposed model was more effective at describing insulin dynamics overall. IVGTT was used to conduct physiological research on the function of the canine insulin secreter using the proposed minimal model. In 1984, Defronzo et al. [48] used the insulin clamp technique to assess the tissue sensitivity to insulin in 36 control patients and 19 individuals with insulin-dependent diabetes. Following hyperinsulinemia, hepatic glucose synthesis was suppressed by approx 95% in both diabetics and controls, indicating that peripheral tissues are mostly to blame for the observed decrease in insulin-mediated glucose uptake. In 1985, Bergman et al. [19] proposed the methods of determination of insulin sensitivity. To determine the impact of closed

loop feedback relation between insulin action and insulin secretion, they examined pancreatic suppression test [20, 143, 155], glucose clamp [22, DeFronzo et al.], and minimum model approach [22, 61]. Two key elements: insulin sensitivity and pancreatic responsiveness to control glucose tolerance were proposed as a mathematical model by Pacini and Bergman [130] in 1986. Bergman presented a computer software based MINMOD (Minimal Modelling Approach) for finding the model parameters S_G, and S_I. Welch et al. [187] established the exogenous insulin infusion in the minimum model to analysis of dynamic of glucose-insulin in 1990. It also included the information on insulin sensitivity, insulin secretion, and both insulin-mediated and non-insulin-mediated glucose absorption. A six-dimensional ODE model was established in 1991 by Sturis et al. [164]. The model was reduced by Tolic et al. [175] later in 2000, and it has served as the foundation for other DDE models [67, 77, 102, 141, 182]. Fisher [62] presented a mathematical model for the interplay of glucose and insulin in the circulatory system in 1991. To develop an insulin infusion schedule, mathematical optimization techniques are applied to a mathematical model. It is suggested that diabetic patients receive continuous insulin therapy using a semi-closed algorithm. The frequently sampled intravenous glucose tolerance test (FSIGT) was studied by Coates et al. [38] in 1995. This test evaluates insulin response to a glucose load and is dependent on a sufficient insulin response. Individuals with T2DM were not included in MINMOD. As a result, the procedure has been altered to use an intravenous insulin bolus approach. Additionally, they contrasted estimates of insulin sensitivity in people with T2DM generated from minimum modeling of a 4-hour insulin modified FSIVGTT with the glucose clamp. In 1997, Vicini et al. [60] demonstrated that the 2-compartment minimal model provides indices of insulin sensitivity, plasma clearance rate, and glucose effectiveness. The reasonable profile of endogenous glucose production was also used to circumvent the drawback of the one compartment minimum model [33]. To address the limitations of the one compartment minimum model, Topp et al. [176] used a reasonable profile of endogenous glucose production. In 2000, they developed a mathematical model, called the β-insulin glucose model, which fo-

cuses on the kinetics of β-cell mass, insulin, and glucose in diabetes. Model was extended in 2001 by Ryan et al. [78] in which the impacts of insulin receptor dynamics were incorporated, which played a significant role in the diabetes therapy. They also demonstrated how exercise can boost insulin sensitivity by 36% and lower the amount of insulin needed to maintain blood glucose levels. The system makes it possible to forecast β-cell mass values quantitatively and offers a theoretical explanation for this. To get over the linked minimum model's limits and shortcomings, Gaetano and Arino [46] presented the "dynamical model" in 2000. Their assertion was that the model does not possess an unstable equilibrium, however, Li et al. [100] found that these models may have unstable positive equilibria leading to periodic solutions. In order to come up with a different method of adding time delay, Li and Kuang [100] generalized the Arino et al. [45] study in 2000. An innovative method to calculate insulin sensitivity from an OGTT using a "integral equation" was used by Cobelli et al. [43] in 2002 . The research proposed three distinct models: piecewise linear, spline, and dynamic to calculate the rate of oral glucose appearance in plasma . The insulin sensitivity was estimated by each of the three models. Derouich and Boutayeb [50] analyzed the behaviour of normal, NIDD, and IDD individuals in 2002 and added the effect of physical activity and exercise via parameters in a mathematical model provided by Bergman et al. [21]. The newly included metrics showed how physical activity affected a diabetic person's body. In 2002, Mari et al. [113] study used 17 healthy volunteers to examine the link between insulin sensitivity and β-cell function. Using the euglycemic insulin clamp technique, a mathematical model was applied to the meal test and oral glucose tolerance test to quantify insulin secretion and sensitivity. The 2-compartment minimum model (2CMM) [180] underwent some improvements in 2003 thanks to Toffolo and Cobelli [174]. The updated 2-CMM version turned out to be a more accurate and dependable measure of glucose metabolism during an IVGTT. In 2004, Della Man et al. [42] examined the outcomes using a database of 88 people and the reference approach, the tracer two-step method. To assess the insulin sensitivity during an OGTT, the author'approach [114] was contrasted with the homeostasis model assessment

[122, 181], and quantitative insulin sensitivity . Using the Oral Minimal Model, the outcomes precisely confirmed the amount of emergence of glucose absorption and insulin sensitivity [20]. Oral Minimal Model (OMM) was described by Dalla Man et al. [114] in 2005 by including a tracer in the oral dose and labeling insulin sensitivity (S_I). OMM accurately measures the insulin sensitivity (S_I) in addition to estimating the rate of oral glucose appearance in plasma . Bergman [18] showed in 2005 that insulin sensitivity index can be determined from the minimal model's parameters by conducting a frequently sampled intravenous glucose tolerance test (IVGTT) to measure glucose and insulin levels, fitting the data to the minimal model, and calculating insulin sensitivity. Furthermore, he found that the product of insulin sensitivity and insulin secretion remains relatively constant. This conclusion was made based on the minimal model. Boutayeb et al. [29] provided a model predicting the prevalence of diabetes mellitus in 2006. The nonlinear situation was described, and the population's critical values were examined for stability. As per Nittala et al.'s [126] analysis of MINMOD in 2006, the non-dimensionalization process specifies the pathological characteristics of D_I in the model, which represents insulin sensitivity at a unit first-phase pancreatic response. They discovered a new technique that provides strongly correlated parameter estimates to the original dimensional formulation using simulated data and human FSIVGTT data. In 2006, Wang et al. [18] developed a mathematical model to address the heterogeneity between type 1 diabetes with young and adult onset. The study found that while β-cell turnover is rapid in a stable state, it is delayed once autoimmunity is triggered. In 2007, Silber et al. [83] used IVGTT data from 30 healthy and 42 diabetic individuals to develop an integrated model for type 2 diabetes patients to control glucose and insulin levels. The data was analyzed using non-linear mixed effect modeling (NONEM). By simulating and bootstrapping the model, author [83] expanded the previously created integrated model to include the oral glucose tolerance test (OGTT) in healthy volunteers. This newly created model was based on the incretin effect, where oral glucose provocations result in a stronger insulin response compared to intravenous provocations. The minimum model [187] was expanded by

Roy and Parker [157] in 2007 , who also took into account the significant impacts of exercise on the body's levels of insulin and plasma glucose. Gaetano et al. [46] made an effort in 2008 to use a mathematical model to discuss the course of type 2 diabetes. With the aid of various physiological presumptions, a model of the pancreatic islet compensation was created and compared to the model created by Topp et al. [176] Through evaluation of the pertinent factors, it was discovered that the model was more reliable and suitable for clinical purposes. Stahl and Johansson [162] made an attempt in 2009 to demonstrate how system identification and control may be utilised to estimate predictive quantitative models that can be employed in the creation of ideal insulin regimens. To assess the combined impact of insulin on lipolysis and glucose utilization during an insulin-modified frequently sampled intravenous glucose tolerance test, Periwal et al. [136] studied several mathematical models in comparison to the minimal model of glucose disposal. The investigated models have compartments for insulin, glucose, and plasma free fatty acids (FFA). By applying the Bayesian model comparison method, which reduced model complexity, the best matched model out of 23 models was chosen. In 2010, Pacini et al. [131] examined the glucose effectiveness and the insulin sensitivity index. Regular-FSIGT and insulin-modified FSIGT are part of the standard protocol, and an additional insulin injection is given after 20 minutes. The same S_I, a very reliable index, is provided by both FSIGT's with minimal model work. In 2011, Javier et al. [84] expanded upon the model developed by Topp et al. [176]. They proposed two additional models to examine the impact of adipose tissue on insulin sensitivity and the consequences of fat accumulation on the regulatory system. The relationship between fat accumulation, insulin, and glucose was analyzed based on three different formulations for fat accumulation, including linear and two nonlinear cases. Kahar et al. [85] in their study incorporated the glucose infusion rate in the minimal model and calculated an error of 0.977 in glucose concentration, which indicates a high level of accuracy. Adams et al. [4] introduced an extended model that considers the target glucose level based on insulin-dependent and insulin-independent glucose usage rates. The comprehension

of the complex glucose-insulin dynamics is crucial and mathematical models have a significant role in this understanding. Different models, ranging from clinical studies to health service research, concentrate on various aspects of diabetes [84]. Although there are many mathematical models in the literature aimed at capturing the complexity of the disease, there is still a discrepancy between experimental knowledge and its mathematical representation.

Diabetes is becoming increasingly prevalent globally and over the past few decades, more cases have been reported worldwide. In 2002, Boutayeb proposed a population dynamic model of diabetes to track the number of diabetics and address the transition from diabetes without complications to diabetes with complications..The mathematical formulation of model is given as:

$$\left.\begin{aligned} \frac{dD(t)}{dt} &= I-(\lambda+\mu)D(t)+\gamma C(t) \\ \frac{dC(t)}{dt} &= \lambda D(t)-(\gamma+\nu+\delta+\mu)C(t) \end{aligned}\right\} \tag{1.7.10}$$

The total number of diabetics is represented by the $D(t)$ with complications and $C(t)$ without complications at time t. The incidence rate of diabetes without complications is represented by the I, the mortality rate from other causes by the μ, the mortality rate from complications by the ν, the development of complications by the δ, and the recovery from complications by the γ. By taking into account the nonlinear component of the disease transmission, Boutayeb and Abdelaziz[29] suggested another population model for diabetes mellitus. Later, Boutayeb and Chetouani [28] included a second state variable to their nonlinear population model of diabetes mellitus, which is the pre-diabetes stage. Admu et al. [5] proposed a three compartment mathematical model for the dynamics of diabetes by incorporating a control parameter, so as to investigate how to control diabetes in a population. Appuhamy et al. [10] have proposed generic mechanistic mathematical model including birth, death, migration, aging, and diabetes incidence factors. The model was used to calculate the parameters for death rates as well as the sensitivity of prevalence to each population dynamic. Mahikul et al. [109] developed a model to estimate and predict diabetes burden and

deaths due to undiagnosed diabetes in Thailand, accounting for demographic shifts and the effectiveness and completeness of screening programs.

1.7.2 Delay differential equation mathematical models

The complex characteristics of the dynamical event cannot be captured by the mathematical model of the biological system based on ordinary differential equations. One of the best ways to handle these complications is to incorporate the delay factor into mathematical models. The physiological glucose-insulin metabolic system frequently experiences the following time delays: delayed insulin secretion stimulated by elevated glucose concentration by pancreatic β-cells, delayed inhibition of hepatic glucose production, delayed insulin absorption, and delayed insulin action. Sturis et al. [164] have reported the ultradian oscillations of insulin and glucose in their model which occures in the model because of delay term and this factor forms an unstable system. In 1995, Drozdov et al. [54] proposed a model for mechanisms underlying ultradian oscillations of insulin and glucose. The model showed that at the moment of change in the rate of glucose delivery, ultradian oscillations of insulin and glucose occurs because of lost stability but if the change rate is very small, the model becomes stable. An ODE mathematical model with six dimensions was developed in 1991 by Sturis et al. [164]. According to Sturis, who included a delay term in the model, oscillations rely on whether an increase in insulin concentration has time to affect glucose synthesis. If the delay term is removed, the model solutions does not oscillate. Oscillations were dampened for delays as little as 25 minutes and as long as 50 minutes, and persistent oscillations were achieved for delays between 25 and 50 minutes with periods between 95 and 140 minutes. The glucose-insulin regulatory system can be mathematically formulated using equations that account for the dynamics of glucose, insulin, and their interactions, including time delays in the system:

$$\left.\begin{aligned} \frac{dG(t)}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t-\tau_2)) \\ \frac{dI(t)}{dt} &= f_1(G(t-\tau_1)) - d_i I(t) \end{aligned}\right\} \tag{1.7.11}$$

with the initial conditions $I(0) = I_0 > 0$, $G(0) = G_0 > 0$ and $G(t) \equiv G_0$, for $t \in [-\tau_1, 0]$ and $I(t) \equiv I_0$ for $t \in [-\tau_2, 0]$. τ_1 and τ_2 are positive time lags. d_i is the insulin degradation rate. The biological meaning of function f_i, i=1,2,3,4,5 and its mathematical formulation are discussed.

Glucose concentration to control pancreatic insulin production can be given by function f_1:

$$f_1(G) = \frac{R_m}{1 + exp\left(\frac{C_1 - \frac{G}{V}}{a_1}\right)} \tag{1.7.12}$$

therefore τ_1 in model (1.7.11) is the time delay in insulin secretion. Utilization of insulin-independent glucose is given by the function f_2:

$$f_2(G) = U_b\left(1 - exp\left(\frac{-G}{C_2 V_g}\right)\right) \tag{1.7.13}$$

The glucose-dependent term is described glucose utilization in function f_3:

$$f_3(G) = \frac{G}{C_3 V_g} \tag{1.7.14}$$

The insulin-dependent glucose term is given as:

$$f_4(I_i) = U_0 + \frac{U_m - U_0}{1 + exp\Big(-\beta \ln\left(\frac{I_i}{C_4}\left(\frac{1}{V_i} + \frac{1}{Et_i}\right)\right)\Big)} \tag{1.7.15}$$

The influence of insulin on hepatic glucose production is well described by the function:

$$f_5(x_3) = \frac{R_g}{1 + exp(\alpha(x_3/V_P - C_5))} \tag{1.7.16}$$

therefore τ_2 in model (1.7.11) is the time delay in insulin action or absorption. In the study conducted by Bennet et al. [17], they introduced a time delay in the negative loop model by dividing explicit insulin into two compartments to simulate delayed insulin-dependent glucose uptake. This delay, which takes 5-15 minutes to occur due to the complex biochemical reactions in the pancreatic β-cells, cannot be ignored. To demonstrate the presence of oscillations in blood glucose concentration, Engleborghs

et al. [57] developed a new model based on an existing one [164]. This new model supports the idea that the feedback loop between insulin and glucose is sufficient to cause ultradian oscillations. Another study by Athena [110] found that the oscillations were due to the presence of a time delay τ_1 in the model and that bifurcation analysis confirms this. In 2006, Li et al. [102] proposed a model to better understand the glucose-insulin regulation mechanism, which incorporated two explicit time delays. They compared the results of their model with previous models and found that one cause of ultradian insulin secretion oscillations could be the temporal delay of insulin secretion due to high glucose levels. The study also found that a delay of greater than 400 minutes is required for persistent oscillations, which is outside of the normal physiological range. In 2007, Panunzi et al. [133] introduced a unique discrete single delay model for the glucose-insulin regulation system, whereas Wang et al. [101] employed a delay differential equation model to investigate insulin treatments in the same year. In 2009, Li and Kuang [183] discussed some computational results and provided brief summaries of theoretical results for delay mathematical models for ultradian oscillations of insulin and models for diagnostic test. Huang et al. [77] proposed two mathematical models with impulsive insulin injections or its analogues in 2012. S. Rathee et al. [141] introduced a delay factor for the transformation of hexameric to dimeric form, although the range of the delay term has not been determined. The Palumbo et al. [132] used a time-delay model to represent the glucose-insulin regulation system with the goal of describing endogenous pancreatic insulin release, which is important in the treatment of Type 2 diabetes patients. Finally, Vosoughi et al. [67] utilized an ordinary differential equation model to include two time delays to regulate variations in blood glucose levels according to the food intake of an individual throughout the day.

1.8 Fuzzy Logic Approach for Diabetes Management

Fuzzy logic is a mathematical approach to decision-making and control that allows for dealing with uncertainty and imprecision in real-world situations. It provides a

means of modeling complex systems and making decisions based on uncertain and ambiguous information. Fuzzy logic-based insulin infusion systems have been shown to provide improved glucose control compared to traditional insulin infusion methods, while also reducing the risk of hypoglycemia and hyperglycemia. The use of fuzzy logic in insulin infusion is a promising area of research and has the potential to revolutionize the management of diabetes, particularly for individuals with type 1 diabetes and those with uncontrolled type 2 diabetes.

1.8.1 Historical overview

Recently, numerous artificial intelligence applications have been employed to translate human experience into a format that computers can comprehend. Intelligent control refers to sophisticated control methods based on artificial intelligence methods. Machines can become smarter and more like humans in their fuzzy reasoning by using fuzzy logic. In 1965, Lotfy Zadeh [105] used fuzzy logic as a solution to situations involving uncertain, imprecise, or qualitative decision-making. Its application in diabetes management was not realized until the late 20th century. The first fuzzy logic-based controller for diabetes management was introduced in the late 1990s and early 2000s. This system was designed to regulate the insulin delivery for individuals with Type 1 diabetes and was based on continuous glucose monitoring. Over the years, there have been numerous advancements and improvements in the development of fuzzy logic controllers for diabetes management. Some of the latest innovations include the development of hybrid systems that combine fuzzy logic with other control strategies, such as model predictive control [12, 24, 86, 150], neural network system [6, 27, 32, 145], optimal control [15, 30, 97, 112], H_∞ control [35, 93, 125, 134] and other controller [63, 89, 107, 145, 154, 169] to improve the accuracy and effectiveness of insulin delivery. In addition to insulin delivery control, fuzzy logic has also been applied to other aspects of diabetes management, such as glucose prediction, diet planning, and physical activity management. These applications have the potential to significantly improve the quality of life for individuals with diabetes and to help

prevent long-term complications associated with the disease.

1.8.2 Fuzzy sets

Fuzzy sets are a mathematical framework for representing and manipulating uncertainty and vagueness in data. They extend the concept of classical (crisp) sets by allowing an element to belong to a set to a degree between 0 and 1, rather than just 0 or 1. In a fuzzy set, the degree of membership of an object can range between 0 and 1, indicating varying levels of truth. However, in a crisp set, the degree of membership of an object is either 0 or 1, representing either complete membership or non-membership.

1.8.3 Membership functions

A membership function, represented by a curve, determines how each point in a given input space is transformed into a membership value, which ranges from 0 to 1. The input space is often referred to as the ”universe of discourse”. Fuzzy sets can be depicted graphically and quantified using linguistic terms with the help of membership functions. The equation $\mu A : X \rightarrow [0, 1]$ represents a membership function for fuzzy set A in the universe of discourse X. A numerical value can be transformed into a fuzzy value using various membership functions, including triangular, trapezoidal, R, and L functions.

1.8.4 Fuzzy logic controller

Fuzzy logic control systems employ mathematical values that range from 0 to 1 to evaluate analog input values and convert them into logical variables. The approach of fuzzy logic resembles human reasoning and mirrors the way people make decisions.

Types of fuzzy logic controller

- Mamdani
- Tsukamoto

Key elements of a fuzzy logic controller

A fuzzy logic controller is a nonlinear transformation that maps a set of input data to a scalar output data, and it comprises three essential components: fuzzification rules, an inference engine, and a defuzzification process, within a fuzzy logic system.

- **Linguistic variables**: the system's input or output variables, rather than using numbers, have values that are words or sentences from a natural language. The usual breakdown of a linguistic variable into a series of linguistic words.

- **Fuzzification**: Fuzzification is the process of converting a crisp input into a fuzzy set in a fuzzy system, where the membership value of a given element in the fuzzy set ranges from 0 to 1, indicating the degree of membership of the element in the set. It represents the mapping of a crisp value into the fuzzy domain and is used to represent uncertainty and imprecision in the input data.

- **Fuzzy rule**: Fuzzy rules are deemed to encapsulate the knowledge and expertise of a specialist in any relevant connected field. In a closed-loop control system, these rules are expressed in the form of IF-THEN sequences that define algorithms prescribing the output or action to be taken based on the current input and feedback information. The development of a set of fuzzy rules is based on an individual's knowledge or experience, which varies for each specific application. An inference process is then established utilizing the set of rules.

- **Defuzzification**: Defuzzification is the process of converting a fuzzy output back into a crisp value in a fuzzy system. It is the reverse process of fuzzification and is used to obtain a single numerical value from the fuzzy output of a system, representing a decision or control action. There are several methods of defuzzification, including centroid method, mean of maximum method, and others, each with its own advantages and disadvantages. The choice of a defuzzification method depends on the specific requirements and characteristics of the fuzzy system being used.

1.8.5 Why use fuzzy controllers

Fuzzy controllers are often used in black box models because they can effectively handle complex and uncertain systems. Black box models refer to systems where the internal workings are unknown, and inputs and outputs are the only observable aspects. In such cases, traditional control methods may not be effective, as they require a good understanding of the internal workings of the system. Fuzzy controllers, on the other hand, are able to reason with uncertainty and vagueness. They are able to generate appropriate outputs based on input conditions, without requiring a precise understanding of the system dynamics. By using fuzzy controllers in black box models, it is possible to effectively control the system without a complete understanding of its inner workings. This makes them particularly useful in fields such as process control, robotics, and other areas where systems are complex and difficult to model accurately

1.9 Motivation

Diabetes is a complex metabolic disorder that requires precise and continuous management of blood glucose levels to prevent complications and promote overall well-being. Traditional approaches for diabetes management often rely on static guidelines and empirical methods, which may not account for the dynamic nature of glucose regulation and the individual variability among patients. To address these limitations, mathematical modeling combined with advanced control techniques can offer a systematic and personalized approach to diabetes management. The motivation behind this thesis is to explore more advance techniques like FLC in development of artificial pancreas for better management of glucose level is diabetes. By integrating fuzzy logic controllers into mathematical models of diabetes, it becomes possible to develop intelligent systems that can adapt and respond to the complex and variable glucose dynamics observed in individuals with diabetes.

1.10 Thesis Objective

The objective of this thesis is to explore the application of fuzzy logic control (FLC) in the management of type 1 and type 2 diabetes, and to identify the various factors that play a role in diabetes management. The research aims to investigate the potential of FLC as a tool for improved decision-making in the management of diabetes, and to examine the impact of different factors, such as diet, physical activity, Vitamin D and medication, on diabetes control. The study will contribute to the development of more effective strategies for managing diabetes and increase our understanding of the complex interplay of factors that influence diabetes management.

1.11 Contributions

While addressing the majority of the aforementioned issues, this thesis aims to provide practical solutions to improve the management of diabetes patients. To this end, a mathematical model of the complex interplay between blood glucose and insulin dynamics will be used as the foundation for the design and development of an autonomous insulin administration system. This system will be capable of functioning under various scenarios, including the management of hyperglycemia and hypoglycemia.

In order to cater specifically the needs of persons with type 2 diabetes, the mathematical model will be modified to include those factors that play a critical role in decreasing insulin resistance and increasing insulin sensitivity. The model will take into account the impact of physical activity, diet, and other lifestyle factors on blood glucose levels and insulin sensitivity. By doing so, the proposed insulin administration system will be better equipped to manage the unique needs of individuals with type 2 diabetes.

Moreover, the system will be designed to be user-friendly and intuitive, allowing patients to easily monitor their blood glucose levels and insulin doses. The system

will also be able to interact with other devices and healthcare providers, ensuring that the patient's progress is tracked and their treatment is adjusted as necessary. The goal of this thesis is to improve the lives of diabetes patients by providing them with a more effective and efficient way of managing their condition.

1.12 The Organization of Thesis

The thesis consists of seven chapters, and a brief explanation of each is provided below:

Chapter 1: The chapter provides a brief review of previous and current knowledge about the physiology of diabetes using significant models. The forms of diabetes, their diagnoses, risk factors, symptoms, and treatments, all have been covered in this chapter's review of the literature. The chapter discusses the fundamental mathematical model that precisely and concisely explains the dynamics of glucose and insulin. To develop a closed loop insulin delivery command, a brief introduction of fuzzy logic controllers has alsobeen discussed. The objective of this chapter is to present the rationale for the research conducted in the thesis.

The work reported in the chapter has been published in the paper entitled, "**A methodical survey of mathematical model-based control techniques based on open and closed loop control approach for diabetes management**" in *International Journal of Biomathematics* (SCI index), Impact Factor - 2.129, Worldscientific (2022).

Chapter 2: Exercise is a common initial treatment option for those recently diagnosed with type 2 diabetes and is a crucial part of diabetes management, along with nutrition and behavior changes. In this chapter, the effect of physical activity on blood glucose is introduced through a mathematical model that compares normal, non-insulin dependent and insulin dependent diabetes. The model exhibits stable equilibrium and insulin sensitivity is measured through the glucose clamp method. Results show that regular exercise reduces insulin needs based on activity intensity.

Numerical simulations have been performed and explain the theoretical analysis of the models.

The work has been accepted for publication in a Scopus-indexed journal.

Chapter 3: The study [11, 55, 116, 140] found that type 1 diabetics have a deficiency of vitamin D and the deficiency is linked to reduced insulin sensitivity and resistance. Vitamin D increases insulin sensitivity and production, leading to better control of glucose and insulin levels. The chapter examines the influence of vitamin D on glucose-insulin dynamics in healthy and diabetic individuals. It investigates the role of vitamin D in maintaining glucose concentration, which is critical but challenging for diabetics. we introduced factors related to the impact of vitamin D into a mathematical model and used numerical simulations to explore how vitamin D affects glucose-insulin regulation in diabetics. The results showed that vitamin D benefits normal, type 1, and type 2 diabetic individuals differently in controlling their glucose and insulin levels.

The work presented in this chapter is *communicated* for publication.

Chapter 4: The chapter aims to evaluate the effectiveness of diabetes awareness campaigns in prevention. A fuzzy logic controller was designed to lower the diabetic population, with positive and bounded solutions. The stability of the model was confirmed through the Jacobian linearization method, with an equilibrium point. The proposed FLC reduced the number of people with diabetes by 40% in 7 months, proving to be more efficient than existing technology. The research suggests that awareness efforts should be time-efficient to save cost for disease management, and fuzzy-based intelligence is the most cost-effective method for lowering the overall cost of diabetes prevention and management.

The work presented in this chapter is *communicated* for publication.

Chapter 5: The chapter focuses on developing a fuzzy logic closed-loop insulin therapy recommendation system for people with type 1 diabetes. Delays in insulin production, absorption, and action are addressed with a non-linear delay mechanism in the glucose-insulin model. The controller has been used to regulate glucose con-

centration in response to changes in delay parameters. The model was tested in four different scenarios including skipping a meal, multiple meals, unusual meals, and uncertainty in parameters. The proposed controller was shown to reduce the amplitude of ultradian glucose oscillation compared to previous results and supports the use of fuzzy-based intelligence in the development of an artificial pancreas for clinical patients.

The work reported in the chapter has been published in the paper entitled, "**Computer-controlled diabetes disease diagnosis technique based on fuzzy inference structure for insulin-dependent patients**" in *Applied Intelligence* (SCI index), Impact Factor - 5.019, Springer (2022).

Chapter 6: The chapter presents a new automatic insulin delivery system called a proportional integral derivative-fuzzy logic controller (PID-FLC) for patients with Type 1 diabetes. The design is based on an upgraded version of Bergman's model and its stability has been proven by Jacobian linearization. A virtual patient was used to validate the model and simulation results show it can maintain glucose levels near 93 mg/dL. The robustness of the controller was tested with a 20% uncertainty in insulin clearance rate. The results show the PID-FLC system's capabilities in comparison to other PID-FLC systems.

The work presented in this chapter is *communicated* for publication.

Chapter 7: Seventh chapter is devoted to describe the conclusion and future work.

1.13 Software Used

We had the privilege of utilizing the remarkable MATLAB software version of 2012b licensed by the Delhi Technological University, and we extend our heartfelt gratitude to the creators of this magnificent software for enabling us to achieve our research goals.

Chapter 2

Positive Effects of Physical Activity on Patients with Diabetes

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Exercise is often one of the first treatment options suggested for individuals who have been diagnosed with type 2 diabetes. It is a crucial part of diabetes, obesity preventive and lifestyle intervention programmed, along with nutrition and behavior change. This chapter presents the incorporation of physical activity parameters into a mathematical model to enable a comparison of blood glucose behavior in individuals with varying exercise levels in normal, non-insulin-dependent diabetes, and insulin-dependent diabetes conditions. The mathematical study of the model demonstrates that the model exhibits an equilibrium, that is stable saddle node. Also, we measured the insulin sensitivity by using the glucose clamp method. We demonstrate that patients who engage in regular exercise need to take less amount of insulin doses, depending on the intensity of the activity. Further, numerical simulations have been presented for clarification of the analytical research.

2.1 Introduction

Regular physical activity has been an essential component of diabetes care since long before the introduction of insulin therapy. Current guidelines recommend that individuals with diabetes engage in regular physical exercise, along with insulin therapy and adequate education, to effectively manage their condition. From low to high-intensity workouts, physical activity can be incorporated into daily routines for people with diabetes. In fact, prominent diabetes specialists recommended exercise as a therapeutic method before insulin was widely available. In 1919, Allen's [7] study was the first to demonstrate that physical activity could lower blood glucose levels and temporarily improve glucose tolerance in people with diabetes . Later on, Lawrence [98] showed that exercise enhanced the hypoglycemic effects of insulin injections . By planning exercise in advance, individuals with diabetes can adjust their insulin dose and timing to minimize the risk of hypoglycemia during or after exercise. Later on, it was reported that for individuals who take intermediate-acting insulin once daily, reducing the dose by 30-35% before exercise or switching to a split-dose regimen is recommended if more insulin is needed after exercise [39]. Those who take both intermediate- and short-acting insulin may reduce the short-acting insulin by 50% or skip it before exercise, while also reducing the intermediate-acting insulin dose and potentially supplementing with additional short-acting insulin after exercise [39]. However, exercise can also pose risks for people with diabetes that require careful consideration [16]. Hypoglycemia can occur during or after exercise in those with type 1 diabetes, and rapid rises in blood glucose and the onset of ketosis can occur when exercise is added to an insulin-deficient state [16]. These challenges can make it difficult for some individuals with type 1 diabetes to engage in sports or other leisure activities involving physical activity of varying intensity and duration, leading to restrictions on young type 1 diabetics participating in organized sports. On the other hand, for individuals with type 2 diabetes, exercise is frequently advised for weight loss and insulin sensitivity improvement. Bordenave et al.[26] presented new data showing that

S_I as measured by the minimum model significantly improves in type 2 diabetic patients and can even reach healthy human levels of glycemia at rest in the short term [26]. Overall, incorporating physical activity into the daily routine of individuals with diabetes is essential for effective management of their condition

Several mathematical models have been proposed to predict the impact of exercise on blood glucose levels in diabetes patients. Parker et al. [148] created a predictive algorithm by incorporating the influence of meals and exercise on a mathematical model by Sorensen [160], while Hernandez-Ordonez and Campos-Delgado [74] developed a model to simulate the blood glucose changes caused by exercise. Other studies, such as those by Derouich and Boutayeb [50], Breton et al. [41], Roy and Parker [148], have incorporated various factors, such as plasma-free fatty acid dynamics and insulin-glucose dynamics, into the mathematical model of glucose insulin system. Kim et al. [94] and Li et al. [94] even developed a multiscale physiological model for the effects of exercise. Since research demonstrates that physical activity increases insulin sensitivity and action and decreases insulin resistance in the body, we are inspired to create a mathematical model that considers the impact of physical activity on glucose and insulin dynamics. It allows us to look at how blood glucose behaves in people with standard, non-insulin-dependent diabetes and people with insulin-dependent diabetes, both with and without physical activity [111, 171, 172].

2.2 Modeling of Glucose Insulin Regulatory System

The mathematical model that captures these bio-mechanics described in the glucose-insulin regulation system is as follows [141]:

$$\left.\begin{aligned} \frac{dG}{dt} &= G_{in}(t) + c - q_1 \cdot f_2(G(t)) - (1+q_2) \cdot f_3(G(t)) f_4(I(t)) \\ \frac{dI}{dt} &= f_1(G(t)) - q_3 \cdot d \cdot I(t) \end{aligned}\right\} \tag{2.2.1}$$

with initial conditions $I(0) = I_0 \geq 0$ and $G(0) = G_0 \geq 0$. $G(t)$ and $I(t)$ denote the glucose concentration and insulin concentration at any time t, respectively. G_{in} shows

exogenous glucose intake. c represents the rate of production of hepatic glucose. d denotes insulin degradation rate which is higher than zero.

The effect of physical exercise on the rate at which glucose is metabolized by the liver and muscles is shown by the parameter q_1. The term q_2 refers to the effect of physical exercise on increasing the sensitivity of the muscle and liver to the action of insulin. The effect of physical exercise on insulin utilization is shown by the parameter q_3.

The mathematical representation of functions f_i, i = 1,2,3,4 are considered from the article [141] which is given below

$$f_1(G) = \frac{Rm}{1 + exp((C_1 - G/V_g)/a_1)} \tag{2.2.2}$$

$$f_2(G) = U_b(1 - exp(-G/(C_2 V_g))) \tag{2.2.3}$$

$$f_3(G) = \frac{G}{C_3 V_g} \tag{2.2.4}$$

$$f_4(I) = U_0 + \frac{(U_m - U_0)}{1 + exp(-\beta log(I/C_4(1/V_i + 1/Et_i)))} \tag{2.2.5}$$

We suppose that all functions f_i, i = 1,2,3,4 of model $(2.2.1)$ satisfy the following conditions:

- Insulin is released in response to raised glucose concentration in the body, implying that $f_1(x) > 0$ and $f_1'(x) > 0$ for $x > 0$. However, since high levels of glucose concentration can saturate the insulin secretion, the amount of insulin produced by the pancreas is finite, and thus $\lim_{x\to\infty} f_1(x) = R_m$. We can set $F_1 = R_m$, and it follows that $\lim_{x\to\infty} f_1'(x) < F_1'$ for $x > 0$. Additionally, a certain amount of insulin may be secreted by the pancreas without glucose stimulation, which can be represented by assuming that $f_1(0) = f_1 > 0$.

- The function $f_2(x)$ represents the glucose utilization by cells and tissues that occurs independently of insulin. It is clear that $f_2(0) = 0$ and $f_2(x) > 0$, as well as $f_2'(x) > 0$ for $x > 0$. Additionally, we assume that the utilization is bounded,

and therefore we consider the limit of $f_2(x)$ as x approaches infinity, denoted by $\lim_{x\to\infty} f_2(x) = U_b$. We let $F_2 = U_b$, and we also require that $f_2'(x) < F_2'$ for $x > 0$.

- 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 $f_3(0) = 0, f_3'(x) > 0, f_4(0) = f_4 > 0, f_4(x) > 0$, and $f_4'(x) > 0$ for $x > 0$. From [164], we assume that there exists constants $m_3 > 0, F_4 > 0$ and $F_4' > 0$ such that $0 < f_3(x) \leq m_3 x$, and $\lim_{x\to\infty} f_4(x) = U_m$. Let $F_4 = U_m$ and $f_4'(x) < F_4'$ for $x > 0$.

The biological meaning of parameters in functions f_1 to f_4 are discuss in Table 2.1

Parameter	Biological Explanation
R_m	Maximum insulin production rate by pancreas.
U_m	Maximal muscle/tissues insulin utilization rate
U_0	Minimal muscle/tissues insulin utilization rate
U_b	Brain and nerve cells' maximum glucose consumption rate.
C_1	Concentration of glucose at which the pancreas is most effective
C_2	Brain and nerve cells' maximum glucose consumption rate.
C_3	Scale factor controls muscle glucose sensitivity.
C_4	Scale factor controls muscle insulin sensitivity.
V_i	Volume of insulin distribution in interstitial fluid compartment
V_g	Volume of glucose space (plasma and the intracellular space)
t_i	Time for self insulin degradation in interstitial fluid compartment
E	Insulin diffusion rate.
a_1	Pancreas sensitivity scaling factor.
β	Parameter is used for employing the function f_4 shape.

Table 2.1: Bilogical Meaning of parameter of functions (f_1,f_2,f_3 and f_4)

The graphical representations of f_i, i=1,2,3,4 are shown in the diagram below:

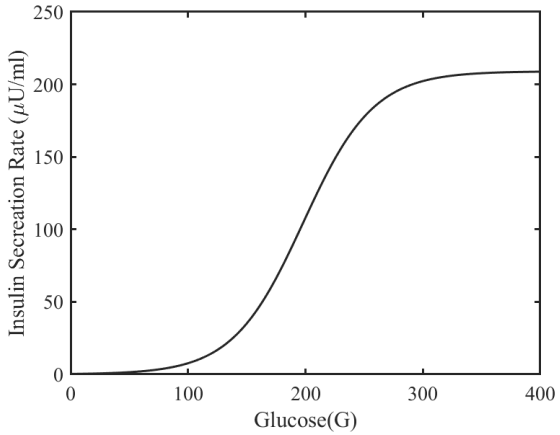

Fig 2.1(a). $f_1(G)$ Pancreatic insulin production in responce of raised glucose level

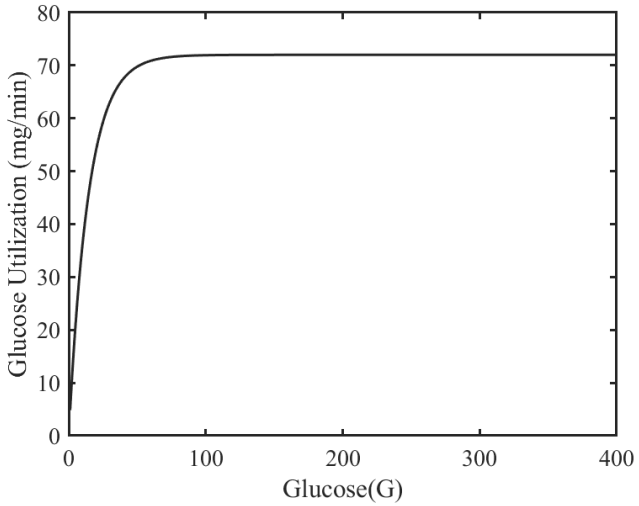

Fig 2.1(b). $f_2(G)$ Glucose utilization by insulin-independent cells

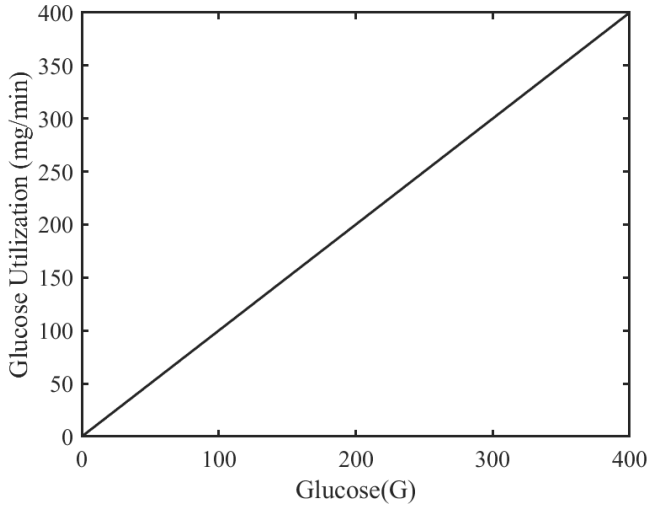

Fig 2.1(c). $f_3(G)$Glucose utilization by insulin-dependent cells

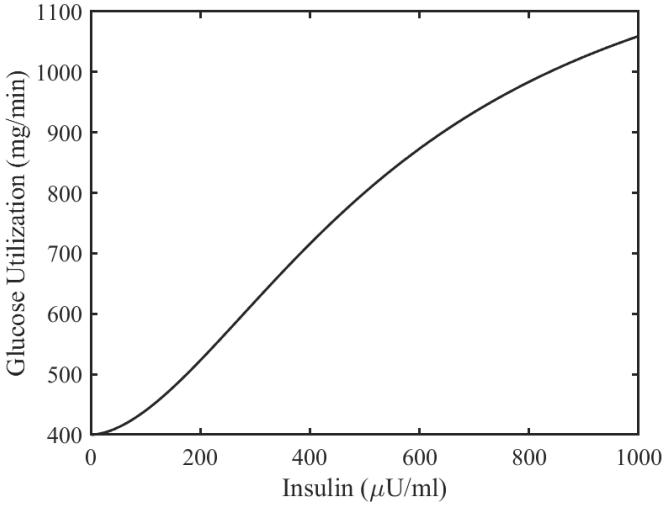

Fig 2.1(d). $f_4(I)$ Insulin utilization by muscles/fat cells

Figure 2.1: Graphical representation of f_1, f_2, f_3 and f_4

2.3 Mathematical Analysis of Model

The subsequent sections will cover the uniqueness, positivity, boundedness, and stability of model.

Lemma 2.3.1. *[141] Suppose $f : R \to R$ is a differentiable function. If*

$$l = \lim_{t\to\infty} \inf f(t) < \lim_{t\to\infty} \sup f(t) = L$$

then there exist sequences t_k and s_k such that for all k, $f'(t_k) = f'(s_k) = 0$, $\lim_{k\to\infty} f(t_k) = L$ and $\lim_{k\to\infty} f(s_k) = l$.

2.3.1 Existence of equilibrium point

The model's singular equilibrium point is characterized by (G^* and I^*), and can be ascertained by solving the equations $\frac{dG}{dt} = 0$ and $\frac{dI}{dt} = 0$.

$$G_{in}(t) + c - q_1 f_2(G^*(t)) - (1+q_2) f_3(G^*(t)) f_4(I^*(t)) = 0 \tag{2.3.1}$$

$$f_1(G^*(t)) - q_3 \cdot d \cdot I^*(t) = 0 \tag{2.3.2}$$

We obtained by Eq (2.3.2),

$$I^*(t) = \frac{f_1(G^*(t))}{q_3 \cdot d} \tag{2.3.3}$$

2.3.2 Uniqueness of solution

We define the $A(x)$ such that

$$A(x) = G_{in}(t) + c - q_1 f_2(x) - (1+q_2) f_3(x) f_4(d^{-1} q_3^{-1} f_1(x)) \tag{2.3.4}$$

On differentiating the Eq (2.3.4). we have

$$A'(x) = 0 - q_1 f_2'(x) - (1+q_2)(f_3'(x) f_4(d^{-1}q_3^{-1} f_1(x)) + f_3(x) f_4'(d^{-1}q_3^{-1} f_1(x)) d^{-1}q_3^{-1} f_1'(x)) \tag{2.3.5}$$

Since $q_1,\ q_2 \geq 0$ therefore $A'(x) < 0$ (2.3.5). We have $f_2(0) = 0$ and $f_3(0) = 0)$, so by Eq. (2.3.4)

$$A(0) = G_{in} + c - q_1 f_2(0) - (1+q_2) f_3(0) f_4(d^{-1}q_3^{-1} f_1(0)) = G_{in} + c > 0$$

$$\begin{aligned} \text{also,} \quad \lim_{x\to\infty} A(x) &= \lim_{x\to\infty} (G_{in} - q_1 f_2(x) - (1+q_2) f_3(x) f_4(d^{-1}q_3^{-1} f_1(x)) + c) \\ &< G_{in} - q_1 K_2 - (1+q_2) K_4 \lim_{x\to\infty} f_3(x) + c < 0 \end{aligned} \tag{2.3.6}$$

Hence, $A(0) > 0$, and $\lim_{x\to\infty} A(x) < 0$. From Eq (2.3.5) and (2.3.6), it has been concluded the A(x) is decreasing function and it cuts x-axis which indicates that model's (2.2.1) has a unique solution.

2.3.3 Positiveness of solutions

Suppose that, $G(t)$ is not positive in $(0,\infty)$, then there exists a t_0 such that $G(t_0)$ equal to 0 and $G(t) > 0$ for all $0 < t < t_0$, then $G'(t_0) \leq 0$. We observe that

$$\begin{aligned} G'(t_0) &= G_{in} - q_1 f_2(G(t_0)) - (1+q_2) f_3(G(t_0)) f_4(I(t_0)) + c \\ &= G_{in} - q_1 f_2(0) - (1+q_2) f_3(0) f_4(I(t_0)) + c \\ &= G_{in} + c \not\leq 0 \ \ (\because f_2(0) = f_3(0) = 0) \end{aligned}$$

It implies that $G(t) > 0\ \forall\ t > 0$. Similarly, we assumed $I(t)$ is not positive in $(0,\infty)$. There exists a t_0 such that $I(t_0) = 0$ and $I(t) > 0$ for $0 < t < t_0$. Then, $I(t_0) < 0$ and

$$I'(t_0) = f_1(G(t_0)) - q_3 \cdot d \cdot I(t_0) \geq f_1(G(t_0))$$

It conclude that $G(t)$ and $I(t)$ are positive for all t in (0,∞).

2.3.4 Boundedness of solution

Assume that $G(t)$ is not bounded solution and supremum of $G(t)$ is infinity. We observe $G'(t_n) \geq 0$ by lemma 2.3.1 and we get

$$\begin{aligned} G'(t_n) &= G_{in} - q_1 f_2(G(t_n)) - (1+q_2) f_3(G(t_n)) f_4(I(t_n)) + c \\ &\leq \lim_{n\to\infty} (G_{in} - q_1 f_2(G(t_n)) - (1+q_2) k_4 f_3(G(t_n)) + c) \\ \Rightarrow \quad \lim_{n\to\infty} G'(t_n) &\leq \lim_{n\to\infty} (G_{in} - q_1 f_2(G(t_n)) - (1+q_2) K_4 f_3(G(t_n)) + c) \\ &\leq G_{in} - q_1 K_2 - (1+q_2) K_4 \cdot \infty + c = -\infty \end{aligned}$$

It implies that $G(t)$ is bounded for every $t > 0$. Consider the case where $I(t)$ is not bounded for any $t > 0$. Since, $f_1(x)$ is bounded function in x$\in$ (0,∞) , and $I(t)$ will satisfy the $\lim_{t\to\infty}$ sup $I(t) = \infty$ then there exists a sequence $< t_n' >$ such that $\lim_{n\to\infty}$sup $I(t_n')$=∞ and $I'(t_n') \geq 0$. We get

$$\begin{aligned} \lim_{n\to\infty} I'(t_n) &= \lim_{n\to\infty} f_1(G(t_n')) - d \cdot q_3 \lim_{n\to\infty} I(t_n') \\ &= R_m - d \cdot q_3 \lim_{n\to\infty} I(t_n') = -\infty \end{aligned}$$

This implies $I(t)$ is bounded above.

2.3.5 Stability analysis of the model

To assess the stability of the non-linear model at its equilibrium point, we use the linearized approach method. The linearized model (2.2.1) about the steady point (G^*, I^*) is written as:

$$\begin{bmatrix} \frac{dG}{dt} \\ \frac{dI}{dt} \end{bmatrix} = \begin{bmatrix} -L_{11} & -L_{12} \\ L_{21} & -L_{22} \end{bmatrix} \cdot \begin{bmatrix} G(t) \\ I(t) \end{bmatrix} \tag{2.3.7}$$

where,

$L_{11} = q_1 f_2'(G^*) + (1+q_2) f_3'(G^*) f_4(I^*) > 0$, $L_{12} = (1+q_2) f_3(G^*) f_4'(I(t)) > 0$, and $L_{21} = f_1'(G^*) > 0$ $L_{22} = q_3 d > 0$.

The characteristics equation is given as

$$\lambda^2 + (L_{12} + L_{22})\lambda + L_{11}L_{22} + L_{12}L_{21} = 0 \tag{2.3.8}$$

$$(L_{11} + L_{22}) > 0,$$

$$L_{11}L_{22} + L_{12}L_{21} > 0$$

The roots of Eq (2.3.8) are say,

$$\lambda_1 = \frac{-(L_{11} + L_{22}) - \sqrt{(L_{11} - L_{22})^2 - 4L_{12}L_{21}}}{2} \tag{2.3.9}$$

$$\lambda_2 = \frac{-(L_{11} + L_{22}) + \sqrt{(L_{11} - L_{22})^2 - 4L_{12}L_{21}}}{2} \tag{2.3.10}$$

There are three cases arise:

Case 1: if $(L_{11} - L_{22})^2 - 4L_{12}L_{21} < 0$, then roots are imaginary and having the negative real parts. It implies that system is stable at (G^*, I^*).

Case 2: if $(L_{11} - L_{22})^2 - 4L_{12}L_{21} = 0$, then $\lambda_1 = \lambda_1 = -(L_{11} + L_{22})$. Both are negative real roots. It shows that the system is stable at steady point.

Case 3: if $(L_{11} - L_{22})^2 - 4L_{12}L_{21} > 0$, we write $(L_{11} - L_{22})^2 - 4L_{12}L_{21} = (L_{11} + L_{22})^2 - 4(L_{11}L_{22} + L_{12}L_{21})$.

Claim: $\sqrt{(L_{11} + L_{22})^2 - 4(L_{11}L_{22} + L_{12}L_{21})} < -(L_{11} + L_{22})$

Proof: Let $\sqrt{(L_{11} + L_{22})^2 - 4(L_{11}L_{22} + L_{12}L_{21})} > -(L_{11} + L_{22})$

$$(L_{11} + L_{22})^2 - 4(L_{11}L_{22} + L_{12}L_{21}) > (L_{11} + L_{22})^2$$

$$\Rightarrow -4(L_{11}L_{22} + L_{12}L_{21}) > 0$$

$$\Rightarrow (L_{11}L_{22} + L_{12}L_{21}) < 0$$

The condition $(L_{11}L_{22} + L_{12}L_{21}) > 0$ is contradicted, indicating that both λ_1 and λ_2 are negative real roots. As per Theorem 3.1 in Nath et al. [44], the model demonstrates stability in every possible scenario.

2.4 Insulin Sensitivity

Insulin sensitivity is measured using the glucose clamp technique [177]. Perfusing or injecting glucose into humans to maintain a constant blood glucose level is known as the glucose clamp technique. Model (2.2.1) can be written as follows using this method:

$$\left.\begin{aligned} \frac{dG}{dt} &= g_{inf}(t) + c - q_1 f_2(G(t)) - (1+q_2) f_3(G(t)) f_4(I(t)) \\ \frac{dI}{dt} &= f_1(G(t)) - q_3 \cdot d \cdot I(t) \end{aligned}\right\} \tag{2.4.1}$$

where g_{inf} is the glucose infusion per unit of volume. Eq (2.4.1) can be used to determine the equilibrium points.

$$g_{inf}(t) = q_1 f_2(G^*) + (1+q_2) f_3(G^*) f_4(I^*) - c \tag{2.4.2}$$

The Insulin Sensitivity can be written as:

$$S_I = \frac{\partial^2 g_{inf}}{\partial I^* \partial G^*} \tag{2.4.3}$$

We obtained (2.4.2)

$$S_I = (1+q_2) f_3'(G^*) f_4'(\frac{1}{d \cdot q_3} f_1(G^*)) \tag{2.4.4}$$

In the absence of any physical exercise, i.e. when all q_i's are equal to 1 in model (2.2.1), insulin sensitivity can be written in the following mathematical form:

$$S_I = f_3'(G^*) f_4'(\frac{1}{d} f_1(G^*)) \tag{2.4.5}$$

$$f_3'(G^*) f_4'(\frac{1}{d} f_1(G^*)) \leq (1+q_2) f_3'(G^*) f_4'(\frac{1}{d \cdot q_3} f_1(G^*)) \tag{2.4.6}$$

It may be argued that physical exercise increases insulin sensitivity, which aids in blood glucose management within physiological limits. It is quantitatively dependent on the values that quantify the amount of physical activity.

2.5 Numerical Simulation

The system (2.2.1) is numerically integrated into this section using the set of tested parameters provided by the author [141]. The glucose space (V_g) is the most important component of the regulatory system's process as a single compartment. For a healthy adult male with a weight of 75 kg (165 lb) and a blood volume of 5 L [184], a blood glucose concentration of 90 mg/dL is approximately equivalent to 5 g, which is roughly the amount of sugar in a teaspoon. The volume of distribution (V_g) in diabetic patients was assumed to be 10 litres, whereas it was thought to be 5 litre in healthy people. The values of model's (2.2.1) parameters and its unit are shows in Table 2.2:

Parameter	Unit	values
R_m	$mUmin^{-1}$	210
U_m	$mgmin^{-1}$	940
U_0	$mgmin^{-1}$	40
U_b	$mgmin^{-1}$	72
C_1	mgl^{-1}	2000
C_2	mgl^{-1}	140
C_3	mgl^{-1}	1000
C_4	mgl^{-1}	80
V_i	l	11
V_g	l	10
t_i	min	100
E	$lmin^{-1}$	0.2
a_1	mgl^{-1}	300
β	'unit less'	1.77

Table 2.2: Values of parameter of functions (f_1,f_2,f_3 and f_4)

Because everyone's lifestyle and eating habits are different, it's nearly impossible to measure the amount of exercise required for each person. To avoid hypoglycemia, each person must choose the appropriate quantity of exercise. However, depending on the patient, the length and intrinsic factors of exercise may vary. We separated exercise into three categories in this study: mild, moderate, and strong. Table 2.3 shows the values of all parameters of physical exercise [148].

Exercise's effect on glucose-insulin dynamics in a healthy person is depicted in Fig 2.2. When person is involved in a mild, moderate, or strong exercise, their blood glu-

Parameter	Unit	Mild Exercise	Moredrate Exercise	Strong Exercise
q_1	min^{-1}	0.00001	0.00002	0.00003
q_2	unit less	0.65	0.80	0.95
q_3	min^{-1}	0.000008	0.000009	0.00001

Table 2.3: Values of parameters q_1,q_2 and q_3

cose levels were 75, 68, and 63 mg/dl, respectively. When there is no workout, the glucose level rises to 92.13 mg/dl. In mixed type workouts (mild, moderated, strong), the insulin levels were 79, 74, and 71 $\mu U/ml$. It has been observed that exercise

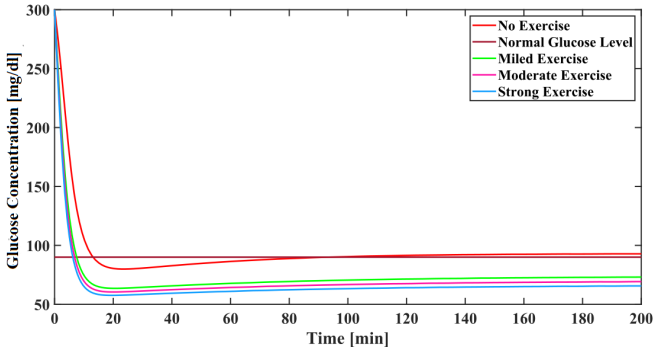

Fig 2.2(a). Glucose concentration

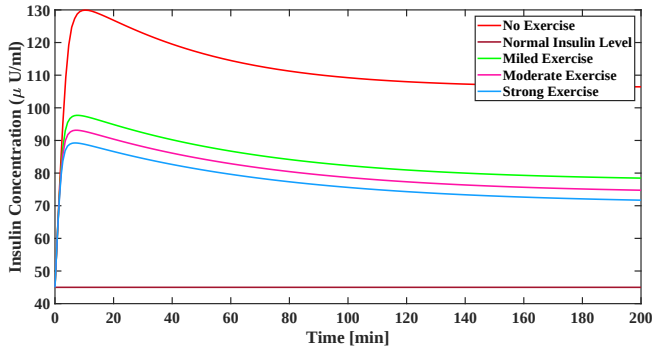

Fig 2.2(b). Insulin concentration

Figure 2.2: Normal person's glucose-insulin dynamics for mixed type and no workout

aids in the tight management of blood glucose levels. In comparison to no, mild, and moderate exercise, strong exercise causes a rapid drop in glucose levels in less time, which subsequently rises over time to reach its basal level. The phase pictures in Fig 2.3 depict the stability of plasma glucose and insulin dynamics in healthy people, where the model's behavior is stable spiral. Figure 2.3(a) and Fig 2.3(b) show phase portraits of a normal person in the situation of no workout and workout, respectively. This illustration demonstrates that all of the paths starting from different initial condi-

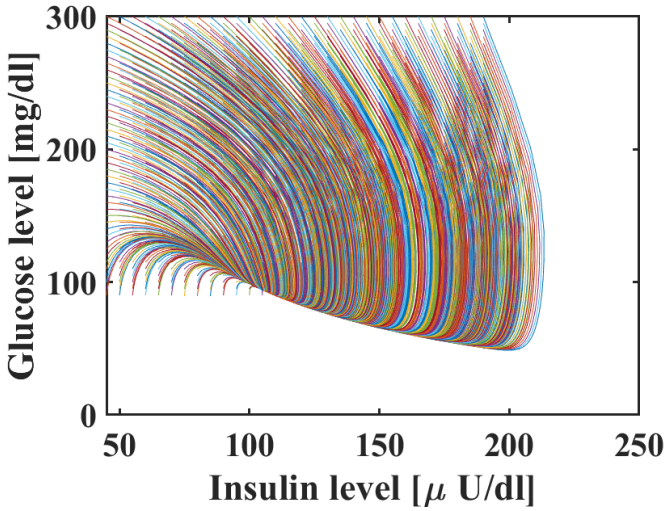

Fig 2.3(a). Diagram of phase-portraits for no-workout

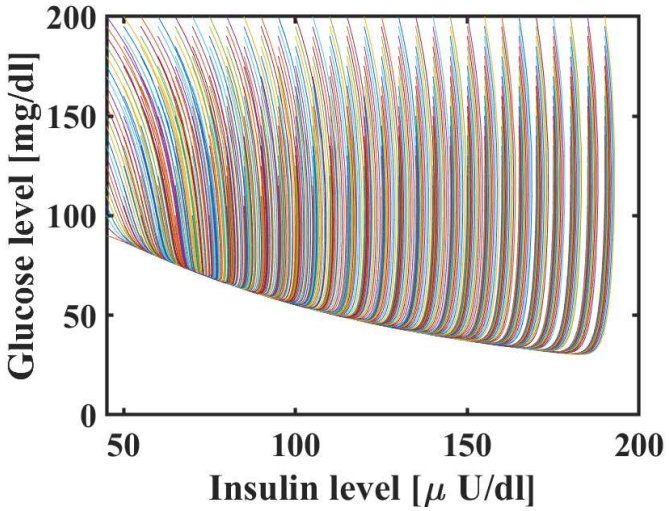

Fig 2.3(b).Diagram of phase-portraits for a mixed-type workout

Figure 2.3: Phase-portraits diagram of normal individual

tions converge to an equilibrium point. Figure 2.4 depicts the influence of exercise on glucose-insulin dynamics in a diabetic patient. Blood glucose levels were 109, 105, and 103 mg/dl, after a mild, moderate, or strong exercise, respectively. The glucose level rises to 120 mg/dl when there is no exertion. Insulin levels were 171, 153.8, and 139.1 μU/dl in mixed type workouts (mild, moderated, strong). In a case of no workout, the insulin level has been 196 μU/dl.

Stronger activity helps diabetics maintain their blood glucose levels in less time than no exercise or light, moderate exercise, as shown in the Fig 2.5. Strong activity brought the blood glucose level closer to the basal level in diabetics, however in other situations, the sugar level approached a number higher than the basal level, resulting

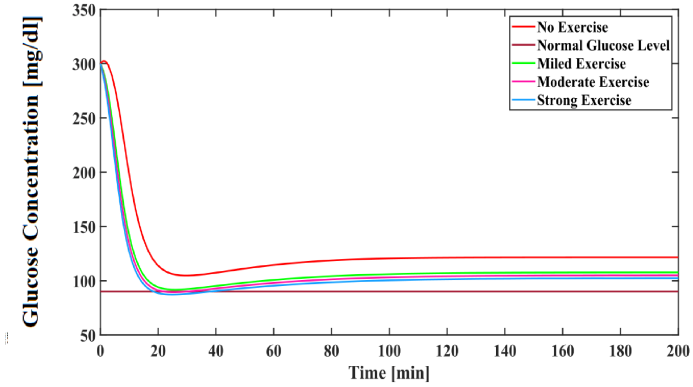

Fig 2.4(a). Glucose concentration

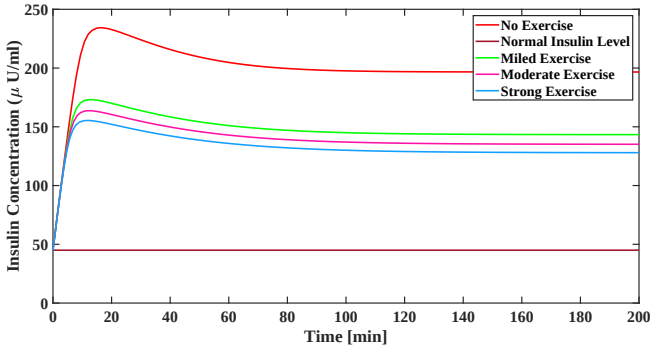

Fig 2.4(b). Insulin concentration

Figure 2.4: Diabetic person's glucose-insulin dynamics for mixed type and no workout

in a higher blood sugar level being maintained in the body. Figure 2.5(a) and 2.5(b) depict phase portraits of a Diabetic in no-exercise and workout situations, respectively. The graph portrays that, despite their differing initial conditions, all of the trajectories eventually converge to the equilibrium point.

Table 2.4 presents a comparative analysis of the average insulin levels in both normal and diabetic individuals after undergoing a typical exercise regimen. Utilizing these findings, we determined the necessary insulin dosage for diabetic patients following mild, moderated, and strong physical activity.

	Mild Exercise	Moderate Exercise	Strong Exercise
Normal Individual	84.4946	80.6969	77.7434
Diabetic Individual	142.5527	135.7392	129.4999
Required insulin amount (I_0%)	29.0179	22.3163	15.0145

Table 2.4: Insulin percentage needs after various types of exercise

It is evident from the Table 2.4, it can be inferred that adherence to a mild, moderate, or strong exercise regimen by patients necessitates 29.0179%, 22.3162%, and

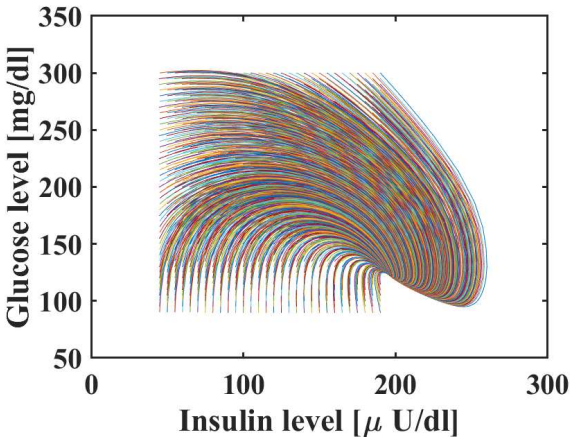

Fig 2.5(a). Diagram of phase-portraits for no-workout

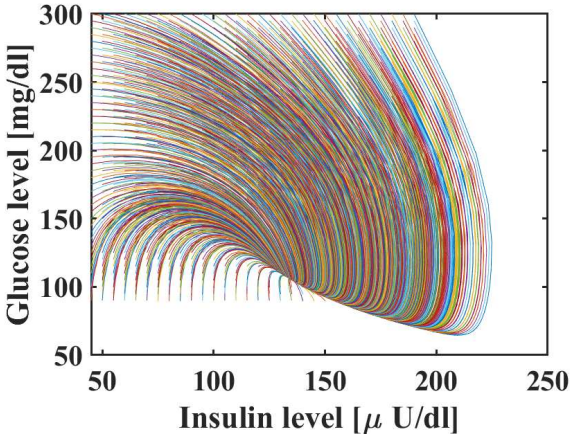

Fig 2.5(b).Diagram of phase-portraits for a mixed-type workout

Figure 2.5: Phase-portraits diagram of diabetic patient

15.0145% of the basal insulin value, respectively, to effectively uphold healthy blood glucose levels.

2.6 Results and Discussion

Physical exercise has been demonstrated to have a crucial role in regulating blood glucose levels, as exemplified by the outcomes portrayed in Fig 2.2 depicting the impact of different physical activities on glucose levels in normal individuals. When compared to no activity or miled to moderate exercise, vigorous exercise triggers a swift and temporary reduction in blood glucose levels, which gradually ascend and return to their baseline. For people with diabetes, intense exercise can help normalize blood glucose levels more expeditiously compared to light or moderate physical activ-

ity (shown in Fig 2.4). Fig 2.3 illustrates the stable spiral behavior of plasma glucose and insulin dynamics in healthy individuals, while Fig 2.5 presents phase portraits of a diabetic individual in both no-exercise and workout situations. The values of the model's parameters are shown in Table 2.2 and Table 2.3. Tab 2.4 compares average insulin levels in normal and diabetic individuals post a typical exercise regimen. Based on these findings, we determined appropriate insulin dosage for diabetic patients following mild, moderate, and intense physical activity. Despite the possibility of blood sugar levels reaching higher than the baseline in some cases, consistent physical exercise is recommended for both diabetic and non-diabetic individuals. This is because physical activity increases insulin sensitivity, diminishes average blood glucose levels, and potentially promotes weight loss, particularly beneficial for those at risk of diabetes. Unfortunately, the declining levels of physical activity globally are contributing to rising obesity rates and consequently, develop diabetes. In regulating blood glucose levels and reducing oxidative stress, aerobic exercise has been found to be particularly effective for individuals with diabetes mellitus.

2.7 Conclusion and Future Aspects

The purpose of this chapter is to provide a comprehensive understanding of how physical activity influences insulin and glucose levels and to demonstrate that regular exercise can help to reduce the risk of insulin resistance and decreased insulin sensitivity. The current model outlines the effects of light, moderate, and intense exercise on insulin, interstitial insulin, and blood glucose levels, taking into account the frequency and duration of physical activity. The chapter emphasizes that all forms of exercise should be encouraged, as long as the proper balance between insulin dosage and physical intensity is maintained, to ensure the well-being of people with diabetes. While it is crucial to maintain control of insulin levels, have a balanced diet, and engaging in physical exercise for managing diabetes, most diabetes management methods in the literature have focused on insulin treatment. These considerations emphasize the importance of physical exercise as a natural and affordable means of

controlling diabetes and its related issues. Future research should incorporate parameters such as insulin secretion time delay and hepatic glucose production into the model to determine the ideal level of exercise for diabetes management and prevent hypoglycemia.

Chapter 3

Vitamin D: The Important Nutrient for Preventing and Managing Diabetes

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Maintaining the glucose level at the safe range is challenging task for diabetic person While it can be hard to pinpoint a sole cause for diabetes due to the complex structure of the human body, major studies have shown that type 1 diabetics often suffer from a vitamin D deficiency. Vitamin D increases insulin sensitivity, reduces insulin resistance, and boosts insulin production. The chapter examined the effect of vitamin D on glucose-insulin dynamics in both healthy individuals and diabetics. A mathematical model was utilized to investigate the impact of vitamin D on glucose-insulin concentration, by incorporating relevant factors. The study explored the way in which vitamin D affects the regulation system of glucose-insulin dynamics in diabetics. The results of the numerical simulations revealed that vitamin D assists normal, type 1, and type 2 diabetics in managing their glucose and insulin levels.

3.1 Introduction

Diabetes Mellitus is one of the most widespread diseases after cancer and a significant concern for healthcare systems globally. In recent years, the lack of vitamin D levels has been identified as a major contributor to the development of several chronic diseases, including diabetes. It is a powerful substance that our body produces when exposed to sunlight. It can also be obtained from fortified foods and dietary supplements. UV radiation from the sun transforms 7-dehydrocholesterol into pre-vitamin D3, which is quickly converted to cholecalciferol (D3). Cholecalciferol (D3) and ergocaliferol (D2) obtained from food are converted into 25-hydroxyvitamin D in the liver, which is the major circulating metabolite and used to determine a person's vitamin D status. The kidneys convert 25-hydroxyvitamin D into active 1, 25-hydroxyvitamin D, which is filtered by the kidneys and reabsorbed through the proximal convoluted tubules. Active 1, 25-hydroxyvitamin D can bind with the vitamin D receptor-retinoic acid X-receptor complex in the gut, bone, and parathyroid glands. Maintaining adequate levels of vitamin D through exposure to sunlight, fortified foods, and dietary supplements is essential to reducing the risk of chronic diseases. The intricate process of vitamin D bio-synthesis is beautifully illustrated in the diagram depicted in Fig 3.1.

Recent studies [2, 40, 79, 90, 99, 188] have established a significant relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction in individuals with diabetes. Vitamin D seems to influence the insulin response to glucose stimulation exclusively, while having no apparent impact on basal insulinemia. Vitamin D penetrates β-cells and interacts with various receptors, which bind together and effectively activate the insulin gene, increasing insulin production. It may improve insulin action by boosting the production of insulin receptors, thereby increasing insulin responsiveness for glucose transport. Cross-sectional studies [69, 76, 167] have linked low vitamin D levels to impaired insulin sensitivity. Authors [103, 146] have shown a strong relationship between insulin resistance and vitamin D deficiency. Vi-

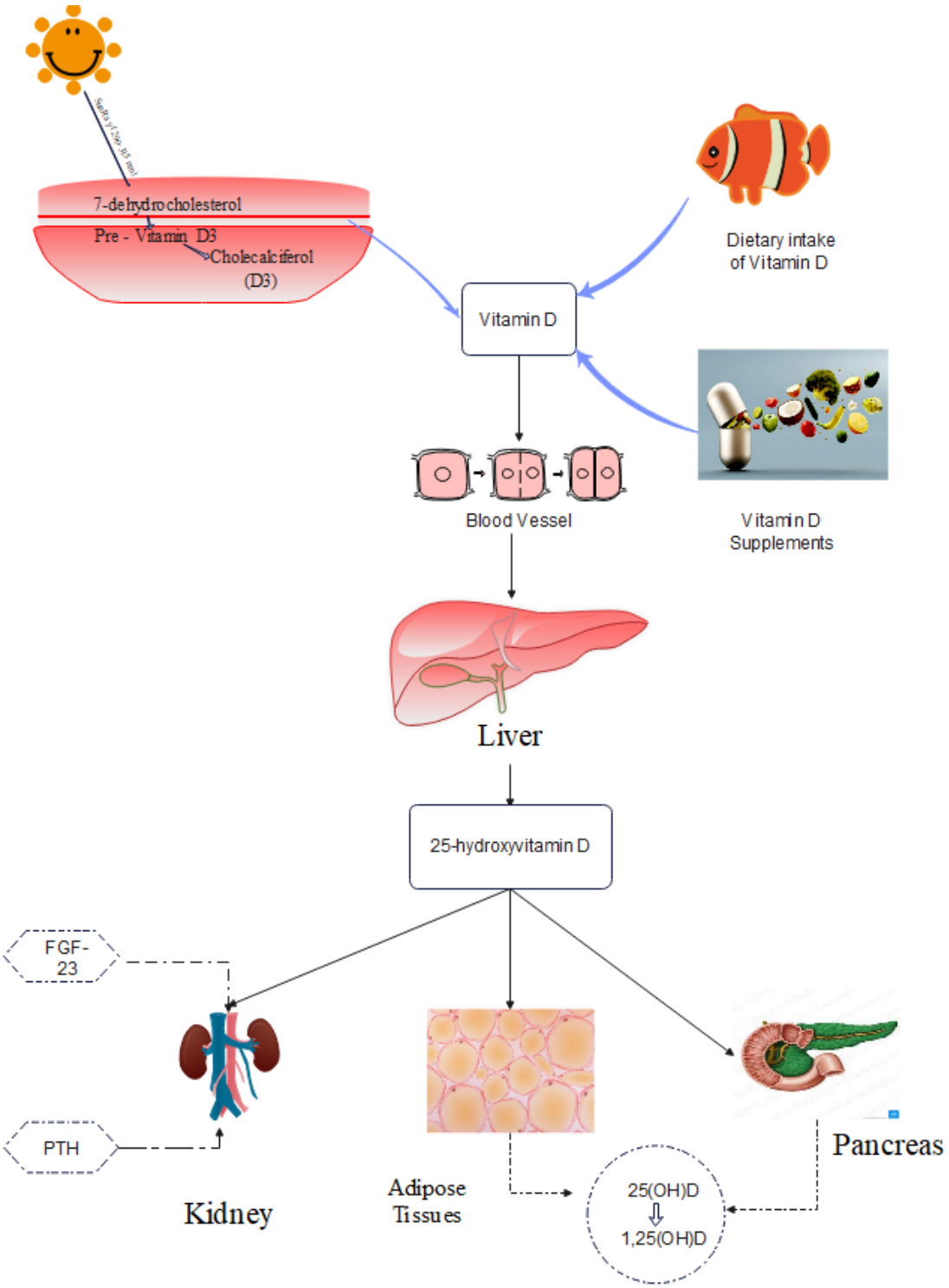

Figure 3.1: Mechanism of Vitamin D Synthesis

tamin D may play an essential role in modulating the risk of T2DM and hypertension, including pancreatic β-cell dysfunction and altered insulin action, according to evidence [55, 99] from animal and human research. Interventional studies have shown that vitamin D administration improves glycated hemoglobin (HbA1c) in T1DM patients, albeit with moderate results, whereas the use of analogs in select subgroups (such as LADA patients) appears to be more promising. Based on the findings, T1DM patients with abysmal glycemic control should be screened for vitamin D deficiency, and supplementing studies should focus on specific patient sub-groups that are likely to be benefited the most from comparable therapies. Vitamin D improves insulin sensitivity [139], reduces insulin resistance [99, 167], and enhances insulin action [71, 170], but the mathematical studies have not been performed to quantify the vitamin D dosages in healthy individuals, those with non-insulin-dependent diabetes, and those with insulin-dependent diabetes. Therefore, a mathematical model has been developed by incorporating these factors of vitamin D for their quantification and assessment of their effect on glucose and insulin level.

3.2 Modeling of Glucose Insulin Regulatory System

The model (3.2.1) includes four new parameters (v_j, j = 1, 2, 3, 4) to study the changes in glucose-insulin dynamics due to Vitamin D's effects and their quantification. The biological meanings of these parameters are discussed as below.

- Parameter v_1 $[min^{-1}]$ represents the influence of vitamin D on the glucose utilization of muscles and fat cells.
- Parameter v_2 relates to the impact of vitamin D on muscle and fat cell insulin sensitivity.
- Because vitamin D stimulates secretion of insulin in the pancreas, v_3 $[ml(U)^{-1}min^2]$ is paired with $f_1(G)$, which explains the same phenomenon.
- The effect of vitamin D on insulin utilization is represented by v_4 $[min^{-1}]$.

The proposed model is as follows after including the above new parameters into the model:

$$\left.\begin{aligned} \frac{dG}{dt} &= G_{in}(t) + c - v_1 f_2(G(t)) - v_2 f_3(G(t)) f_4(I(t)) \\ \frac{dI}{dt} &= v_3 f_1(G(t)) - v_4 d \cdot I(t) \end{aligned}\right\} \tag{3.2.1}$$

with initial condition $I(0) = I_0 \geq 0$ and $G(0) = G_0 \geq 0$. $G(t)$ and $I(t)$ denote the glucose concentration and insulin concentration at any time t, respectively. G_{in} shows exogenous glucose intake. c represents the rate of production of hepatic glucose. d denotes insulin degradation rate which is higher than zero. The biological and mathematical explanation of function f_1, f_2, f_3 and f_4 are discussed in Chapter 2 (Sec. 2.2). The graphical sketch of proposed model is shown in Fig 3.2.

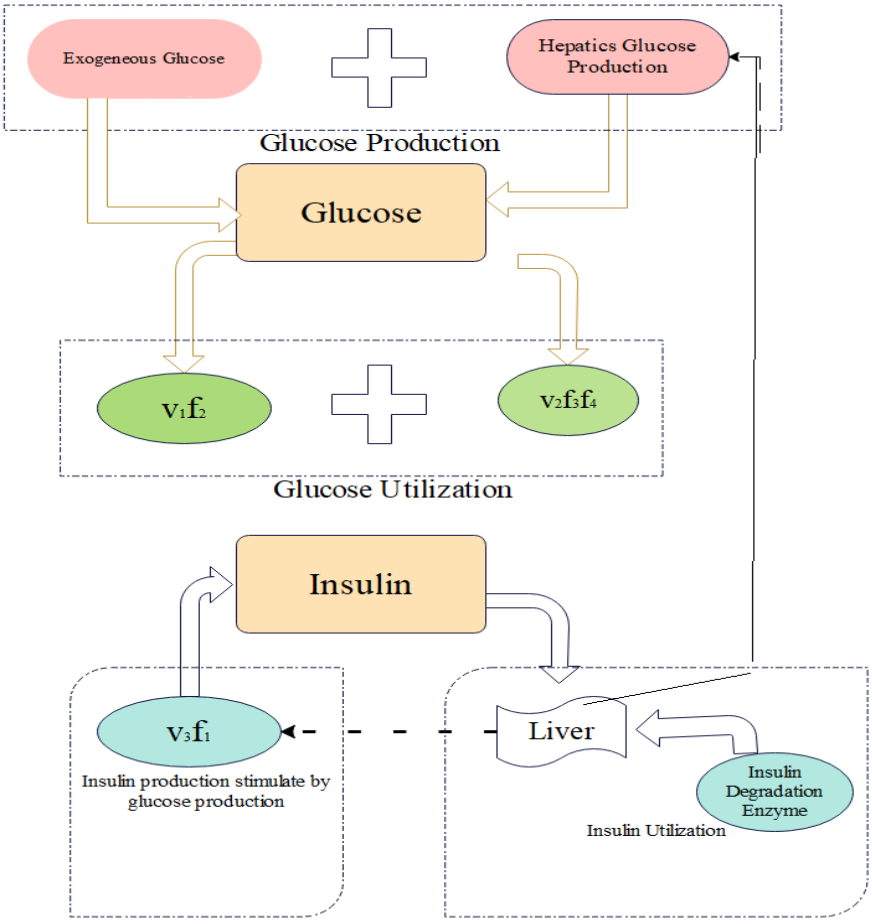

Figure 3.2: Framework of glucose-insulin regulatory mechanism

3.3 Mathematical Analysis of the Model

The positiveness, boundedness, and stability of the model are discussed in this section.

3.3.1 Equilibrium points of model

Assume that G^* and I^* represent the model's equilibrium points. The equilibrium points meet the prerequisite, which $\frac{dG}{dt} = 0$ and $\frac{dI}{dt} = 0$. So, we have

$$G_{in}(t) + c - v_1 f_2(G^*(t)) - v_2 f_3(G^*(t)) f_4(I^*(t)) = 0 \tag{3.3.1}$$

$$v_3 f_1(G^*(t)) - v_4 d \cdot I^*(t) = 0 \tag{3.3.2}$$

we obtained from the Eq (3.3.2)

$$I^*(t) = \frac{v_3 f_1(G^*(t))}{v_4 \cdot d} \tag{3.3.3}$$

3.3.2 Uniqueness of solution

We define the $B(x)$ by Eq (3.2.1)

$$B(x) = G_{in}(t) + c - v_1 f_2(x) - v_2 f_3(x) f_4(d^{-1} v_4^{-1} v_3 f_1(x)) \tag{3.3.4}$$

Since $f_1'(x) > 0$, $f_2'(x) > 0$ $f_3'(x) > 0$, and $f_4'(x) > 0$, then

$$B'(x) = 0 - v_1 f_2'(x) - v_2 (f_3'(x) f_4(d^{-1} f_1(x)) + f_3(x) f_4(d^{-1} f_1(x)) d^{-1} f_1'(x)) \tag{3.3.5}$$

$\because v_i \geq 0$ therefore $B'(x) < 0$. It is known that $f_2(0) = 0$ and $f_3(0) = 0$, so by Eq (3.3.4)

$$\begin{aligned} B(0) &= G_{in} + c - v_1 f_2(0) - v_2 f_3(0) f_4(d^{-1} v_4^{-1} v_3 f_1(0)) \\ &= G_{in} + c > 0 \end{aligned}$$

$$\begin{aligned}\lim_{x\to\infty} B(x) &= G_{in} - \lim_{x\to\infty} v_1 f_2(x) - \lim_{x\to\infty} v_2 f_3(x) f_4(d^{-1} f_1(x)) + c \\ &= G_{in} - v_1 K_2 - v_2 f_4(d^{-1} K_1) \lim_{x\to\infty} f_3(x) + c \\ &< G_{in} - v_1 K_2 - v_2 K_4 \lim_{x\to\infty} f_3(x) + c < 0 \end{aligned} \tag{3.3.6}$$

Hence, $B(0) > 0$, and $\lim_{x\to\infty} B(x) < 0$. From the Eq (3.3.5) and (3.3.6), it can be concluded that $B(x)$ is decreasing function and it cuts x-axis which indicates that model 3.2.1 has unique solution.

3.3.3 Positiveness of solution

Suppose that, $G(t)$ is not positive in $(0,\infty)$. There exists a t_0 such that $G(t_0) = 0$ and $G(t) > 0$ for $0 < t < t_0$, then $G'(t_0) \leq 0$. Now put the $t = t_0$ in model Eq (3.2.1)

$$\begin{aligned} G'(t_0) &= G_{in} - v_1 f_2(G(t_0)) - v_2 f_3(G(t_0)) f_4(I(t_0)) + c \\ &= G_{in} - v_1 f_2(0) - v_2 f_3(0) f_4(I(t_0)) + c \\ &= G_{in} + c \not\leq 0 \end{aligned}$$

It implies that $G(t) > 0$ for $t > 0$. Similarly, we assumed $I(t)$ is not positive in $(0,\infty)$. There exists a t_0 such that $I(t_0) = 0$ and $I(t) > 0$ for $0 < t < t_0$. Then, $I(t_0) < 0$. and

$$I'(t_0) = v_3 f_1(G(t_0)) - v_4 d I(t_0) \geq v_3 f_1(G(t_0)) \not\leq 0$$

The conclusion of the analysis indicates that the solution of the model is positive.

3.3.4 Boundedness of solution

Assum that $G(t)$ is not bounded solution, by lemma $(2.3.1)$ $\lim_{x\to\infty}$ sup $G(t) = \infty$. Then $\exists$ a sequence $< t_n >$ such that $\lim_{n\to\infty}$sup $G(t_n)$=∞ and $G'(t_n) \geq 0$. Thus

$$\begin{aligned} G'(t_n) &= G_{in} - v_1 f_2(G(t_n)) - v_2 f_3(G(t_n)) f_4(I(t_n)) + c \\ &\leq G_{in} - v_1 f_2(G(t_n)) - v_2 k_4 f_3(G(t_n)) + c \\ \Rightarrow \lim_{n\to\infty} G'(t_n) &\leq G_{in} - v_1 \lim_{n\to\infty} f_2(G(t_n)) - v_2 k_4 \lim_{n\to\infty} f_3(G(t_n)) + c \\ &\leq G_{in} - v_1 K_2 - v_2 k_4 \lim_{n\to\infty} f_3(G(t_n)) + c \\ &\leq G_{in} - v_1 K_2 - v_2 k_4 \cdot \infty + c = -\infty \not\geq 0 \end{aligned}$$

This is contradiction for $G(t) \forall t > 0$. Hence, $G(t)$ is bounded $\forall\, t > 0$.

Consider the case where $I(t)$ is not bounded $\forall\, t > 0$. Since, $f_1(x)$ is bounded function in x $\in$ (0,∞). $I(t)$ will satisfy the $\lim_{x\to\infty}$ sup $I(t) = \infty$. Then $\exists$ a sequence $< t_n' >$ such that $\lim_{n\to\infty}$sup I(t_n')=∞ and $I'(t_n') \geq 0$. Taking the $limit_{n\to\infty}$ on both side of above inequality, Therefore

$$\begin{aligned} \lim_{n\to\infty} I'(t_n) &= \lim_{n\to\infty} f_1(G(t_n')) - d \lim_{n\to\infty} I(t_n') \\ &= R_m - d \lim_{n\to\infty} I(t_n') = -\infty \not\geq 0 \end{aligned}$$

Although it is a contradiction, it has been concluded that the $I(t)$ is bounded for all t.

3.3.5 Stability analysis of model

We have linearized model $(3.2.1)$ about the stable point (G^*,I^*) to demonstrate the stability of the model. The linearized model is written as:

$$\begin{bmatrix} \frac{dG}{dt} \\ \frac{dI}{dt} \end{bmatrix} = \begin{bmatrix} -P & -Q \\ R & -D \end{bmatrix} \cdot \begin{bmatrix} G(t) \\ I(t) \end{bmatrix} \tag{3.3.7}$$

where,

$P = v_1 f_2'(G^*) + v_2 f_3'(G^*) f_4(I^*) > 0$; $Q = v_2 f_3(G^*) f_4'(I(t)) > 0$; $R = v_3 f_1'(G^*) > 0$ and $D = v_4 d$. The characteristics equation is given as

$$\lambda^2 + (P+D)\lambda + PD + QR = 0 \tag{3.3.8}$$

$$(P+D) > 0 and$$

$$PD + QR > 0.$$

The roots of Eq (3.3.8) are

$$\lambda_1 = \frac{-(P+D) - \sqrt{(P-D)^2 - 4QR}}{2}, \text{ and } \lambda_2 = \frac{-(P+D) + \sqrt{(P-D)^2 - 4QR}}{2} \tag{3.3.9}$$

There are three cases arise:

Case 1: if $(P-D)^2 - 4QR < 0$, then roots are imaginary and having the negative real parts. It implies that system is stable at (G^*, I^*).

Case 2: if $(P-D)^2 - 4QR = 0$, then $\lambda_1 = \lambda_1 = -(P+D)$. Both are negative real roots. It shows that the system is stable at steady point.

Case 3: if $(P-D)^2 - 4QR > 0$, we write $(P-D)^2 - 4QR = (P+D)^2 - 4(PD+QR)$.

Claim: $\sqrt{(P+D)^2 - 4(PD+QR)} < -(P+D)$

Proof: Let $\sqrt{(P+D)^2 - 4(PD+QR)} > -(P+D)$, On squaring both side

$$(P+D)^2 - 4(PD+QR) > (P+D)^2$$

$$\Rightarrow -4(PD+QR) > 0$$

$$\Rightarrow (PD+QR) < 0$$

which contradict the condition $(PD+QR) > 0$. Hence, λ_1 and λ_2 are negative real roots. Therefore, system is stable at (G^*, I^*). In accordance with the illustrious theorem 3.1 presented in reference [44], a thorough analysis has revealed that the model exhibits exceptional stability in all scenarios.

3.4 Insulin Sensitivity

The glucose clamp method is used to assess insulin sensitivity [177]. It involves administering glucose to maintain constant blood glucose levels and can be used to express model (3.2.1).

$$\left.\begin{aligned} \frac{dG}{dt} &= g_{inf}(t) + c - v_1 f_2(G(t)) - v_2 f_3(G(t)) f_4(I(t)) \\ \frac{dI}{dt} &= v_3 f_1(G(t)) - v_4 d \cdot I(t) \end{aligned}\right\} \tag{3.4.1}$$

where g_{inf} is the infusion of glucose by a unit of volume.

$$g_{inf}(t) = v_1 f_2(G^*) + v_2 f_3(G^*) f_4(I^*) - c \tag{3.4.2}$$

The Insulin Sensitivity (S_I) can be written as:

$$S_I = \frac{\partial^2 g_{inf}}{\partial I^* \partial G^*} \tag{3.4.3}$$

by Eq (3.4.2)-(3.4.3))

$$S_I = v_2 f_3'(G^*) f_4'\left(\frac{v_3}{d v_4} f_1(G^*)\right) \tag{3.4.4}$$

when all v_i are equal to 1 then

$$S_I = f_3'(G^*) f_4'\left(\frac{}{d} f_1(G^*)\right) \tag{3.4.5}$$

we conclude that

$$f_3'(G^*) f_4'\left(\frac{}{d} f_1(G^*)\right) \leq v_2 f_3'(G^*) f_4'\left(\frac{v_3}{d v_4} f_1(G^*)\right) \tag{3.4.6}$$

It can be argued from the Eq (3.4.6) that vitamin D enhances insulin sensitivity and helps regulate blood glucose levels within normal physiological limits.

3.5 Numerical Simulation

The values of the model parameters were taken from Table 2.2 during the simulation process. The baseline value of glucose (G_b) was taken into account, which was around 90 mg/dl. The values of the vitamin D parameters were estimated based on their compatibility with other model factors and their impact on various mechanisms. The patients were divided into three groups: Normal individual, T1DM patients, and T2DM patients, with their respective values listed in Table 3.1, Table 3.2, and Table 3.3. The glucose-insulin dynamics were then compared for each group. The glucose space (V_g) is the most significant component of the regulation process and is considered as a single compartment. In diabetic patients, the volume of distribution (V_g) was assumed to be 10 liters, compared to 5 liters in healthy individuals. Graphs of glucose profiles were plotted for each group to compare the impact of vitamin D on glucose levels.

3.5.1 Role of vitamin D in normal case

For the glucose-insulin dynamics in this procedure, the average normal values for humans were used for the parameters v_1, v_2, v_3, and v_4. The Table 3.1 shows the estimated values of these parameters for a normal individual.

Parameters	Value
v_1	$0.30\ min^{-1}$
v_2	0.75 (unit less)
v_3	$0.95\ ml(\mu U)^{-1}min^{-2}$
v_4	$0.20\ min^{-1}$
v_g	5 litre

Table 3.1: Value of experimental data of normal individuals [142]

Figure 3.3 depicts the influence of vitamin D on glucose-insulin dynamics in the normal scenario. In the presence of vitamin D factors, glucose levels reached 91.91 mg/dl, as shown in Fig 3.3(a). The glucose level was 110 mg/dl without Vitamin D factors, which was outside of the usual range. Figure 3.3(b) illustrates the simulated

insulin disappearance profiles.

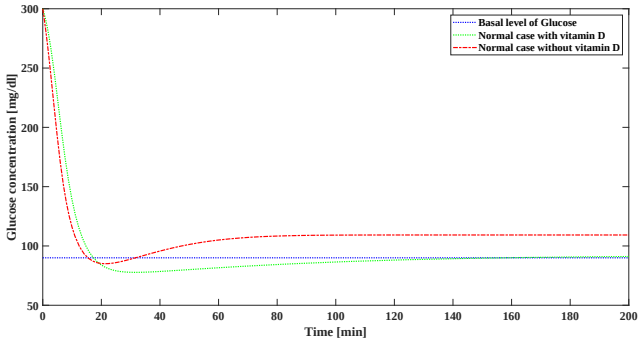

Fig 3.3(a). Sugar level

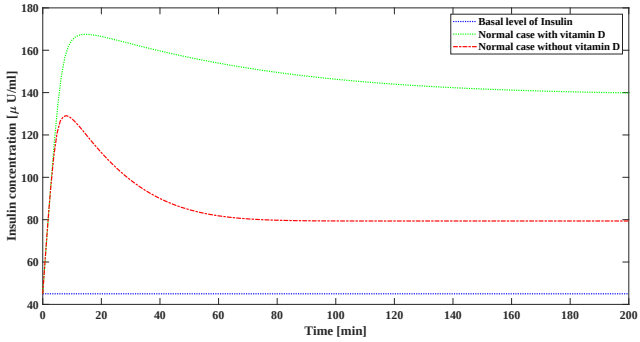

Fig 3.3(b). Insulin level

Figure 3.3: Glucose-Insulin Dynamics in Normal Subject

In Figure 3.4, the phase portraits demonstrate the stability of the plasma glucose and insulin dynamics, where the behavior appears to be a stable spiral. The figure

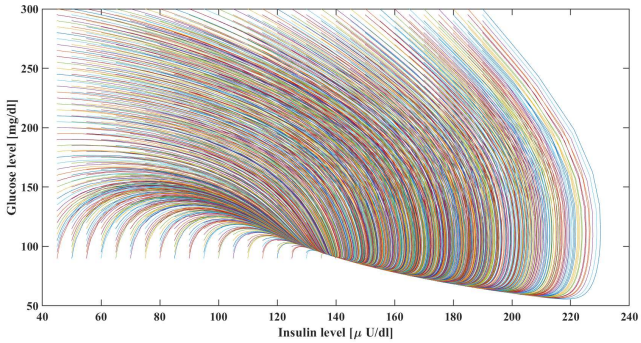

Fig 3.4(a). Phase Portrait in presence of Vitamin D

indicates that all the trajectories, regardless of their initial conditions, converge to a single point.

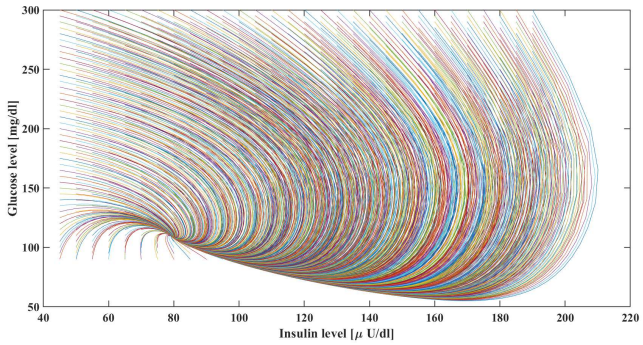

Fig 3.4(b). Phase Portrait in absence of Vitamin D

Figure 3.4: Phase Portrait of Normal individuals

3.5.2 Role of vitamin D to enhance the insulin secretion rate for type 1 diabetes patients

The case of Type 1 diabetic patients is considered in this section. The insulin level was 45 micro units per milliliter , while the glucose level was 350 milligrams per deciliter. It was assumed that the volume of glucose concentration (V_g) was 10 liters. To examine the impact of the v_3 parameter on insulin secretion within 200 minutes, we have chosen values of v_3 in the range of [0.90 0.95]. In case of T1DM, the value of S_I is smaller than its value in normal case because of lake of Vitamin D. Table 3.2 shows the estimated values of the parameters in the insulin dependent diabetic case.

Parameters	Values
v_1	0.12 min^{-1}
v_2	0.90 (unit less)
v_3	0.90 to 0.95 $ml(\mu U)^{-1}min^{-2}$
v_4	0.20 min^{-1}
v_g	10 litre

Table 3.2: Value of experimental data of T1DM patients [142]

Figure 3.5 depicts the comparison of insulin and glucose concentrations of T1DM patients for five different values of v_3. The glucose and insulin levels of T1DM patients were compared in five distinct cases depending on vitamin D levels in Fig 3.5(a) and Fig 3.5(b). Figure 3.5(a) shows how the insulin level changes drastically over the first 50-60 minutes and remained stable after 70 minutes. Insulin levels were 192.1, 192.6,

193.1, 193.6, and 194.1 (μ U/ml) at v_i = 0.9000, 0.9125, 0.9250, 0.9375, and 0.9500, respectively. These numbers are far too close together. This finding supports the theory that Vitamin D stimulates pancreatic insulin rate.

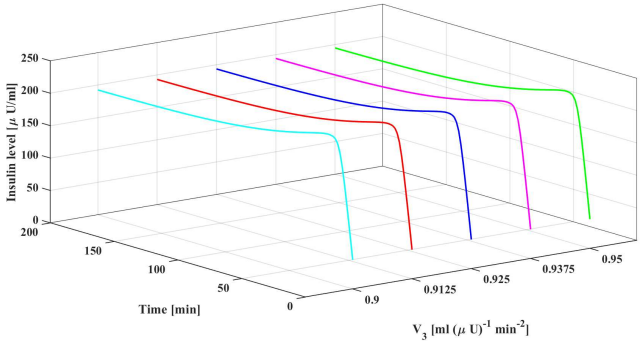

Fig 3.5(a). Comparison of insulin concentration level with varying v_3

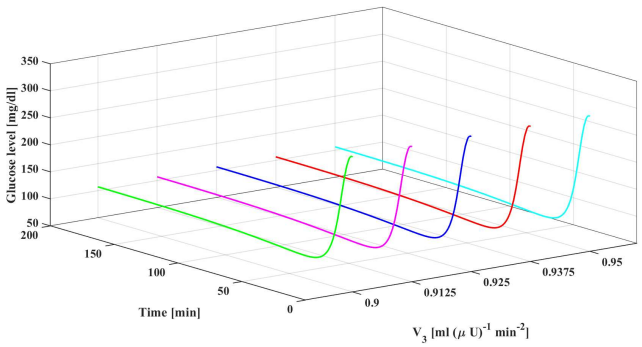

Fig 3.5(b). Comparison of glucose concentration level with varying v_3

Figure 3.5: Glucose-Insulin dynamic of T1DM patients at various cases of v_3

Figure 3.6 depicts the glucose and insulin profile of T1DM patients at a mean value of v_3. The interval [0.90 0.95] is used to find the mean value of v_3. The glucose level was maintained at 107 mg/dl while it was 139.7 mg/dl in the absence of Vitamin D.

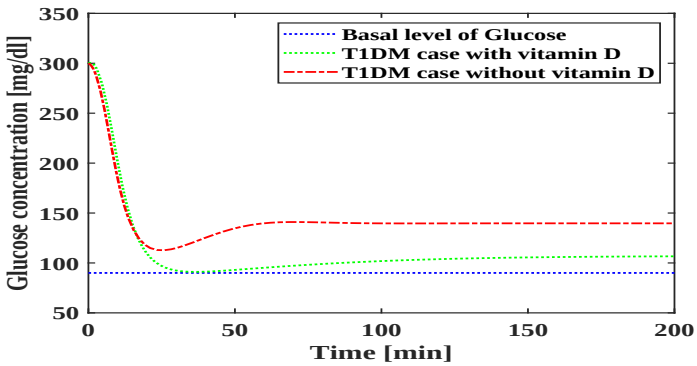

Fig 3.6(a). Glucose profile of T1DM patients

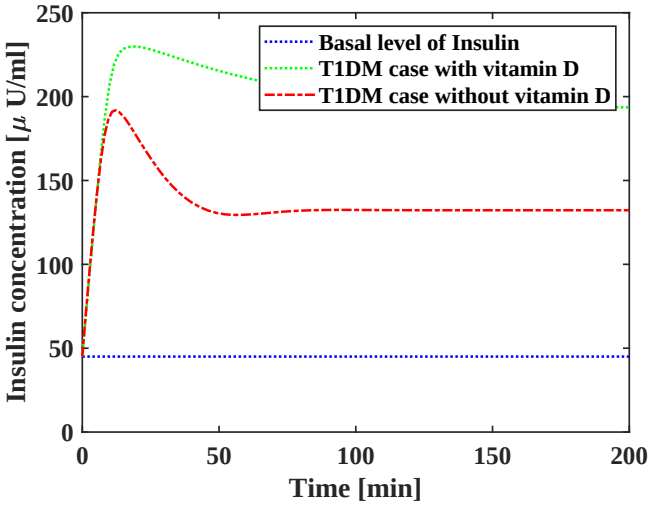

Fig 3.6(b). Insulin profile of T1DM patients

Figure 3.6: Glucose-Insulin dynamic of T1DM patients at $v_3 = 0.9250$

In Fig 3.7, the phase portraits depict the stability of plasma glucose and insulin dynamics in patients with type 1 diabetes mellitus, with the model having the stable spiral. The figure illustrates that all the trajectories, starting from different initial

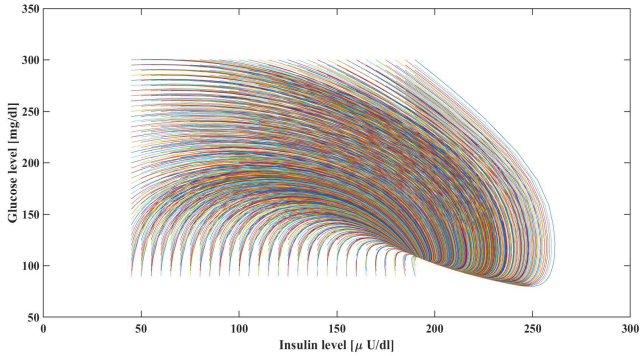

Fig 3.7(a). Phase Portrait in presence of Vitamin D

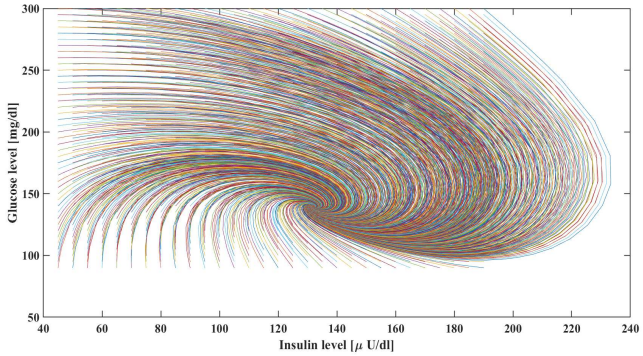

Fig 3.7(b). Phase Portrait in absence of Vitamin D

Figure 3.7: Phase Portrait of T1DM patients

conditions, converge to a single point.

3.5.3 Role of vitamin D to enhance the insulin sensitivity for type 2 diabetes mellitus

This section devotes to study the effect over insulin sensitivity by the Vitamin D in patients of T2DM . It refers to how sensitive the body's cells are in response to insulin. We have chosen the v_2 parameter which deals with the vitamin D's effect on muscles and fat cells to affect the insulin sensitivity. For assessing the impact of v_2 on insulin sensitivity, we used values of v_3 in the [0.85 0.90] range. The estimated values of v_i, i = 1,3 and 4 for T2DM patients are shown in Table 3.3 .

Parameters	Values
v_1	0.20 min^{-1}
v_2	0.85 to 0.90 (unit less)
v_3	0.90 $ml(\mu U)^{-1}min^{-2}$
v_4	0.20 min^{-1}
v_g	10 litre

Table 3.3: Value of experimental data of Vitamin D factors in T2DM patients [142]

The linear relationship between insulin sensitivity and v_2 is depicted in Fig 3.8. Patients' insulin sensitivity improves with a small modification in parameter v_2. Figure 3.9

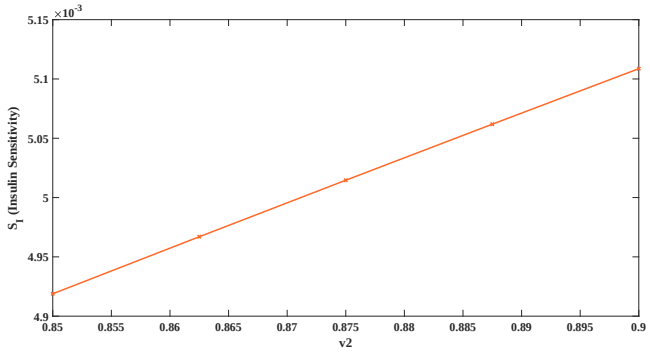

Figure 3.8: Insulin Sensitivity

depicts a considerable change in glucose and insulin levels with variation in the insulin sensitivity of patients S_I varies. In Fig 3.9(a), at S_I = 0.0054, 0.0055, 0.0056, 0.0056, and 0.0057, respectively, insulin levels were 191.8, 190.1, 188.4, 186.7, and 185.1 (μU/ml). In all scenarios, the glucose level ranged from 106 to 107 mg/dl, represent in Fig 3.9(b).

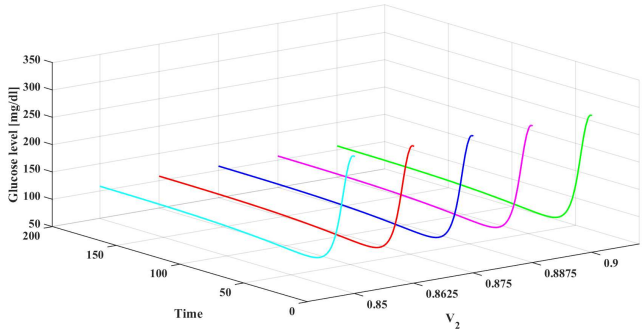

Fig 3.9(a). Comparison of glucose concentration level with varying S_I

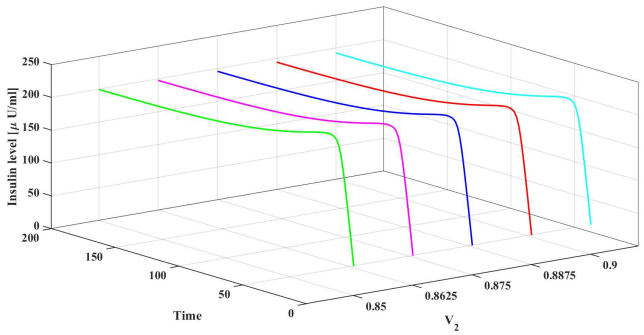

Fig 3.9(b). Comparison of insulin concentration level with varying S_I

Figure 3.9: Glucose-Insulin dynamic of T2DM patients at various cases of v_2

Because vitamin D has a positive association with insulin sensitivity, a slight increase in the value of the v_2 parameter raises the S_I. The elevated glucose level approaches the baseline amount. At a mean value of v_2, Fig 3.10 displays the glucose and insulin profile of T2DM patients. The mean value of v_2 is calculated using the interval [0.85 0.90]. The glucose level in T2DM patients is 139.9 mg/dl in the absence of Vitamin D, but in presence of Vitamin D, the glucose level is 108.9 mg/dl.

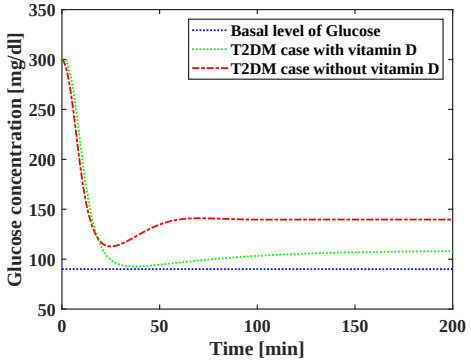

Fig 3.10(a). Glucose profile of T2DM patients

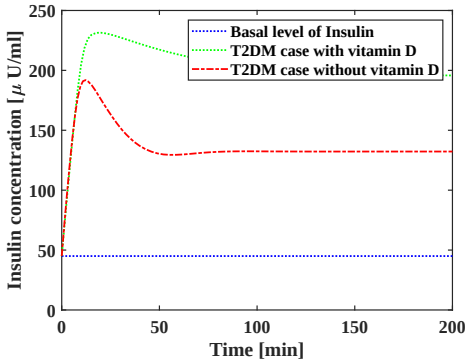

Fig 3.10(b). Insulin profile of T2DM patients

Figure 3.10: Glucose-Insulin dynamic of T2DM patients at $v_2 = 0.8750$

In Fig 3.11, the phase portraits reflect the stability of plasma glucose and insulin dynamics in individuals with type 2 diabetes mellitus and it is stable spiral. The

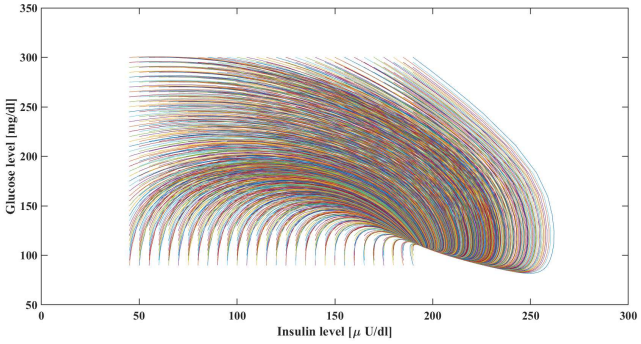

Fig 3.11(a). Phase Portrait in presence of Vitamin D

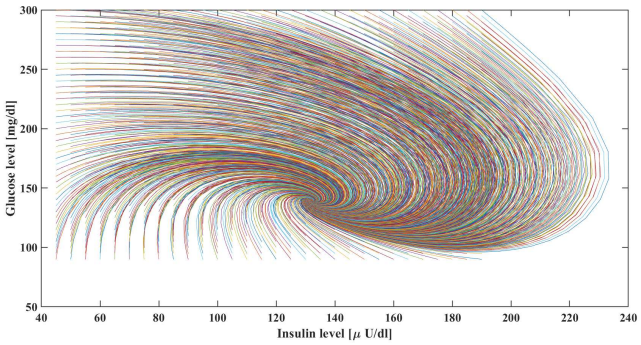

Fig 3.11(b). Phase Portrait in absence of Vitamin D

Figure 3.11: Phase Portrait of T2DM patients

figure demonstrates that all the trajectories, originating from various initial conditions converges to unique point.

3.6 Results and Discussion

Managing diabetes is a complex process that involves regulating insulin production, glucose absorption, and vitamin D intake, as previously discussed. The inclusion of the Vitamin D factor in the model adds a crucial layer of understanding to the intricate biology underlying unbalanced glucose levels in people with diabetes. In T2DM patients, vitamin D parameters (e.g., v_2) help manage glucose levels and lower baseline levels to 107 mg/dl. In T1DM patients, v_3 helps enhance insulin secretion. Low-income diabetes patients struggle to afford insulin therapy, highlighting the need for affordable and simple management strategies.

3.7 Conclusion and Future Aspects

This study presents a novel and sophisticated mathematical model that captures the intricate interplay between vitamin D and plasma glucose-insulin dynamics. By incorporating linear and nonlinear terms, the model provides a comprehensive understanding of the impact of vitamin D on insulin sensitivity and pancreatic responsiveness. The proposed model has the potential to revolutionize diabetes management by accurately determining the optimal vitamin D dosage for diabetic patients based on the severity of their condition. This personalized approach could significantly improve the quality of life for the ever-growing diabetic population with less economy burden in the economy of the country.

Chapter 4

An Effective Fuzzy Logic Controller to Determine the Optimal Awareness Percentage for Diabetes Progression

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The aim of this chapter is to develop a control strategy that calculates the optimal percentage of the aware population with diabetes in the entire population. To achieve this, a Mamdani-based fuzzy logic controller with two inputs and one output is designed.The theoretical results proven that model has unique, positive, bounded, and stable. The proposed fuzzy logic controller reduced the number of people with diabetes by 40% in the seventh month, outperforming existing optimal control technology. This study emphasizes the importance of effective and cost-efficient diabetes prevention methods, highlighting the significance of short and targeted awareness efforts, rather than prolonged campaigns, to conserve resources for the management of the disease. Furthermore, this research concludes that fuzzy-based intelligence techniques are the most cost-effective way to lower the overall cost of diabetes prevention and management for the general population.

4.1 Introduction

Insulin injections and pumps, blood sugar checks, and carbohydrate counting are involved in managing Type 1 diabetes, while Type 2 diabetes is managed with a combination of lifestyle changes, monitoring, medication, and insulin. Along with sufficiency of the management of any country, it is also an economical burden. In 2017, it is reported that cost of managing diabetes is high, with a total of $327 billion , including $237 billion in direct medical costs and $90 billion in lost productivity. Most costs come from hospital care (30%), prescription drugs (30%), supplies (15%), and physician visits (13%). The cost has increased 33.46% from $245 billion in 2012 to $327 billion in 2017. This is a burden for low/middle-income families. 34.5% of the population had pre-diabetes from 2013 to 2016, with 15.3% aware of their diabetes.

Studies by various authors [8, 47, 73, 158, 178] have consistently demonstrated a lack of awareness about diabetes among the general public. Approximately 50.1% of people with diabetes are unaware that they have the condition [149], highlighting the pressing need to improve knowledge and awareness about diabetes. This is one of the key objectives of the current study. Raising awareness of the various aspects of diabetes [14, 34, 124, 189] is an effective method for preventing, managing, and controlling Diabetes Mellitus. By educating people about diabetes, they can better manage their condition and glycemic control, and it would be a cost-effective investment for a significant public health benefit. Research supports that diabetes awareness programs [13, 37, 88, 124] can be effective in combating diabetes, and intensive education on diabetes and glycemic control can reduce risk factors, minimize complications, and improve outcomes for people with diabetes. Self-management education [147, 156] is an important aspect of diabetes management, and patients must have a good understanding of the disease, its risk factors, treatment options, and potential complications to effectively manage their diabetes. Recently, various authors have utilized the optimal control method in their studies [51, 95, 96, 137]. However, these studies have utilized multiple control inputs in their models, making the models

complex and challenging to solve for large-scale problems with interior constraints.

4.2 Modeling of Diabetes using Population Model

We assume that the overall human population density at time t in the region under consideration is $N(t)$. The entire population can be splited into three categories, each of which has its physical meaning. Susceptible humans $S(t)$ means people who never had diabetes problems but can be diabetic in future. Diabetic humans $D(t)$ means those people who are suffering from diabetes. Diabetes-managed humans $M(t)$ means those diabetic population who have controlled their blood glucose level. Although there is currently no treatment for diabetes, the condition can be managed and put into remission. In remission, the body no longer displays signs of diabetes despite persistent hyperglycemia in the individual. As a result, we assumed that the persons in the $M(t)$ compartment would most likely transfer to the $D(t)$ compartment rather than the $S(t)$ compartment. We make the following assumptions in order to build the model:

- We assumed that N(t) is the overall population size taken to be constant at every point of time, implying that no births or migration factors are considered for model formulation.

- The constant rate of immigration in sensitive persons is assumed to be I. Diabetes is a non-infectious condition, and it is well recognized that it cannot be passed from one person to another. However, healthy people are influenced by the habits of diabetic patients, who are more likely to have poor mental health, lack physical activity, and following an unhealthy diet. It is more likely to be diabetic when healthy people contact with diabetic persons and get influenced by them.

- It is believed that the probability of a person's natural death is the same in each compartment. So we have taken the constant natural mortality rate (μ) in each compartment. It means that non-natural causes of death, such as car accidents,

murder, suicide, and disease, are not taken into account.

- Better diabetes education and understanding can help diabetics control and treat their disease at the proper time, lowering their morbidity and mortality. Diabetes incidence rates can be reduced by focusing population-based awareness efforts on modifiable hazard components. As awareness spreads, we back up earlier research findings that show that people who are aware have a lower risk of developing diabetes than people who are oblivious.

We provide a compartment diagram for the diabetes population, as shown in Fig 4.1

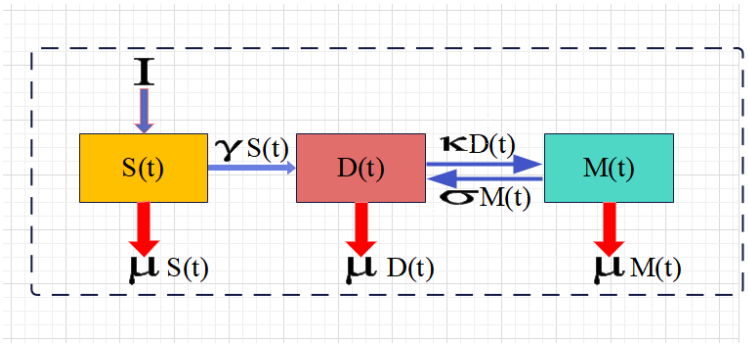

Figure 4.1: Compartmental model for the progression of disease.

Behold the mathematical representation that governs the population dynamics - a system of ordinary differential equations that reads as follows:

$$\left.\begin{aligned} \frac{dS(t)}{dt} &= I - \mu S(t) - \gamma S(t)D(t) \\ \frac{dD(t)}{dt} &= \gamma S(t)D(t) - \mu D(t) - \kappa D(t) + \sigma M(t) \\ \frac{dM(t)}{dt} &= \kappa D(t) - \mu M(t) - \sigma M(t) \end{aligned}\right\} \tag{4.2.1}$$

where I is recruitment rate of diabetes, μ is the natural death rate of population, γ denotes the incidence rate of the first diabetes complication, κ is the rate at which complications are successfully managed and σ is the incidence rate of recurrence of complications. Structure satisfy the condition of

$$N(t) = S(t) + D(t) + M(t) \tag{4.2.2}$$

S_0, D_0 and M_0 are the positive initial values of $S(t)$, $D(t)$ and $M(t)$, respectively. The diabetes system is studied in a biologically plausible domain provided by

$$\Omega = \left\{ (S(t), D(t), M(t)) \in \mathbb{R}^3_+ | S(t) + D(t) + M(t) \leq \frac{I}{\mu} \right\}$$

We use simplify notation S, D, and M which assessed at time t, according to our model's variables notation.

4.3 Mathematical Analysis of the model

The purpose of this section is to analyze existence, uniqueness, boundedness and stability of solution.

4.3.1 Existence of equilibrium points

The equilibrium points of non-linear model appears when $\frac{dS}{dt} = 0$, $\frac{dD}{dt} = 0$ and $\frac{dM}{dt} = 0$ and the steady state is specified as (S^*, D^*, M^*). There are two equilibrium points of model has found which are as follows:

E_1: $(S^*_{E_1}, D^*_{E_1}, M^*_{E_1}) = \left(\frac{I}{\mu}, 0, 0\right)$

E_2: $(S^*_{E_2}, D^*_{E_2}, M^*_{E_2}) = \left(\frac{\kappa\mu+\mu\sigma+\mu^2}{\gamma\mu+\gamma\sigma}, \frac{-(\kappa\mu^2+\mu^2\sigma+\mu^3-I\gamma\mu-I\gamma\sigma}{\gamma\mu^2+\gamma\kappa\mu+\gamma\mu\sigma)}, \frac{-(\kappa^2\mu^2+\kappa\mu^3+\sigma\kappa\mu^2-I\gamma\kappa\mu-I\gamma\sigma\kappa)}{\gamma\mu^3+2\gamma\mu^2\sigma+\gamma\kappa\mu^2+\gamma\mu\sigma^2+\gamma\kappa\mu\sigma} \right)$

Since diabetes is the fastest growing disease and the population of diabetic people will never vanish at any time (meant $D^* \neq 0$), therefore, we consider only the E_2 equilibrium point for the model's stability analysis.

4.3.2 Uniqueness of solution

Theorem 4.3.1. *The system* (4.2.1) *that satisfies a given positive initial conditions (S_0, D_0, M_0) has a unique solutions.*

Proof: Let

$$X = \begin{bmatrix} S(t) \\ D(t) \\ M(t) \end{bmatrix} \quad \dot{X} = \begin{bmatrix} \dot{S}(t) \\ \dot{D}(t) \\ \dot{M}(t) \end{bmatrix} \tag{4.3.1}$$

The matrix form of system (4.2.1) can be rewritten as follows:

$$\phi(\dot{X}) = \dot{X} = AX + B(X) \tag{4.3.2}$$

where

$$A = \begin{bmatrix} -\mu & 0 & 0 \\ 0 & -(\mu+\kappa) & \sigma \\ 0 & \kappa & -(\mu+\sigma) \end{bmatrix} \tag{4.3.3}$$

$$B(X) = \begin{bmatrix} I - \gamma S(t)D(t) \\ \gamma S(t)D(t) \\ 0 \end{bmatrix} \tag{4.3.4}$$

The second term on the right-hand side of equation (4.3.3) satisfies

$$\begin{aligned} |B(X_1) - B(X_2)| &\leq M(|S_1(t) - S_2(t)| + (|D_1(t) - D_2(t)|) \\ &\leq M \|X_1 - X_2\| \end{aligned}$$

where

$$M = \begin{bmatrix} \frac{2I\gamma}{\mu} \\ \frac{2I\gamma}{\mu} \end{bmatrix}$$

then

$$\|\phi(X_1) - \phi(X_2)\| \leq V \|X_1 - X_2\| \tag{4.3.5}$$

where V = max (M,$\|A\|$)$<\infty$.

As a result, the function ϕ is uniformly Lipschitz continuous and proved that system (4.2.1) has a unique solution in the domain Ω.

4.3.3 Positiveness of solution

Theorem 4.3.2. *Assuming that $S(0) \geq 0$, $D(0) \geq 0$, and $M(0) \geq 0$, the positive solutions of the system (4.2.1) for $t \geq 0$ are given by $S(t)$, $D(t)$, and $M(t)$.*

Proof: Suppose that, S(t) is not positive in (0,∞). There exists a t_0 such that $S(t_0) = 0$ and S(t) $\geq$ 0 for $0 < t < t_0$, then $S'(t_0) \leq 0$. Now we put the $t = t_0$ in the model (4.2.1)

$$\begin{aligned} \frac{dS(t_0)}{dt} &= I - \mu S(t_0)) - \gamma S(t_0) D(t_0) \\ &\leq I \end{aligned}$$

Since I is greater than zero so it is contradiction which implies $S(t) >$0 for $t >$0. Similarly, we can prove that $D(t)$ and $M(t)$ are also positive in domain Ω.

4.3.4 Boundedness of solution

Theorem 4.3.3. *The solutions of model (4.2.1) over the set $\Omega = \{(S(t), D(t), M(t)) \in \mathbb{R}^3_+ / 0\}$ is bounded with initial condition $S_0 \geq 0$, $D_0 \geq 0$ and $M_0 \geq 0$*

Proof: By adding the equation of system (4.2.1), we obtain

$$\frac{dS(t)}{dt} + \frac{dD(t)}{dt} + \frac{dM(t)}{dt} = I - \mu(S(t) + D(t) + M(t)) \tag{4.3.6}$$

$$\frac{dN(t)}{dt} = I - \mu N(t) \tag{4.3.7}$$

This implies

$$N(t) = \frac{I}{\mu} + N(0)e^{-\mu t} \tag{4.3.8}$$

The initial value of the total population is represented by $N(0)$. Thus, $\lim_{x \to \infty}$ sup $N(t) = \frac{I}{\mu}$ which implies that all solution is bounded.

4.3.5 Stability analysis of model

The direct solution of the model's time-dependent variables $S(t)$, $D(t)$, and $M(t)$, as described by model (4.2.1), is notably challenging. To assess the stability of the non-linear model at its equilibrium point, we employ a linearized approach. Specifically, we consider the linearized system of model (4.2.1) at the steady point E_2, which is given as follows:

$$\begin{bmatrix} \frac{dS}{dt} \\ \frac{dD}{dt} \\ \frac{dM}{dt} \end{bmatrix} = \begin{bmatrix} J_{11} & J_{12} & J_{13} \\ J_{21} & J_{22} & J_{23} \\ J_{31} & J_{32} & J_{33} \end{bmatrix} \begin{bmatrix} S(t) \\ D(t) \\ M(t) \end{bmatrix} \tag{4.3.9}$$

where,

$J_{11} = \frac{\gamma(\kappa\mu^2+\mu^2\sigma+\mu^3-I\gamma\mu-I\gamma\sigma)}{(\gamma\mu^2+\gamma\kappa\mu+\gamma\mu\sigma)} - \mu, \qquad J_{12} = \frac{-(\gamma(\kappa\mu+\mu\sigma+\mu^2))}{(\gamma\mu+\gamma\sigma)}, \qquad J_{13} = 0$

$J_{21} = \frac{-(\gamma(\kappa\mu^2+\mu^2\sigma+\mu^3-I\gamma\mu-I\gamma\sigma))}{(\gamma\mu^2+\gamma\kappa\mu+\gamma\mu\sigma)}, \qquad J_{22} = \frac{(\gamma(\kappa\mu+\mu\sigma+\mu^2))}{(\gamma\mu+\gamma\sigma)} - \mu - \kappa, \qquad J_{23} = \sigma$

$J_{31} = 0, \qquad J_{32} = \kappa, \qquad J_{33} = -\mu - \sigma$

The characteristics equation of matrix J is given as:

$$a_3\chi^3 + a_2\chi^2 + a_1\chi + a_0 = 0 \tag{4.3.10}$$

where,

$$a_3 = \frac{\mu^3 + 2\mu^2\sigma + \kappa\mu^2 + \mu\sigma^2 + \kappa\mu\sigma}{(\mu+\sigma)(\kappa\mu+\mu\sigma+\mu^2)} \tag{4.3.11}$$

$$a_2 = \frac{\begin{array}{c}\kappa^2\mu\sigma + \kappa\mu^3 + 3\kappa\mu^2\sigma + 2\kappa\mu\sigma^2 + \mu^4 + 3\mu^3\sigma + 3\mu^2\sigma^2 + I\gamma*\mu^2 + \mu\sigma^3 \\ + 2I\gamma\mu\sigma + I\gamma\sigma^2\end{array}}{(\mu+\sigma)(\kappa\mu+\mu\sigma+\mu^2)} \tag{4.3.12}$$

$$a_1 = \frac{\begin{array}{c} -\kappa^2\mu^3 - 2\kappa\mu^4 - 2\kappa\mu^3\sigma + I\gamma\kappa\mu^2 + 2I\gamma\kappa\mu\sigma + I\gamma\kappa\sigma^2 - \mu^5 - 2\mu^4\sigma \\ -\mu^3\sigma^2 + 2I\gamma\mu^3 + 5I\gamma\mu^2\sigma + 4I\gamma\mu\sigma^2 + I\gamma\sigma^3 \end{array}}{(\mu+\sigma)(\kappa\mu+\mu\sigma+\mu^2)} \tag{4.3.13}$$

$$a_0 = \frac{\begin{array}{c} -\kappa^2\mu^4 + \kappa^2\mu^3\sigma + 2\kappa\mu^5 + 4\kappa\mu^4\sigma + 2\kappa\mu^3\sigma^2 - I\gamma\kappa\mu^3 - 2I\gamma\kappa\mu^2\sigma - I\gamma\kappa\mu\sigma^2 \\ +\mu^6 + 3\mu^5\sigma + 3\mu^4\sigma^2 + I\gamma\mu^4 + \mu^3\sigma^3 + 3I\gamma\mu^3\sigma - 3I\gamma\mu^2\sigma^2 - I\gamma\mu\sigma^3 \end{array}}{(\mu+\sigma)(\kappa\mu+\mu\sigma+\mu^2)} \tag{4.3.14}$$

The roots of Equation 4.3.10 are provided as follows:

$$\chi_1 = -\mu \tag{4.3.15}$$

$$\chi_2 = \frac{-(\mu\sigma^3 + \mu^3\sigma + 2\mu^2\sigma^2 + 2\kappa\mu\sigma^2 + 2\kappa\mu^2\sigma + \kappa^2\mu\sigma + I\gamma\mu^2 + I\gamma\sigma^2 + 2I\gamma\mu\sigma) - \sqrt{\Delta}}{2(\mu^3 + 2\mu^2\sigma + \kappa\mu^2 + \mu\sigma^2 + \kappa\mu\sigma)} \tag{4.3.16}$$

$$\chi_3 = \frac{-(\mu\sigma^3 + \mu^3\sigma + 2\mu^2\sigma^2 + 2\kappa\mu\sigma^2 + 2\kappa\mu^2\sigma + \kappa^2\mu\sigma + I\gamma\mu^2 + I\gamma\sigma^2 + 2I\gamma\mu\sigma) + \sqrt{\Delta}}{2(\mu^3 + 2\mu^2\sigma + \kappa\mu^2 + \mu\sigma^2 + \kappa\mu\sigma)} \tag{4.3.17}$$

$$\begin{aligned} \Delta = {} & I^2\gamma^2\mu^4 + 4I^2\gamma^2\mu^3\sigma + 6I^2\gamma^2\mu^2\sigma^2 + 4I^2\gamma^2\mu\sigma^3 + I^2\gamma^2\sigma^4 - 4I\gamma\kappa^2\mu^4 - 10I\gamma\kappa^2\mu^3\sigma \\ & - 8I\gamma\kappa^2\mu^2\sigma^2 - 2I\gamma\kappa^2\mu\sigma^3 - 8I\gamma\kappa\mu^5 - 28I\gamma\kappa\mu^4\sigma - 36I\gamma\kappa\mu^3\sigma^2 - 20I\gamma\kappa\mu^2\sigma^3 \\ & - 4I\gamma\kappa\mu\sigma^4 - 4I\gamma\mu^6 - 18I\gamma\mu^5\sigma - 32I\gamma\mu^4\sigma^2 - 28I\gamma\mu^3\sigma^3 - 12I\gamma\mu^2\sigma^4 - 2I\gamma\mu\sigma^5 \\ & + \kappa^4\mu^2\sigma^2 + 4\kappa^3\mu^5 + 8\kappa^3\mu^4\sigma + 8\kappa^3\mu^3\sigma^2 + 4\kappa^3\mu^2\sigma^3 + 12\kappa^2\mu^6 + 36\kappa^2\mu^5\sigma \\ & + 42\kappa^2\mu^4\sigma^2 + 24\kappa^2\mu^3\sigma^3 + 6\kappa^2\mu^2\sigma^4 + 12\kappa\mu^7 + 48\kappa\mu^6\sigma + 76\kappa\mu^5\sigma^2 + 60\kappa\mu^4\sigma^3 \\ & + 24\kappa\mu^3\sigma^4 + 4\kappa\mu^2\sigma^5 + 4\mu^8 + 20\mu^7\sigma + 41\mu^6\sigma^2 + 44\mu^5\sigma^3 \\ & + 26\mu^4\sigma^4 + 8\mu^3\sigma^5 + \mu^2\sigma^6 \end{aligned} \tag{4.3.18}$$

Hence three case occur and its conclusion are :

Case 1: If $\Delta < 0$ then χ_2 and χ_2 are complex conjugates with negative real parts, so that critical point E_2 is a stable spiral.

Case 2: If $\Delta = 0$ then χ_2 and χ_3 both are equal negative real number so that critical point E_2 is a stable node.

Case 3: If $\Delta > 0$ then χ_2 and χ_3 is always be distinct negative real number. Hence model forms stable node at equilibrium point E_2.

As determined by Theorem 3.1 from the reference [44], the model was found to exhibit stability in all instances.

4.4 Control Strategy

We developed a new fuzzy control that takes the inputs, which are the rate of diabetes and the number of people sensitive to it, and determines the minimal awareness percentage. The control variable $U(t)$ represents the optimal awareness percentage over the total population and practically, it will be achieved through media and other diabetic education program. The Mamdani fuzzy system-based fuzzy optimal controller has two input linguistic variables and one output linguistic variable. The first input linguistic variables $\frac{dS}{dt}$ and second input variable $\frac{dD}{dt}$ which represent the rate of change in population of susceptible and diabetic people, receptively. In FLC, the output linguistic variable is given as the percentage of people aware of diabetes. The following system of differential equations provides a mathematical control system.

$$\left.\begin{aligned} \frac{dS(t)}{dt} &= I - \mu S(t) - \gamma(1-U(t))S(t)D(t) \\ \frac{dD(t)}{dt} &= \gamma(1-U(t))S(t)D(t) - \mu D(t) - \kappa D(t) + \sigma M(t) \\ \frac{dM(t)}{dt} &= \kappa D(t) - \mu M(t) - \sigma M(t) \end{aligned}\right\} \tag{4.4.1}$$

In order to design the fuzzy logic controller the features of input and output variables are shown in Table 4.1 and 4.2, respectively.

Fig 4.2 and Fig 4.3 exhibit the graphical representations of input variables, respectively. The membership functions of fuzzy sets are taken according to the classical

Input Variables	Interval	Membership Functions		
$\frac{dS}{dt}$	[-1 1]	Negative	zero	Positive
$\frac{dD}{dt}$	[-1 1]	Negative	Zero	Positive

Table 4.1: Characteristics of Input Variables

Output Variables	Interval	Membership Functions	
Diabetic Awareness (%)	[0 1]	Decreasing	Increasing

Table 4.2: Characteristics of Output Variables

fuzzy classified function. The input variables of FLC is defined using the triangle membership function. We assumed that if awareness is between 0% and 5%, it is

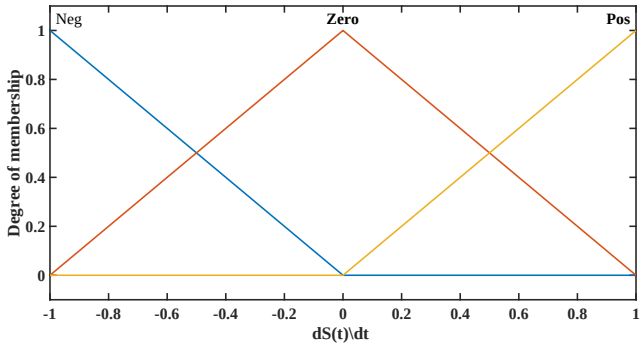

Figure 4.2: Membership Function of first input Variable

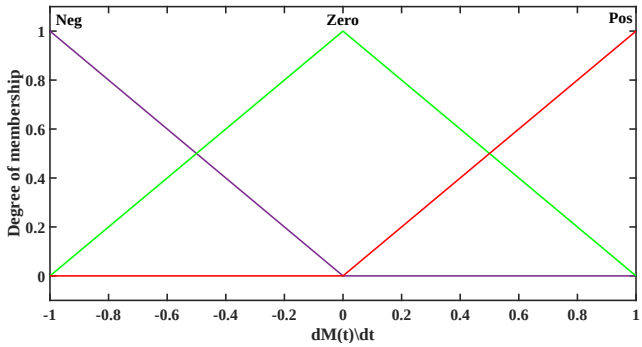

Figure 4.3: Membership function of second input variable

likely to be insignificant in a large population, so we considered as it no awareness in the population. Similarly, if awareness is between 95% and 100%, it can be assumed that the almost entire population is having awareness about the disease. The trapezoidal membership function has been used for defined the output of FLC. The graphical representation is pictured in Fig 4.4.

The structure of the input and output fuzzy sets was used to define nine IF-THEN

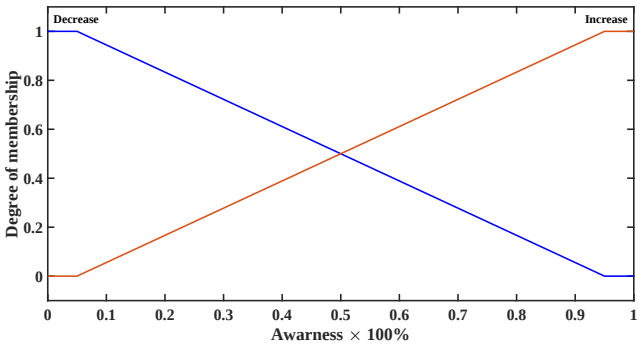

Figure 4.4: Membership function of output variable

rules. These AND (minimum) type antecedent rules were used to reduce the number of diabetic patients. The input and output membership function were coupled to the IF-THEN fuzzy rules. The centroid approach was used for defuzzification. The controller's fuzzy rules are shown in Table 4.3.

	$\frac{dD(t)}{dt}$		
$\frac{dS}{dt}$	Neg	Zero	Pos
Neg	Decreasing	Decreasing	Increasing
Zero	Decreasing	Increasing	Increasing
Pos	Decreasing	Increasing	Increasing

Table 4.3: Fuzzy Rules of FLC

The pictorial diagram of fuzzy logic controller is represented by Fig 4.5. Figure 4.6 shows the graphical structure of control surface.

4.5 Numerical Simulation & Results

This section presents the results of numerically solving the optimality system (4.2.1). All computations were performed using MATLAB 2012(b) with the aid of the fuzzy toolbox. The initial population of each compartments is S_0 = 100, D_0 = 10.5 and M_0 = 2 millions, respectively. The model's parameters [52, 95] are considered according to the following Table 4.4

Figure 4.7 depicts the paths of all system (4.2.1) variables, which begin at various initial conditions. The solution convergences to the equilibrium point, which demonstrates that the model has a stable saddle node.

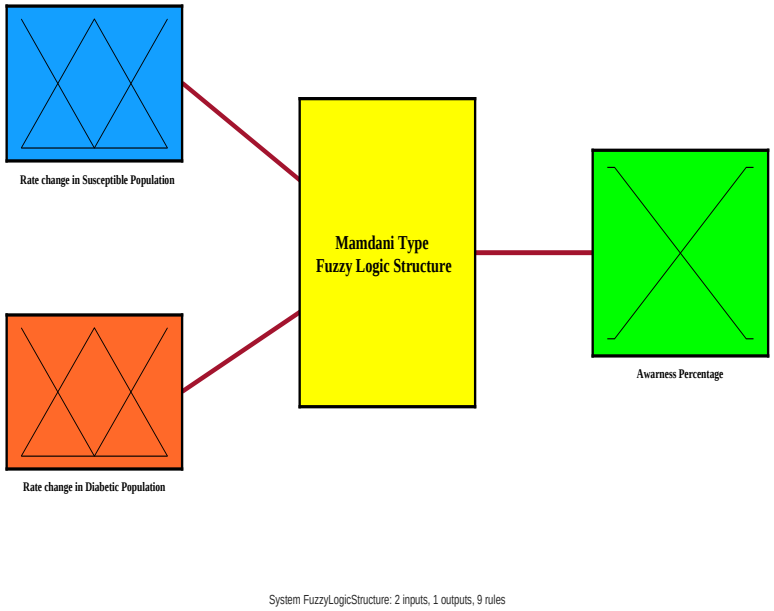

Figure 4.5: Graphical structure of fuzzy logic controller

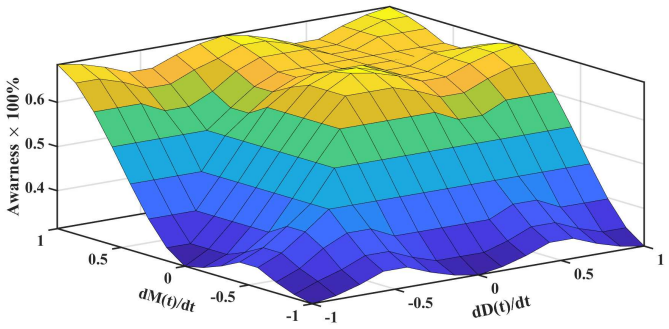

Figure 4.6: Control surface

Parameter	Values	Units	Biological meaning
μ	0.0390	$\frac{1}{years}$	Natural mortality
γ	0.05	$\frac{years}{millions}$	Incidence rate of diabetes
I	1.25	$\frac{millions}{years}$	Recruitment rate of healthy people
κ	0.15	$\frac{1}{years}$	Rate of diabetes managed people
σ	0.25	$\frac{1}{years}$	Incidence rate of diabetes recurrence

Table 4.4: Value of model's parameters used in numerical simulation

We obtained the disease equilibrium points E_2(1.1848, 256.3897, 133.0742) on taking the data set from Table 4.4. Figure 4.8 shows that in the presence of a control variable in the system (4.2.1), the model's trajectories goes toward a equilibrium point which pictured a stable saddle node. It shows under the control variables, model

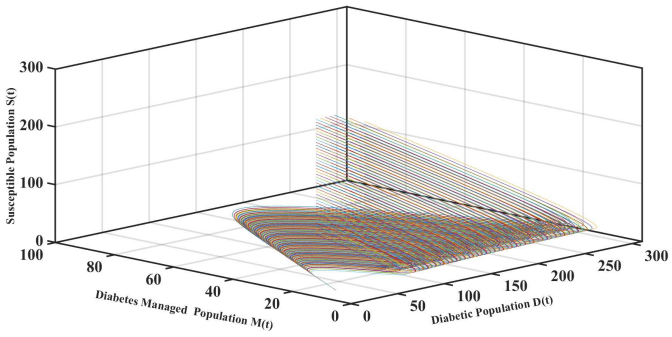

Figure 4.7: Graph of Phase Portrait of model without controller

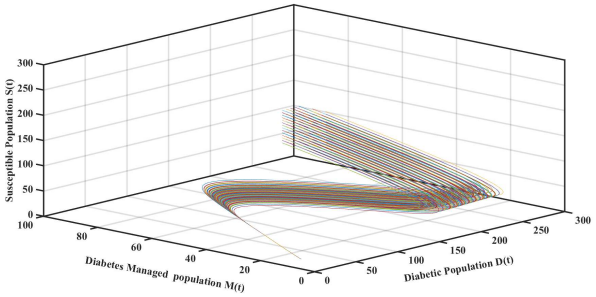

Figure 4.8: Graph of Phase Portrait of model with controller

became stable for all time. We obtained that the disease equilibrium points E_2(1.17, 256.23, 133.165) in the presence of control variable in model.

Figure 4.9 depicts a comparison of the simulation of susceptible individuals with and without the FL controller in model. We observe that after raising diabetes awareness for five years, the number of people vulnerable to diabetes increased by 40.84%. This increase is because diabetes awareness programs create curiosity in the common public to get themselves tested for disease at regular interval.

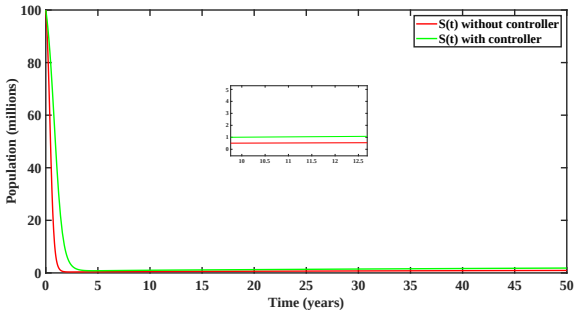

Figure 4.9: Time series of susceptible people population

Figure 4.10 shows an intriguing result that after disseminating diabetes awareness to the entire population, the susceptible population increases significantly at 7 months,

then slowly for the next 4 year and three month. After five year, there is a small growth in the sensitive population, leading to the conclusion that conducting awareness initiatives further is no longer helpful. Since according to Saeedi et al. [149] one-half of people with disease (50.1%) , therefore this results can be proved extremely helpful in reducing the unaware population significantly and therefore in managing the development and further severity of the disease.

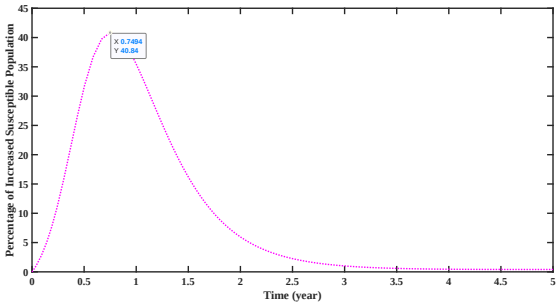

Figure 4.10: Percentage error in Susceptible population

Figure 4.11 illustrates the considerable change in the diabetic population in the presence and absence of the FLC strategy in system. We can see that if we undertake a diabetes awareness campaign across the population for five years, the number of diabetic patients drops by 38.66%. This reduction has happened because they are aware of the symptoms of diabetes, so patients start managing diabetes on their own by doing regular physical exercise, following a healthy lifestyle, avoiding junk food, and following other preventing and treating measure. This Fig 4.12 demonstrates that the

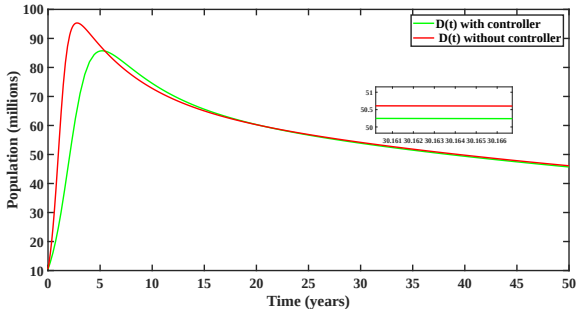

Figure 4.11: Time series of diabetes population

diabetes population decreased by 38.86 % in the first seven months after the complete community was exposed to the awareness program. After that, it continues to

decline for the next one year and three months, with just a 0.32% growth in the diabetic population for the next three year. This finding demonstrate a very important results that awareness program should not run unnecessarily for long duration then required which may have economic burden while this amount can be utilized in the management of the disease. The findings of the controlled diabetes population ob-

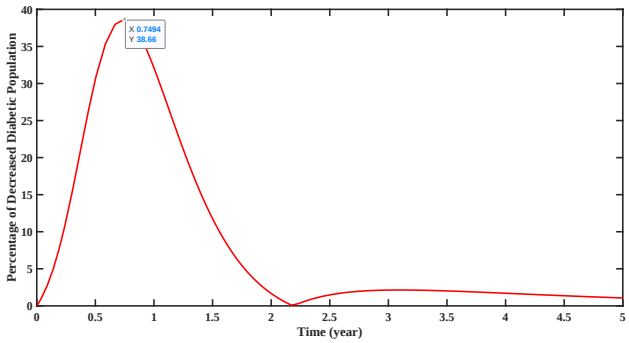

Figure 4.12: Percentage error in Diabetic population

tained with and without the implantation of FLC are shown in Fig 4.13. It is clear from the figure that the impact of the awareness program reduces the population of managed diabetes by 4.4%. This is due to the fact that diabetes awareness initiatives tend to reduce the diabetic population, resulting in a slight drop in the diabetes-managed population when compared to the managed population without a diabetes awareness campaign. Figure 4.14 shows that one year and seven months following the aware-

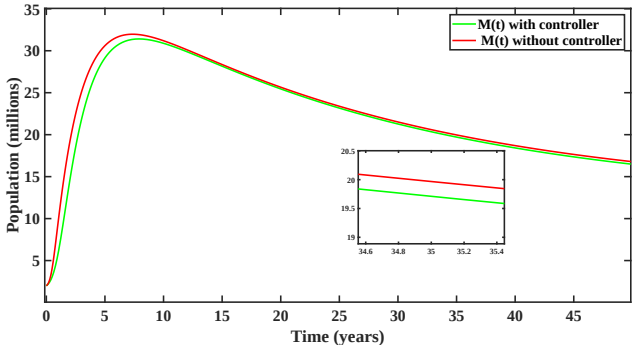

Figure 4.13: Time series of diabetes managed population

ness campaign, the managed population immediately decreases, and then gradually decreases over the next three year and three month, from 4.4% to 1.5%. In order to show that in next couple of years proposed controller will work effectively, we have

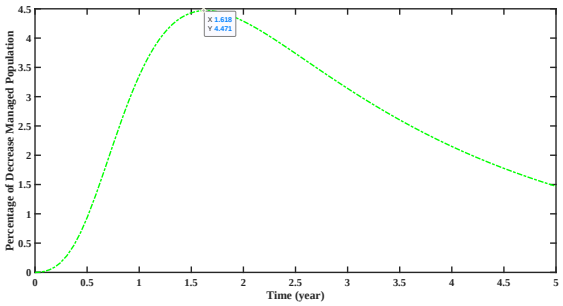

Figure 4.14: Percentage error of diabetes managed population

considered the large variations in transmission and recruitment rate of diabetes population. We plot graphs of diabetes populations at various values of β, assuming that the transmission rate will grow by 2.5 times in the following fifty years. Fig 4.15 highlights the trajectory of diabetes population on taking the β = 0.05, 0.08, 0.10, and 0.12.

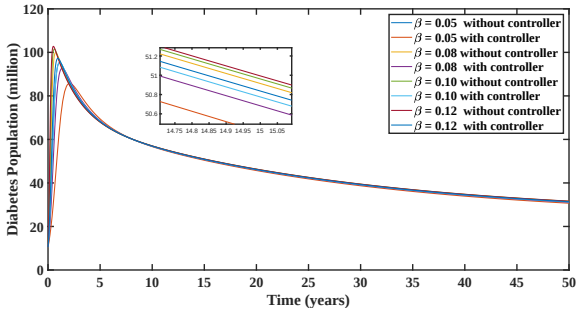

Figure 4.15: Diabetes population on varying transmission rate (β) at $I = 1.50$

Since diabetes is a disease that worsens over time, we expect the recruitment rate to rise to 50% of what it is now. We used I = 1.50, 2.0, 2.50, and 3.0 to examine the impact of diabetes knowledge. We can see from the Fig 4.16 that the proposed FL controller is capable of reducing the diabetes population on increment of diabetes recruitment rate.

4.6 Conclusion and Future Works

The worldwide rise of diabetes is placing an increasingly heavy burden on the healthcare system, but this study provides a promising solution. Through the implementation of a Mamdani type fuzzy logic controller in a three-compartment mathemat-

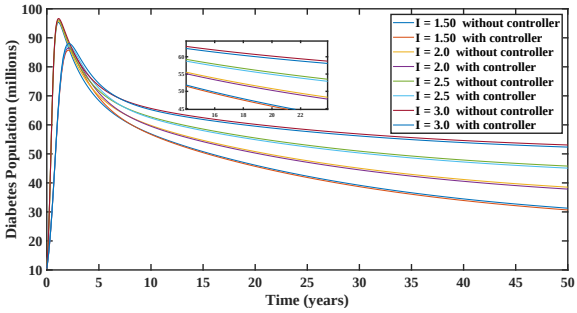

Figure 4.16: Diabetes population on varying recruitment rate (I) at $\beta = 0.05$

ical model, the researchers were able to determine the optimal population awareness of diabetes. The results demonstrated the highly effective reduction of the diabetic population by 40% within just five years, alongside an increase in the susceptible population. Although the authors' optimal controller design had significant reductions in patients with treatable, serious, and complicated diabetes, it was complex and costly. This study emphasizes the importance of cost-effective and time-efficient diabetes awareness campaigns, with future research incorporating type-2 fuzzy logic and fuzzy differential equation models to further improve fuzzy logic controllers.

Chapter 5

Diabetes Management in Insulin-dependent Patients using Computer-controlled Fuzzy Inference Structure Technique

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This current chapter focuses on the development of a fuzzy logic control technique to maintain glucose levels within a normal range despite time lags in insulin secretion, absorption, and action, which can lead to ultradian oscillations in glucose dynamics outside the normal range in diabetic patients. To address this, a nonlinear delay mechanism is incorporated, which limits the oscillation and maintains glucose levels in a healthy range. The delay of more than 15 minutes without insulin action, and more than 38 and 43 minutes with insulin secretion delays of 10 and 15 minutes respectively, can lead to unhealthy glucose levels. Four experiments were conducted on the model, including meal disturbance, no meal disturbance, ingesting unusual meals, and uncertainty in the model's parameters. The proposed mechanism not only maintains glucose levels in a healthy range but also limits the oscillation of the glucose-insulin dynamic, similar to that of healthy individuals in each experimental

setup, which has not been reflected in other existing control techniques [161, 183]. These findings suggest that fuzzy-based intelligence techniques can be used in the development of an artificial pancreas for clinical patients.

5.1 Introduction

Maintaining the ultradian oscillation of glucose dynamics like healthy patients is a challenging but important goal in the diabetes care. In healthy individuals, the regular fluctuations in blood glucose levels occur in a cyclical pattern and are tightly controlled within a narrow, healthy range. However, in individuals with diabetes, these oscillations can become erratic, leading to unstable blood glucose levels and a higher risk of complications. Unfortunately, traditional treatment methods are unable to limiting the amplitude of ultadian oscillation and fully address the difficulties associated with unpredictable meal times, multiple meals, and varying physiological responses, which can lead to unstable blood sugar levels and complications. However, the emergence of artificial pancreas technology is revolutionizing diabetes management by offering patients a solution that can adapt to their unique needs. With the use of sophisticated algorithms, the artificial pancreas can continuously monitor glucose levels in real-time and administer insulin precisely as needed, regardless of a patient's eating patterns or individual physiological responses. This cutting-edge technology empowers patients with an unprecedented level of control over their diabetes management, providing a much-needed solution to the challenges that traditional treatment methods cannot address. By automating insulin delivery and monitoring, the artificial pancreas offers a transformative approach to diabetes management that promises to improve the quality of life for patients and reduce the risk of life-threatening complications. In recent years, research has focused on developing computer-controlled systems to automate insulin delivery and provide a more effective and efficient approach to diabetes management. One such system is the Fuzzy Inference Structure Technique, which utilizes fuzzy logic to create a closed-loop insulin delivery system for individuals with type 1 diabetes. This technique has shown promising results in controlling blood glucose levels and reducing the risk of complications associated with the disease

Recent studies have explored the potential of Fuzzy Logic Controllers (FLC) in insulin therapy, resulting in a sensitive and secure approach to monitoring a patient's vi-

tal signs. Grant [70] reported on the successful application of FLC schemes for insulin delivery to diabetic patients based on a closed-loop strategy. Several researchers [1, 6, 9, 36, 66, 81, 82, 87, 92, 106, 144, 152] have proposed various types of fuzzy controllers, including fuzzy-PID, interval type-2 fuzzy, and Mamdani-type structures, for regulating glucose levels in insulin-dependent patients. These controllers have been shown to improve system performance and quality, offer quick responses, and dynamically respond to different glycaemic challenges. Moreover, some of these controllers do not require the mathematical form of the diabetic system and provide personalized dosage, making them suitable for practical applications such as insulin infusion micro-pumps. The results of these studies suggest that fuzzy logic controllers offer a promising approach for diabetes management.

Studies suggest that mathematical models based on nonlinear delay differential equations are more effective in predicting glucose-insulin dynamics compared to models based on nonlinear ordinary differential equations. The DDE model used in this study considers the time delays that occur in insulin secretion, absorption, and endogenous glucose production, which are the primary causes of diabetes. Recent controller designs, such as those by Gaz et al.[64], and Soylu et al. [161], have employed the DDE architecture that includes the glucose volume factor to maintain glucose levels within a safe range. However, these designs have not been able to reduce the amplitude of ultradian oscillations that are an important part of healthy insulin dynamics and appear after two hours in the metabolic system. To address this issue, Saloni et al. [141] proposed a delay interval for glucose management, but it can be challenging to maintain the proper interval for delay parameters. In this study, we investigate the effect of disruptions in the delay interval on glucose concentration and aim to regulate glucose levels within a physiological range with the help of a controller

Our model utilizes a controller to regulate glucose levels even when the delay parameter value is increased, which is a common occurrence in diabetic patients. The mathematical model applied in this study overcomes the challenges of maintaining strict delay parameter intervals and preventing hypoglycemia, which are important

considerations in closed-loop strategies such as those used in artificial pancreas systems.

5.2 Problem Statement and Control Strategy

The regulation of blood glucose levels is a significant challenge in the treatment of Type-1 Diabetes Mellitus (T1DM), a condition in which patients either lack insulin production or have difficulty in absorbing it. This results in high levels of glucose in the blood, which can exceed the normal range of 90 mg/dL. To address this issue, a better control system is required that can keep blood glucose levels within the range of 90 to 100 mg/dL, despite the varying doses and factors that impact glucose-insulin dynamics, such as delays in insulin secretion and absorption, as well as factors like diet, exercise, and stress. To tackle this challenge, a two-delay mathematical model of the glucose-insulin system has been proposed, which incorporates the time lags in insulin secretion and absorption that are common in T1DM patients. The proposed control system uses a closed-loop feedback architecture, where the controller's goal is to regulate the glucose concentration to the target range despite different disturbances. The model comprises two crucial factors: the glucose concentration rate and insulin concentration rate. The glucose concentration rate is maintained by functions f_2, f_3, and f_4, while the insulin concentration rate is regulated by the f_1 function. The glucose space (V_g) is the most crucial element of the regulatory system and appears in all functions except f_4. The inputs for the controller are the glucose level and rate, and based on this information, the controller calculates the output, which is the glucose volume. The controller then signals the artificial pancreas to release the necessary amount of insulin to regulate glucose levels using the calculated value of V_g. To regulate sugar levels, the V_g parameter of the f_3 function is chosen to be controlled by the controller, as described by the following equation:

$$f_3(G) = \frac{G}{C_3(V_g - U)} \tag{5.2.1}$$

The glucose level (mg/dl) is denoted by G, and the control input is denoted by U.

5.3 Modeling of Glucose Insulin Regulatory System

The delay term in the glucose-insulin model is chosen to represent the physiological processes involved in glucose regulation in the body more accurately, which are subject to time lags. Time delays play a crucial role in glucose regulation, such as delays in insulin secretion, hepatic glucose production, glucose absorption by insulin-dependent cells, and insulin therapies. For the purpose of development of closed-loop control system, we adopted a model that reflects insulin functionality and glucose volume distribution parameters, which can be represented by mathematical equations: [77, 141]:

$$\left.\begin{aligned} \frac{dG}{dt} &= G_{in}(t) - f_2(G(t-\tau_1)) - f_3(G(t))f_4(I(t-\tau_2)) + 150 \\ \frac{dI}{dt} &= f_1(G(t-\tau_1)) - d \cdot I(t) \end{aligned}\right\} \tag{5.3.1}$$

with the initial conditions $G(t) = G_0$ for $t \in [-\tau_1, 0]$ and $I(t) = I_0$ for $t \in [-\tau_2, 0]$. Parameter d denotes the self degradation rate of insulin. G_{in} is meal intake rate. The biological meaning of parameter of functions of model is taken from the Table 2.1

5.4 Mathematical Analysis of Model

In this section, we discus the positive solution of the model, the boundedness of the solution, and the stability of the system.

Assume Ω is a subset of $\mathbb{R} \times \mathbb{C}$, $f : \Omega \to \mathbb{R}^n$ is a given function, then

$$\dot{x}(t) = f(t, x_t) \tag{5.4.1}$$

a related delay differential equation on Ω.

Lemma 5.4.1. *Considered the following delay differential equation:*

$$\ddot{x}(t) + p\dot{x}(t) + qx(t) + rx(t-\tau) = 0, \tau \geq 0$$

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

$$\lambda^2 + p\lambda + q + re^{-\lambda\tau} = 0, \tau \geq 0 \tag{5.4.2}$$

can be zero, one, or two only.

1. *If the condition q>r and* $2q - p^2 < 0$ *and* $2q - p^2 < 2\sqrt{q^2 - r^2}$ *is satisfied, there are no non-zero solutions for* $\tau > 0$ *of Eq* (5.4.2)*, and the trivial (zero) solution is stable for all* $\tau > 0$*.*

2. *For q < r and* $2q - p^2 > 0$*, there exists one root for* $\tau > 0$*. The trivial (zero) solution of Eq.* (5.4.2) *is uniformly asymptotically stable for* $\tau < \tau_0$ *and unstable for* $\tau > \tau_0$*, where* τ_0 *is a positive constant.*

3. *For* $q > r$ *with* $2q - p^2 > 0$ *and* $2q - p^2 > 2\sqrt{q^2 - r^2}$*, two roots exist for* $\tau > 0$ *and the stability of the trivial (zero) solution of Eq* (5.4.2) *can change as* τ *increases, ultimately becoming unstable.*

Theorem 5.4.2. *In Eq* (5.4.1)*, suppose* Ω *is an open subset in* $\mathbb{R} \times \mathbb{C}$ *and f is a continuous on* Ω*. If* $(\sigma, \phi) \in \Omega$ *then there is a solution of Eq* (5.4.1) *passing through* (σ, ϕ)*. We say* $f(t, \phi)$ *is Lipschitz in* ϕ *in a compact set K of* $\mathbb{R} \times \mathbb{C}$ *if there is a constant k>0 such that for any* $(t, \phi_i) \in$ *K, i=1,2*

$$|f(t, \phi_1) - f(t, \phi_2)| \leq k|\phi_1 - \phi_2|$$

Theorem 5.4.3. *Suppose* Ω *is an open set in* $\mathbb{R} \times \mathbb{C}$*,* $f : \Omega \to R_n$ *is continuous and f(t, phi) is Lipschitz in* ϕ *in each compact set in* Ω*. If* $(\sigma, \phi) \in \Omega$ *then there is a unique solution of Eq* (5.4.1) *passing through* (σ, ϕ)*.*

Theorem 5.4.4. *Suppose* Ω *is an open set in* $\mathbb{R} \times \mathbb{C}$*,* $f : \Omega \to R^n$ *is completely continuous, and x is a noncontinuable solution of Eq* (5.4.1) *on* $[\sigma - r, b]$*. Then for any closed bounded set* $\mathbb{U}$ *in* $\mathbb{R} \times \mathbb{C}$*,* $\mathbb{U} \subset \Omega$ *there is a* t_U *such that* $(t, x_t) \notin \mathbb{U}$ *for* $t_U \leq t < b$*.*

5.4.1 Positiveness and boundedness of the model's solution

Assuming that Section 2 of Chapter 2 in the same document provides conditions that the functions f_i, $i = 1,2,3,4$ in model $(2.2.1)$ must satisfy for the analysis to be valid, we assume that these conditions hold for all the functions in the model.

Cond1: If $\lim_{x\to\infty} f_3(x) > (G_{in} - F_2 + c)/f_4$, the model in $(5.3.1)$ will have a single, positive steady state (G,I) where $I = d^{-1}f_1(G)$. Additionally, all solutions will exist in the interval $(0,\infty)$ and will be both positive and bounded.

Cond2: If $\lim_{x\to\infty} f_3(x) < (G_{in} - F_2 + c)/f_4$, then $\lim_{x\to\infty}$sup $G(t) = \infty$.

Proof of Cond1: Let us assume the equation

$$A(x) = G_{in} - f_2(x) - f_3(x)f_4(d^{-1}f_1(x)) + c = 0, x \geq 0 \tag{5.4.3}$$

Claim 1: Eq $(5.3.1)$ has unique root in (0,∞)

Proof: Observe that $f_1'(x) > 0$, $f_2'(x) > 0$, $f_3'(x) > 0$, $f_4'(x) > 0$, we have

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

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

$$\begin{aligned}
\lim_{x\to\infty} A(x) &= G_{in} - \lim_{x\to\infty} f_2(x) - \lim_{x\to\infty} f_3(x)f_4(d^{-1}f_1(x)) + c \\
&= G_{in} - F_2 - f_4(d^{-1}F_1)\lim_{x\to\infty} f_3(x) + c \\
&< G_{in} - F_2 - f_4\lim_{x\to\infty} f_3(x) + c > 0
\end{aligned}$$

which implies $A(0) > 0$, and $\lim_{x\to\infty} A(x) < 0$. Hence by Mean Value Theorem, Eq $(5.4.3)$ has unique root in (0,∞). It is clear that G^* is a root of and $I^* = d^{-1}f_1(G*)$. Note that $|f_i'(x)|$, i = 1,..,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$([-max\{\tau_1,\tau_2\},0])$ respectively. Then by theorem5.4.2, theorem5.4.2, theorem5.4.2, the solution of the model with the given

initial condition exists and is unique for all $t \geq 0$.

It is noted that insulin appears to assist the cells in metabolizing adequate glucose, according to condition Cond1. If Cond2 is true, the glucose concentration level won't be constrained, and the system won't work. Therefore, throughout this work, we will assume that Cond1 is true in order to preserve the system's viability.

Claim 2: The solution $(G(t), I(t))$ of the model (5.3.1) is positive.

Proof. Suppose that, there exists a t_0 such that $G(t_0) = 0$ and $G(t) > 0$ for $0 < t < t_0$, then $G'(t_0) \geq 0$. So we have

$$\begin{aligned} 0 \geq G'(t_0) &= G_{in} - f_2(G(t_0)) - f_3(G(t_0))f_4(I(t_0 - \tau_2)) + c \\ &= G_{in} - f_2(0) - f_3(0)f_4(I(t_0 - \tau_2)) + c \\ &= G_{in} + c > 0 \end{aligned}$$

which is a contradiction. Hence $G(t) > 0$ for all $t > 0$. If there exists a t_0 such that $I(t_0) = 0$ and $I(t) > 0$ for $0 < t < t_0$. Therefore,

$$I(t_0) = f_1(G(t_0)) - dI(t_0 - \tau_2) \geq f_1(G(t_0)) > 0$$

Since it is a contradiction, it follows that $I(t)$ must be greater than 0 for all $t > 0$. As a result, the solution $(G(t), I(t))$ of the model is positive.

Claim 3: The solution $(G(t), I(t))$ of the model (5.3.1) is bounded for $t > 0$.

Proof: If $lim_{t\to\infty} G(t) = \infty$, then there exist a sequence $< t_n >$ such that $\lim_{n\to\infty} G(t_n) = \infty$ and $G'(t_n) \geq 0$. Thus

$$\begin{aligned} 0 < G'(t_n) &= G_{in} - f_2(G(t_n)) - f_3(G(t_n))f_4(I(t_n - \tau_2)) + c \\ &= G_{in} - f_2(G(t_n)) - f_4 f_3(G(t_n)) + c \end{aligned}$$

Therefore,

$$0 \leq \lim_{n\to\infty} G'(t_n) \leq G_{in} - \lim_{n\to\infty} f_2(G(t_n)) - f_4 \lim_{n\to\infty} f_3(G(t_n)) + c$$
$$\leq G_{in} - F_2 - f_4 \lim_{x\to\infty} f_3(x) + c < 0$$

It shows that there exist a $F_G > 0$ such that $G(t) < F_G$ for all $t > 0$, which is contradiction. Hence $G(t)$ is bounded above. Since $|f_1(x)| \leq F_1$, for all $\varepsilon > 0$,

$$0 < I'(t) \leq f_1(F_G + \varepsilon) - dI(t) \text{for large t} > 0$$

which implies

$$\lim_{t\to\infty} sup\ I(t) \leq d^{-1} f_1(F_G + \varepsilon)$$

The inequality $\lim_{t\to\infty} \sup I(t) \leq d^{-1} f_1(F_G) = F_I$ implies that the supremum of $I(t)$ as t approaches infinity is bounded above by F_I for all $\varepsilon > 0$. This implies $I(t)$ is bounded above.

Proof of Cond2: If the limit of $f_3(x)$ as x tends to infinity is greater than or equal to $(G_{in} - F_2 + c)/f_4$, there is a continuous decrease in glucose utilization, leading to an increase in glucose concentration until $f_3(x)$ approaches $(G_{in} - F_2)/f_4$ as x approaches infinity, and the upper limit of glucose concentration tends towards infinity when $f_3(x)$ is less than $(G_{in} - F_2)/f_4$. This situation contradicts human physiology. As the steady-state is unique for any system, the inequality $(G_{in} - F_2)/f_4 \leq \lim_{x\to\infty} f_3(x) < (G_{in} - F_2 + c)/f_4$ becomes infeasible.

5.4.2 Stability analysis of model

The linearized form of the non-linear model (5.3.1) around the steady state (G^*, I^*) is given as follows:

$$\left.\begin{aligned} \frac{dG}{dt} &= -PG(t) - QI(t-\tau_2) \\ \frac{dI}{dt} &= R(G(t-\tau_1)) - d \cdot I(t) \end{aligned}\right\} \tag{5.4.4}$$

where $P = f_2'(G^*) + f_3'(G^*)f_4(I^*) > 0, \quad Q = f_3(G^*)f_4'(I(t)) > 0, \quad R = f_1'(G^*) > 0$

The characteristics equation is given as

$$\lambda^2 + (P+d)\lambda + Pd + QRe^{-\lambda(\tau_1+\tau_2)} = 0 \tag{5.4.5}$$

Case 1. τ_1=τ_2=0. The Eq (5.4.5) can be written as:

$$\lambda^2 + (P+d)\lambda + Pd + QR = 0 \tag{5.4.6}$$

and $P+d > 0, Pd+QR > 0$ implies (G^*, I^*) is stable.

Case 2. $\tau_1 > 0$, $\tau_2 = 0$. The characteristics equation is

$$\lambda^2 + (P+d)\lambda + Pd + QRe^{-\lambda(\tau_1)} = 0 \tag{5.4.7}$$

The inequality $2q - p^2 = -P^2 - d^2 < 0$ implies that $Pd > QR$. As a result, according to lemma 5.4.1, the trivial solution of the linearized model (5.4.4) is always stable for $\tau_1 > 0$. Additionally, if $Pd < QR$, then there exists a value $\tau_{1,0} > 0$ such that the trivial solution of the linearized model (5.4.4) is stable for $\tau_1 \in (0, \tau_{1,0})$ and unstable for $\tau_1 \geq \tau_{1,0}$. This is based on lemma 5.4.1.

Case 3: The same outcomes will be produced for the scenario where $\tau_1 = 0$ and $\tau_2 > 0$ because the characteristic equation remains unchanged (only need to replace τ_2 with τ_1 in Eq. (5.4.7)).

Case 4: $\tau_1 > 0$, $\tau_2 > 0$. Let $\lambda = i\xi$, $\xi > 0$ be an eigenvalue of Eq (5.4.5) , then we have,

$$-\xi^2 + (P+d)i\xi + Pd + QR(cos(\tau_1+\tau_2)\xi - isin(\tau_1+\tau_2)\xi) = 0 \tag{5.4.8}$$

We have,

$$-\xi^2 + Pd + QRcos(\tau_1+\tau_2)\xi = 0 \tag{5.4.9}$$

$$(P+d)\xi - QRsin(\tau_1+\tau_2)\xi = 0 \tag{5.4.10}$$

This leads to

$$\xi^4 + (P^2 + d^2)\xi^2 + P^2 d^2 = Q^2 R^2$$

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

5.5 Controller's Methodology

The Fuzzy Optimal Controller based on the Mamdani Fuzzy System has two input variables (glucose level G(t) and its rate of change $\frac{dG}{dt}$) and one output variable (insulin volume in the Fuzzy Logic Controller). The input linguistic variables are described in Table 5.1 and the output linguistic variable is described in Table 5.2.

Input Variables	Interval	Membership Functions				
Glucose Level G(t) (mg/dl)	[40 300]	Negative Big	Negative Small	zero	Positive Small	Positive Big
Glucose Deviation dG/dt	[-0.5 0.5]	Negative	Zero	Positive		

Table 5.1: Characteristics of Input Variables

Output Variables	Interval	Membership Functions				
Volume of glucose (v_g)	[-15 5]	Negative Big	Negative Small	Zero	Positive Small	Positive Big

Table 5.2: Characteristics of Output Variables

The membership functions of the fuzzy sets are selected based on the fuzzy classification of the input and output variables and are depicted using triangular membership functions. Figure 5.1 and fig 5.2 provide graphical representation of the input and output variables, respectively.

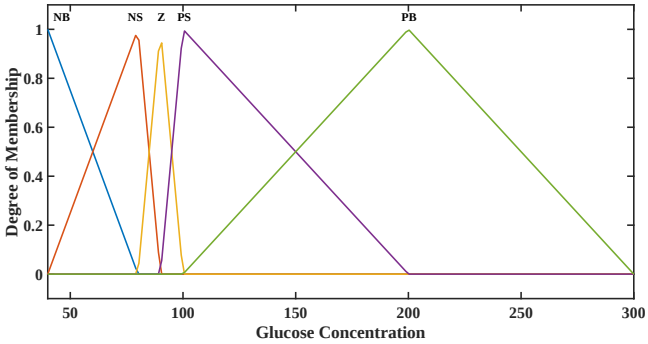

Fig 5.1(a). Glucose Concentration

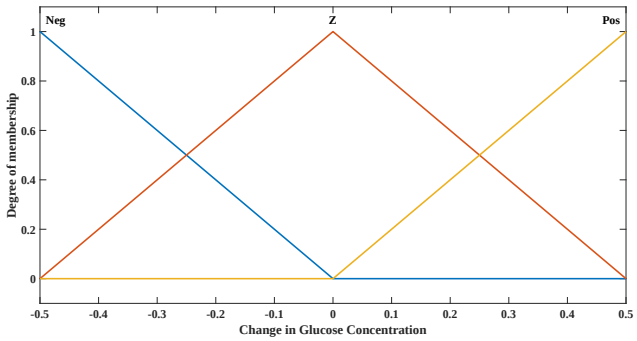

Fig 5.1(b). The rate of Change in Glucose Con.

Figure 5.1: Membership Function of Input Variables

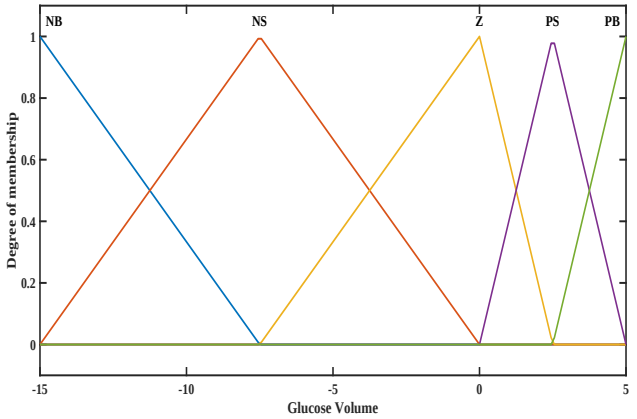

Figure 5.2: Membership function of output variable

To reduce the error between desired and actual glucose concentration, fifteen fuzzy rules with AND type antecedent were developed. These rules were connected to input and output membership functions, and the CENTROID defuzzification method was employed to obtain a crisp value. Table 5.3 shows the fuzzy rules.

	Change in Glucose Rate		
Glucose level rate	Negative	Zero	Positive
NB	NB	NB	NB
NS	NS	NB	Z
Z	Z	Z	PS
PS	PB	PB	PS
PB	PS	PS	PB

Table 5.3: Fuzzy Rules

The Fig 5.3 shows the surface view of control action.

It is a three-dimensional surface that shows how the glucose volume changes in response to changes in the glucose level and change in glucose level.

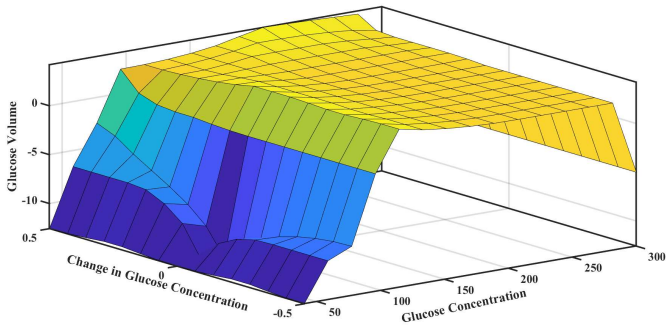

Figure 5.3: Control Surface

5.6 Numerical Simulations

The numerical simulations of the two-delay model were performed using the DDE23 solver in MATLAB 2012b. According to authors in [141], insulin secretion in the glucose-insulin dynamics exhibits ultradian oscillations in a normal person within the range of (50 - 150) minutes, and the same oscillatory behavior is observed in type 1 diabetic individuals within the range of (50 - 200) minutes. Within this range, the glucose concentration oscillates from 105 mg/dl to 145 mg/dl in type 1 diabetic people. The authors established an interval for delay parameters that maintain normal glucose levels. However, following this strict interval is challenging. In this study, we aim to examine the effect of variations within this interval on glucose concentration and apply a fuzzy logic controller to control glucose even when the delay parameters increase, which may occur frequently in real life. The FLC controller is implemented on the model with delay parameters beyond their typical values. The proposed advisory control system is tested on two cases in diabetic patients.

Case 1: Delay in insulin secretion in diabetic patients ($\tau_1 \geq 0$ and $\tau_2 = 0$)

In this situation, insulin secretion in diabetic patients is delayed, while there is no delay in insulin absorption by the cells and tissues. The delay parameter τ_1 corresponds to the time between food intake and insulin secretion. According to Saloni et al. [141], the glucose level is maintained within the normal range when τ_1 lies in the interval (5, 15) min. However, when τ_1 goes beyond this period, the glucose concentration becomes abnormal. Thus, in this study, to simulate the situation, we have considered

values of τ_1 beyond 15 min, such as 20, 25, 30, and 35 min.

Case 2: Presence of delay in both insulin secretion and insulin action ($\tau_1 \geq 0$ and $\tau_2 \geq 0$)

According to Saloni et al. [141], two cases were considered for simulation of the two-delay glucose-insulin model. In the first case, the delay τ_1 was set to 5 minutes and τ_2 was within the range of (31, 43) minutes. In the second case, τ_1 was equal to 10 minutes, and τ_2 was within the range of (26, 38) minutes. The authors concluded that after ignoring the first oscillation in both cases, the ultradian oscillations range of glucose concentration for a period of 182 minutes was safe for diabetic patients. The results indicate that when $\tau_1 = 5$ min and τ_2 is between 31 to 43 min, the normal range of glucose level is achieved in diabetic patients, while when τ_1 = 10 min, the normal range is achieved when τ_2 is from 26 to 38 min. The simulation employed the parameters presented by Sturis et al. [164], as indicated in Table 2.2 for a diabetic patient. To evaluate the controller's efficacy, we examined its performance for glucose profile under four distinct scenarios: without meal disturbance, meal disturbance, abnormal meal intake, and uncertainty in insulin clearance rate, which are explained below in detail.

5.6.1 Glucose profile of patients without meal disturbance

In this setup, the normal glucose-insulin dynamics was simulated with no meal disturbance. It has been considered that the patient had not taken any meal, and the performance of the controller was evaluated by monitoring the patient's blood glucose level response. The simulation was conducted for a duration of 800 minutes, with the initial glucose level of the patient set at 140 mg/dl. The Fuzzy Logic Controller effectively maintained the glucose concentration at 90.4 mg/dl for two hours after the simulation started, ensuring a safe level for the diabetic patient.

The response of the glucose concentration in patients with delayed insulin secretion by the pancreas is displayed in Fig 5.4. The delays in insulin secretion, represented by τ_1, were considered in range of from 20 to 35 minutes with an increment of 5-min.

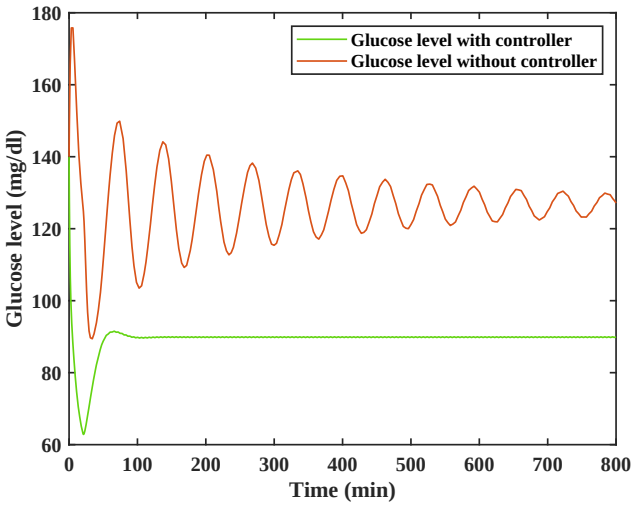

Figure 5.4(a). $\tau_1 = 20$ and $\tau_2 = 0$

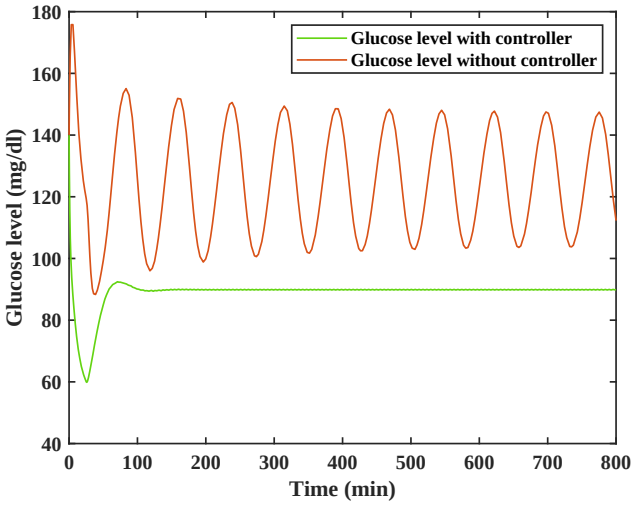

Figure 5.4(b). $\tau_1 = 25$ and $\tau_2 = 0$

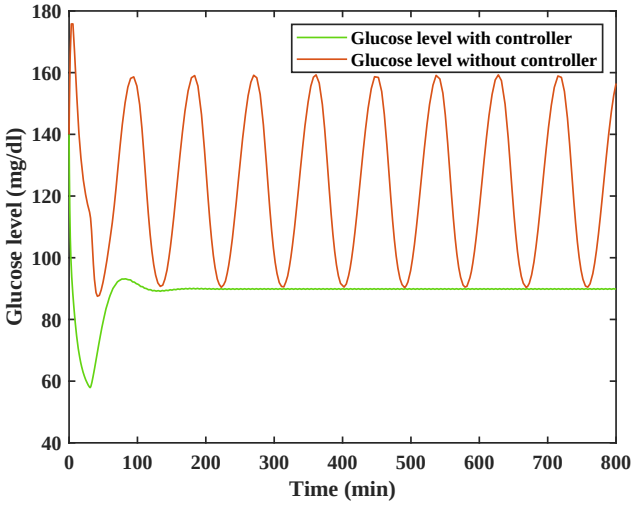

Figure 5.4(c). $\tau_1 = 30$ and $\tau_2 = 0$

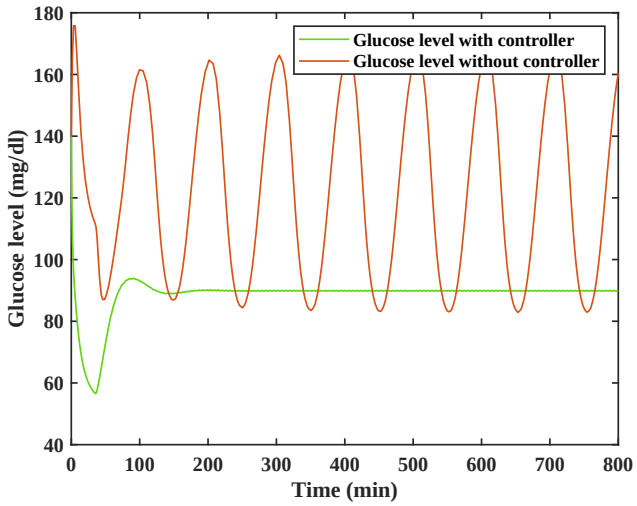

Figure 5.4(d). $\tau_1 = 35$ and $\tau_2 = 0$

Figure 5.4: Glucose concentration for different values of τ_1

The response of glucose concentration of diabetic patients with a delay in insulin action and secretion is shown in Fig 5.5. The τ_2 was fixed at 50 minutes while the τ_1 value varied from 10 to 25 minutes with a 5-minute increment.

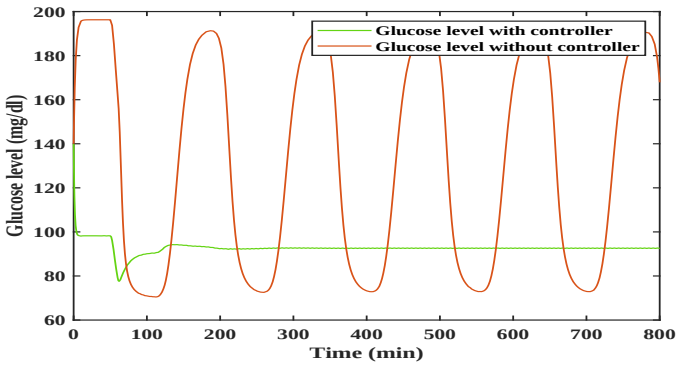

Figure 5.5(a). $\tau_1 = 10$ and $\tau_2 = 50$

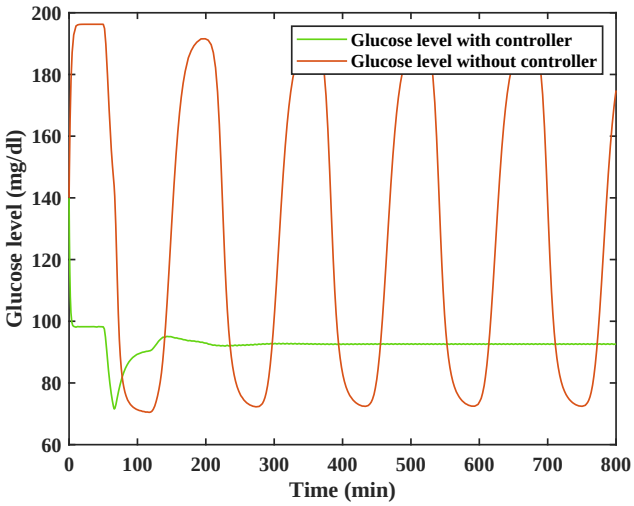

Figure 5.5(b). $\tau_1 = 15$ and $\tau_2 = 50$

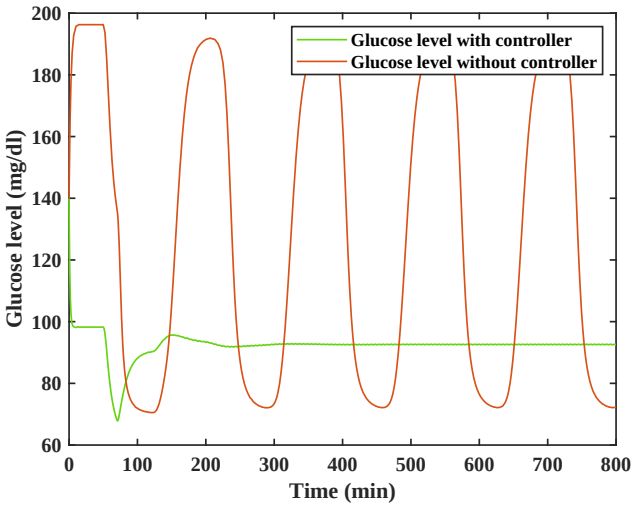

Figure 5.5(c). $\tau_1 = 20$ and $\tau_2 = 50$

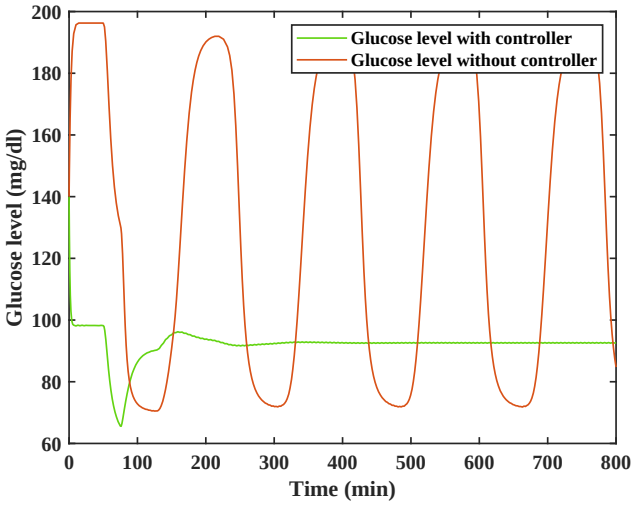

Figure 5.5(d). $\tau_1 = 25$ and $\tau_2 = 50$

Figure 5.5: Glucose concentration for $\tau_2 = 50$ and different values of τ_1

5.6.2 Glucose profile of patients with meal disturbance

In this setup, a meal disturbance was introduced in the normal glucose-insulin dynamics, which caused an abrupt change in glucose level. The purpose of this test was to assess the ability of controllers to handle the disruption caused by multiple mixed meals in diabetic patients. The breakdown of food into glucose and its entry into the body was simulated as a time-dependent function, represented by G_{in}. The highest glucose intake rate of 5.25 mg/min was reached at 15 minutes, and the total duration of glucose intake was 35 minutes. The proposed controller was able to maintain the glucose level close to 90 mg/dl.

$$G_{in} = \begin{cases} 0.25 + \frac{5}{15}t & 0 \leq t \leq 15(min) \\ 0.25 + 5\frac{35-t}{35-15} & 15 \leq t \leq 45 \\ 0.25 & 35 \leq t \leq 240 \end{cases}$$

The Fig 5.6 displays the glucose level in a patient with a delay in insulin secretion following a meal. In this scenario, the minimum and maximum values of τ_1 from the set of 20 to 35 were selected, with τ_2 being equal to 0.

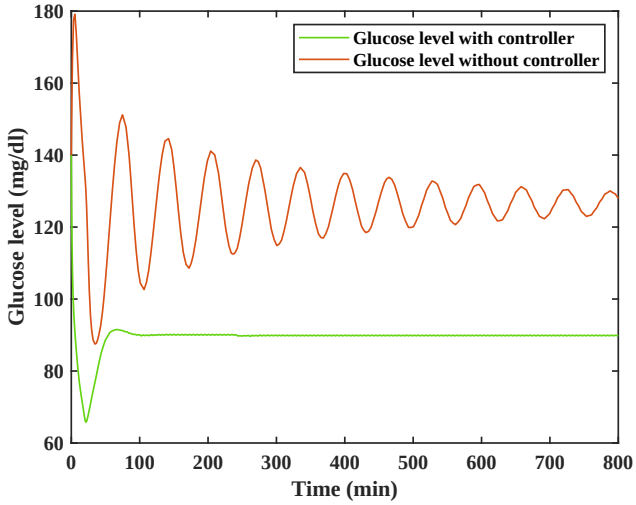

Figure 5.6(a). $\tau_1 = 20$ and $\tau_2 = 0$

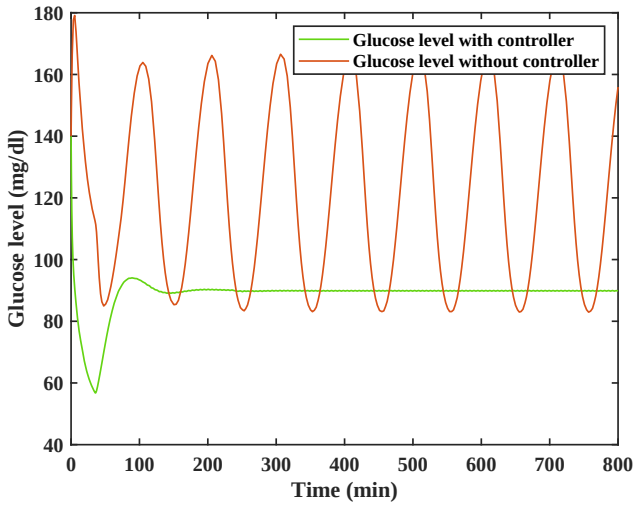

Figure 5.6(b). $\tau_1 = 35$ and $\tau_2 = 0$

Figure 5.6: Glucose concentration for values of $\tau_1 = 20, 35$ and $\tau_2 = 0$

The Fig 5.7 shows the glucose levels of patients with a delay in insulin secretion and insulin action after meal consumption. The range of τ_1 was taken from 10 to 25 minutes, with τ_2 fixed at 50 minutes.

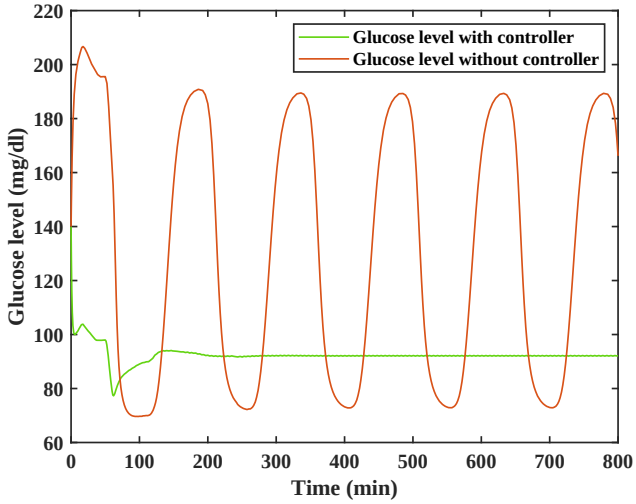

Figure 5.7(a). $\tau_1 = 10$ and $\tau_2 = 50$

5.6.3 Unusual glucose intake by patients

In this scenario, an unusual large meal was taken, which caused a significant increase in glucose level. The patient had a highest glucose intake rate of 5 (mg/dL) per minute. A sudden spike in glucose consumption was observed between 400 and 410 min, with a rate of 5 (mg/dL) per minute, resulting in a total glucose intake rate of

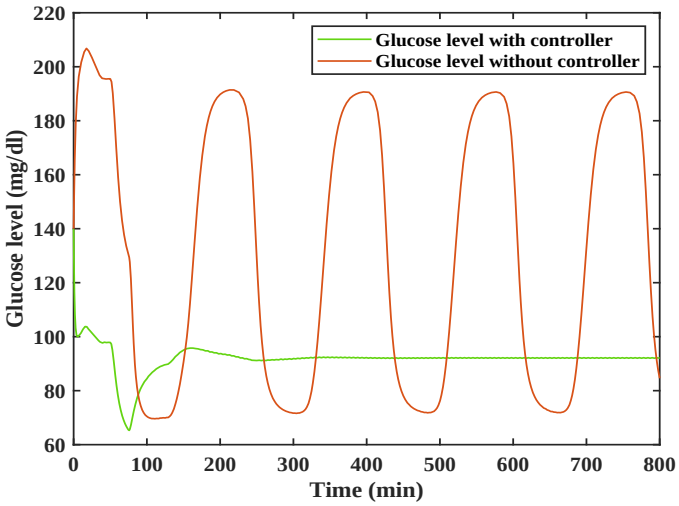

Figure 5.7(b). $\tau_1 = 25$ and $\tau_2 = 50$

Figure 5.7: Glucose concentration for values of $\tau_1 = 10, 25$ and $\tau_2 = 50$

15 (mg/dL) per minute. Fig 5.8 depicts the glucose level response of diabetic patients when the delays in insulin secretion and insulin action were set to 20 and 35 minutes respectively ($\tau_1 = 20, 35$ and $\tau_2 = 0$). The highest recorded glucose levels without the controller intervention were 148.8 mg/dl and 187.3 mg/dl. However, after the implementation of the controller, the peak glucose levels were reduced to 101.1 mg/dl and 101.4 mg/dl respectively.

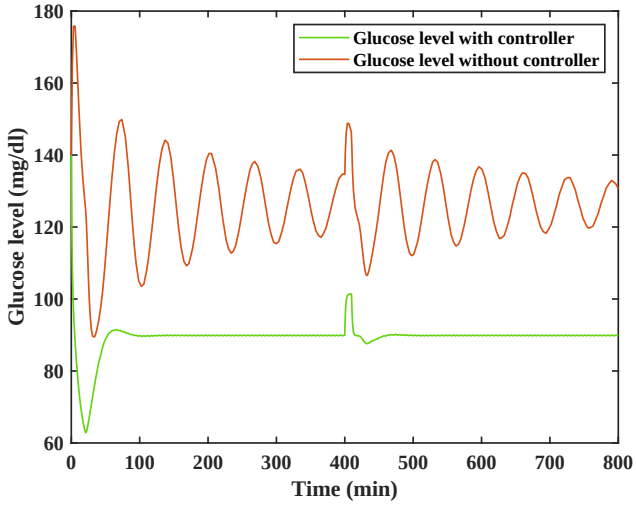

Figure 5.8(a). $\tau_1 = 20$ and $\tau_2 = 0$

In Fig 5.9, the performance of the controller is displayed when τ_1 is set to 10 and 25, while τ_2 is fixed at 50. The maximum glucose level observed during the unusual meal disturbance was 80 mg/dl and 212 mg/dl. After the implementation of the controller,

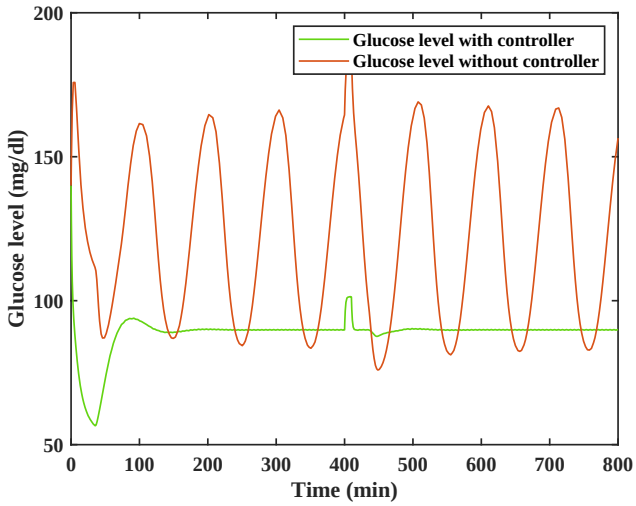

Figure 5.8(b). $\tau_1 = 35$ and $\tau_2 = 0$

Figure 5.8: Glucose concentration for values of $\tau_1 = 20$, 35 and $\tau_2 = 0$

the peak glucose levels were recorded at 101.1 mg/dl and 103.9 mg/dl throughout the 800-minute simulation period.

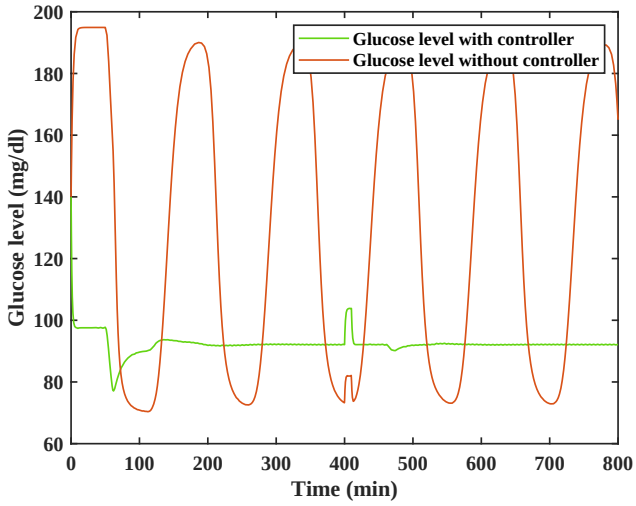

Figure 5.9(a). $\tau_1 = 10$ and $\tau_2 = 50$

5.6.4 Uncertainty in the clearance rate parameter

In this setup, uncertainty was introduced in the insulin clearance rate, which affected the glucose-insulin dynamics. The insulin clearance rate d represents the rate at which insulin is absorbed, which varies in patients. A higher value of this parameter means a faster rate of insulin degradation leading to higher glucose levels in diabetic patients. The simulation in this part takes into account the differences in insulin ab-

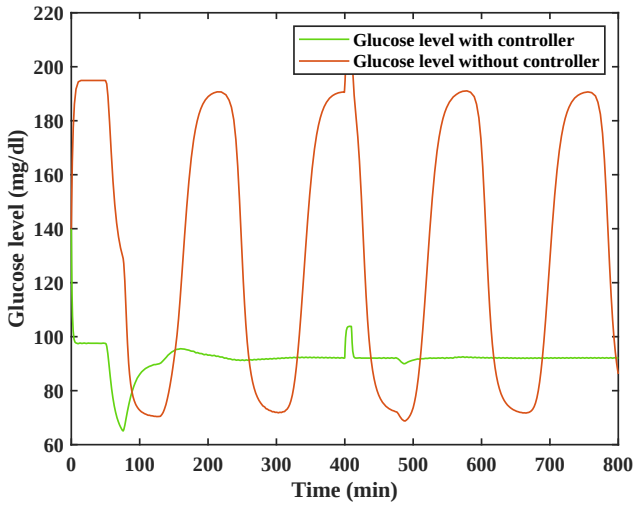

Figure 5.9(b). $\tau_1 = 25$ and $\tau_2 = 50$

Figure 5.9: Glucose concentration for values of $\tau_1 = 10, 25$ and $\tau_2 = 50$

sorption ability among patients. The clearance rate was considered uncertain, with a variation of up to 20%. The nominal value of the parameter d was 0.08 in the model. The fuzzy logic controller was able to preserve the glucose concentration within the acceptable range. The glucose level for diabetic patients with insulin secretion delays of 20 minutes was maintained by the controller within the range of [90.37, 93.01] mg/dL and [90.77, 93.54] mg/dL after 105 minutes, as depicted in Fig 5.10, even when there was $\pm$ 20% uncertainty in d

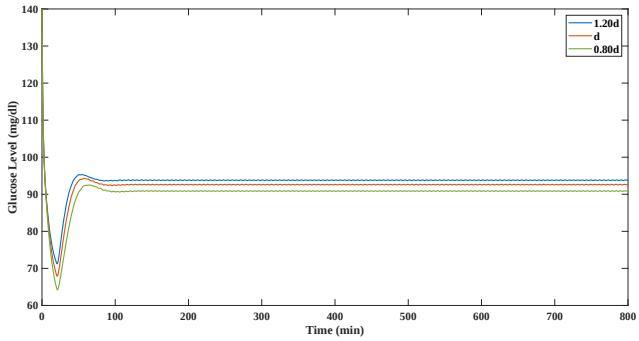

Figure 5.10(a). $\tau_1 = 20$ and $\tau_2 = 0$

The Fig 5.11 depicts the glucose level of diabetic patients with delayed insulin action. The delay was 10 and 25 minutes for the first and second case, respectively, and insulin absorption was 50 minutes. The results show that the glucose levels were within the range of [90.72, 93.54] and [90.92, 93.86].

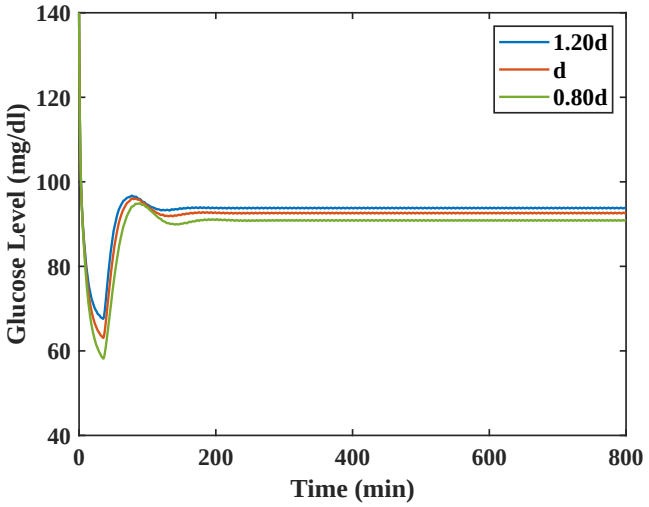

Figure 5.10(b). $\tau_1 = 35$ and $\tau_2 = 0$

Figure 5.10: Glucose concentration for values of $\tau_1 = 20, 35$ and $\tau_2 = 0$

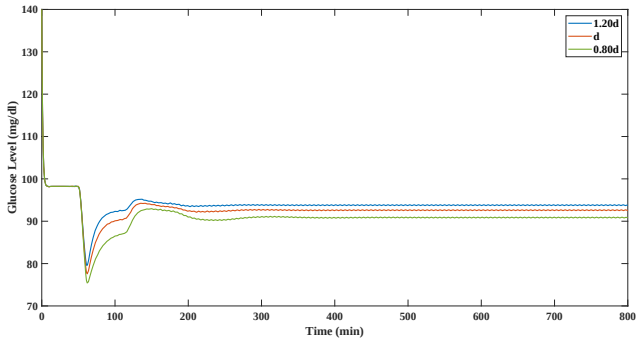

Figure 5.11(a). $\tau_1 = 10$ and $\tau_2 = 50$

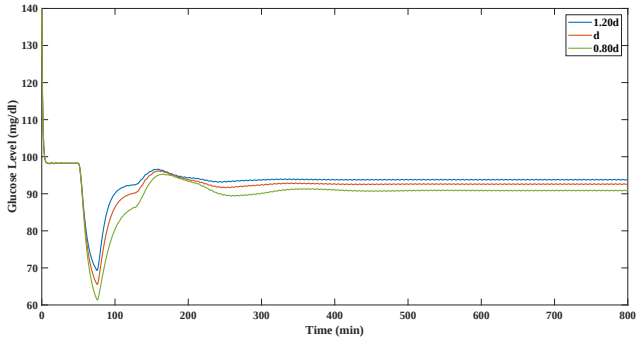

Figure 5.11(b). $\tau_1 = 25$ and $\tau_2 = 50$

Figure 5.11: Glucose concentration for values of $\tau_1 = 10, 25$ and $\tau_2 = 50$

5.7 Results and Discussion

An innovative closed-loop recommendation system utilizing fuzzy logic is currently under development for insulin therapy in individuals with type 1 diabetes. Elevated

blood glucose levels in these patients often result from the failure of the gluconeogenesis homeostatic mechanism, leading to both delayed insulin action and secretion. The system targets two cases: i) delayed insulin action (τ_1), and ii) delayed insulin secretion and action (τ_2), with identified hazardous delay ranges of $(\tau_1 > 15, \tau_2 = 0)$, $(\tau_1 = 15, \tau_2 > 43)$, and $(\tau_1 = 10, \tau_2 > 38)$ minutes. Four experiments, including no meal consumption, multiple meals, unusual meals, and model parameter uncertainty, were conducted to evaluate the system. In all experiments, the controller maintained glucose levels between 90 and 95, roughly half of the high glucose threshold. The findings suggest that the proposed system can effectively regulate glucose levels in type 1 diabetes individuals, reducing ultradian glucose oscillation amplitudes and demonstrating the potential of the fuzzy-based approach in a closed-loop manner. These results offer a promising path for future research into artificial pancreas systems for individuals with type 1 diabetes.

5.8 Conclusion and Future work

This chapter presents a non-linear delay differential model with two delays to describe the glucose-insulin regulatory system in type 1 diabetic patients. A closed-loop controller based on the Mamdani-type fuzzy scheme is proposed to maintain glucose levels within a safe range. The delays in insulin secretion and absorption are identified as crucial factors in the malfunctioning of the blood regulatory system. The proposed FLC is robust and can keep glucose levels within a safe range, even in the presence of a 20-35 minute delay in insulin secretion and a 50-minute delay in insulin absorption. The controller can be easily modified for various patient differences and can be further improved by incorporating more sophisticated techniques, such as type-2 fuzzy logic, to handle disturbances and uncertainties in model parameters. The proposed controller's effectiveness and feasibility in real-world applications can be validated by evaluating it on a larger scale, involving more patients and different patient profiles. Additionally, the integration of the proposed controller with the micro-pump of insulin infusion can create a fully functional artificial pancreas.

Chapter 6

An Optimal PID-Fuzzy Logic Insulin Infusion Mechanism for Type 1 Diabetes in the Advancement of Artificial Pancreas

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Managing blood sugar levels in Type 1 diabetes patients can be complex and time-consuming through manual computation of insulin doses. This chapter introduces the PID-FLC (Proportional Integral Derivative-Fuzzy Logic Controller) control system for automatic insulin therapy. Based on an updated version of Bergman's model, the system is proven stable using Jacobian linearization and has shown effective results in virtual patient tests. The PID-FLC system was able to maintain glucose levels near 93 mg/dl, even with a 20% uncertainty in insulin clearance rate, providing a potential solution for automating insulin therapy in Type 1 diabetes patients.

6.1 Introduction

Type 1 Diabetes Mellitus (T1DM) requires tight control of blood glucose levels to prevent serious health complications. Artificial Pancreas Systems (APS) have been developed to automate insulin delivery, where the insulin infusion mechanism is a crucial component responsible for controlling the amount of insulin delivered to the body. A variety of control algorithms have been used for closed-loop management of diabetes, including linear controllers like PID and feed-forward, as well as non-linear controllers included linear controllers like PID [89, 186] and feed-forward [123, 163], as well as non-linear controllers like back stepping [75, 165], sliding mode [53, 118, 135], artificial neural networks [82, 115, 168], H_∞ [72, 93] controller and optimal controllers [15, 30, 51, 97]. Among these control strategies, the PID-Fuzzy Logic Control (FLC) insulin infusion mechanism has gained significant attention due to its ability to regulate insulin levels in response to changes in glucose levels, maintaining glucose levels within a safe range. This approach combines a proportional-integral-derivative (PID) controller and a fuzzy logic controller, with the PID controller regulating glucose concentration and the fuzzy logic controller making necessary adjustments based on various factors. Compared to other control strategies, the PID-FLC controller offers several advantages. It is simple, computationally efficient, and has been shown to perform well in controlling glucose levels in T1DM patients. Moreover, the PID controller provides a baseline control action, while the fuzzy logic controller is responsible for handling uncertainties and nonlinearities in the system, such as meal disturbances, insulin clearance rate uncertainty, and insulin secretion delays.

A number of authors have proposed fuzzy logic control schemes for diabetes control based on the Bergman minimal model. Ibbini and Fereydouneyan [59, 81] introduced a fuzzy logic control system that helps maintain normoglycemic levels in the face of glucose meal disturbances or measurement errors. Campos-Delgado et al. [31] developed an advisory/control algorithm for Type-1 diabetes patients undergoing intensive insulin treatment based on a multiple daily injections regimen that incorpo-

rates expert knowledge about the treatment of diabetes using fuzzy logic controllers. The fuzzy-PI controller was designed by Ibbini et al. [80] using a simplified design and was simulated with two common diabetes disturbances, such as sudden glucose meal and system parameter variations. Yasini et al. [191], Kardar et al. [87], and Sasi et al. [152] designed a closed-loop control system for continuous drug infusion that outperforms traditional discrete methods, even with significant glucose disturbances such as mealtime nutrition absorption. Nossair et al. [6] developed a recurrent neural network as a nonlinear predictor and a fuzzy logic controller to determine insulin dosage to regulate blood glucose levels. Liu et al. [106] proposed a fuzzy-logic-based supervisor for insulin bolus delivery that can be gradually updated meal-by-meal and only requires two blood glucose measurements. A type-2 fuzzy logic controller was developed by Goharimanesh et al. [68] for maintaining a safe glucose level with fast and accurate responses, even under normal conditions and parameter uncertainties. Yadav et al. [190] presented a Fuzzy-PID controller for blood glucose control in type-1 diabetic patients, where the parameters of the PID controller were tuned by the Cuckoo Search Algorithm. Gharghory et al. [66] developed a fuzzy logic controller implemented on a Field Programmable Gate Array. Amuthameena [9] proposed a Fuzzy-PID controller and found that it performed more robustly under changing insulin clearance rate, unexpected glucose intake, and meal disturbance compared to other controllers (PI-FLC and PD-FLC). Farahmand [58] proposed a Takagi-Sugeno based fuzzy inference system to minimize the impact of meal glucose disturbance on blood glucose concentration and confirmed that the proposed controller could effectively keep the blood glucose concentration within the desirable range. Mohammadzadeh and Bernal [23, 120] proposed a type-2 fuzzy controller system for healthy glucose regulation in diabetic patients. Nizam et al. [127] proposed a modified fuzzy particle swarm optimization algorithm for predicting blood glucose levels 30 minutes after the last measurement, which is crucial for insulin dose. Mosavi et al. [121] proposed a deep learned type-II fuzzy logic system to compensate for estimation errors and ensure stability for glucose regulation in type-I diabetes patients.

6.2 Modeling of Glucose Insulin Regulatory System

The model given by Saloni [141] has been used for the design of PID-Fuzzy logic controller which is given as follows:

$$\left.\begin{aligned} \frac{dG}{dt} &= G_{in}(t) + c - f_2(G(t)) - f_3(G(t))f_4(I(t)) \\ \frac{dI}{dt} &= f_1(G(t)) - d \cdot I(t) + U(t) \end{aligned}\right\} \tag{6.2.1}$$

with the initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0$, $G(t) \equiv G_0$. The $U(t)$ is the controller for insulin infusion rate which is calculated by proposed PID-FLC scheme. The detail explanation and biological meaning of function are discussed in Chapter 2.

Measurement noise and robustness are crucial considerations when analyzing the performance of a Fuzzy-PID controller. Measurement noise refers to the inherent fluctuations or disturbances present in the measured process variable, which can significantly affect the controller's behavior. The presence of measurement noise can introduce uncertainties and inaccuracies in the feedback signal, leading to undesired control actions. Therefore, it becomes essential to evaluate the controller's robustness, which refers to its ability to maintain stable and accurate control despite uncertainties and disturbances. Robustness analysis helps ensure that the PID controller can handle measurement noise effectively and produce reliable control actions.

6.3 Mathematical Analysis of Model

The existence,uniqueness, boundedness and stability of model has been already discussed in section 5.4 of chapter 5.

6.4 Controller's Methodology and Proposed Expert System

To address the challenge of managing glucose levels in Type 1 diabetes, we have employed the technique of combining PID control with fuzzy logic control. This ap-

proach was chosen because of its ability to handle uncertainty in model parameters and achieve the target glucose level quickly in case of hyperglycemia. The fuzzy logic controller works to minimize the error between the target and output glucose levels when the output glucose concentration deviates significantly from the basal value. Once the output glucose value is close to the desired point, the PID controller takes over to fine-tune the parameters and achieve the optimal value.

Proportional Integral Derivative (PID) control is a well prominent way of driving a system towards the desired position or level. The controller profile can be given as in the terms of function [89] :-

$$u(t) = k_p e(t) + k_i \int_0^t e(t)dt + k_d \frac{de(t)}{dt} \tag{6.4.1}$$

where

- $u(t)$ is the output function of controller,
- $e(t)$ is the error given by $e(t) = G_{desired}(t) - G(t)$ with $G_{desired}(t) = 90$; and $G(t)$ is the plasma-glucose concentration at time t,
- The parameters k_p, k_i and k_d denotes the relative gain of proportional, integral and derivative components respectively.

6.4.1 Development of PID-FLC structure

The optimal PID-Fuzzy controller based on Mamdani fuzzy system is structured with two input linguistic variables and one output linguistic variable, namely the glucose concentration $G(t)$ and the rate of change in glucose concentration $\frac{dG(t)}{dt}$. The output linguistic variable is represented as the insulin infusion rate in FLC. Table 6.1 show the characteristics of input variable. We take the range of the variable $G(t)$ to be [0 , 200] because it is always positive and less than 200 mg/dl. During the first 180 minutes, the dynamic behavior of glucose changes as it increases and subsequently drops. As a result, the rate of change in glucose level is estimated to be between -25 and +25.

Input Variables	Interval	Membership Functions							
Glucose Level G(t) (mg/dl)	[0 200]	NB	NM	NS	NOM	PS	PM	POS	PL
Glucose Deviation dG/dt	[-25 25]	Neg	Zero	Pos					

Table 6.1: Characteristics of input variables

Insulin is usually administered at a rate of 15 mL/h (6 U/h) until the blood glucose level falls below 180 mg/dL, at which point the rate of infusion is reduced to 5-7.5 mL/h (2-3 U/h). So that we have considered the range of output variable 0 to 30 μ U per ml per hr. The attributes of the output variable are shown in the Table 6.2. where the

Output Variables	Interval	Membership Functions							
Insulin Infusion rate (μ U/ml hr)	[0 30]	NB	NM	NS	NOM	PS	PM	POS	PL

Table 6.2: Characteristics of output variables

full form of variables NB: Negative Big, NM: Negative Medium, NS: Negative Small, NOM: Normal, PS:Positive Small, PM: Positive Medium, POS: Positive, PL: Positive Large, Neg: Negative, and POS: Positive. The graphs of the input variables is shown in Fig 6.1

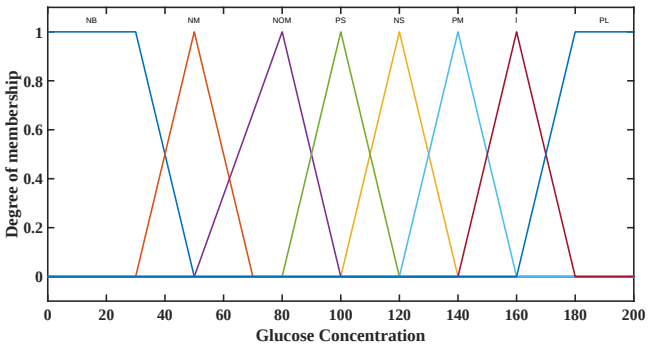

Figure 6.1(a). Glucose concentration

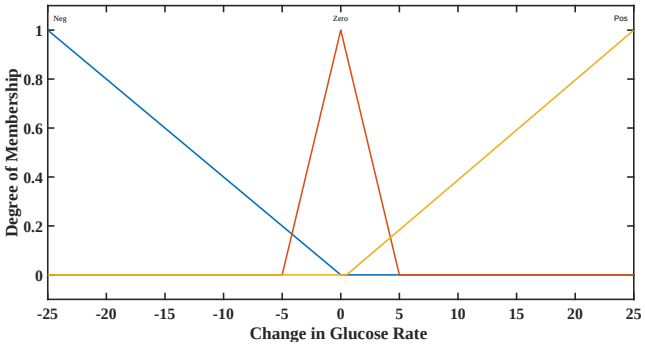

Figure 6.1(b). The rate of change in glucose con.

Figure 6.1: Membership Function of Input Variables

The figure referenced as Fig 6.2 displays the graphs of the output variables.

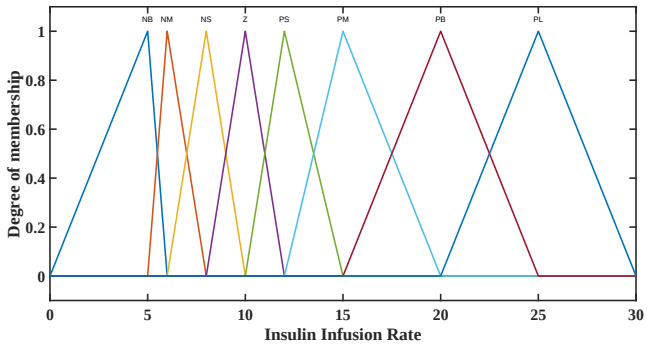

Figure 6.2: Membership function of output variable (insulin infuse rate)

The input and output fuzzy sets were used to define 24 IF-THEN rules, which employed an AND (minimum) type antecedent for the purpose of minimizing the error between the desired and actual glucose concentration. These rules were associated with the input and output membership functions, and the CENTROID defuzzification method was utilized to obtain a crisp value. Table 6.3 displays the fuzzy rules of the controller. The Fig 6.3 shows the surface view of control action. We have tuned the

	Change in Glucose Rate		
Glucose level rate	Negative	Zero	Positive
NB	NB	NB	NB
NM	NB	NM	NM
NS	NB	NS	Z
NOM	Z	Z	Z
PS	Z	PS	PB
PM	PM	PM	PB
PB	PB	PB	PB
PL	PL	PL	PL

Table 6.3: Fuzzy Rules

parameters manually. The values of PID controller's parameters in our PID-FLC are given in Table 6.4. Figure 6.4 suggests the block diagram of the PID-Fuzzy logic controller based on the glucose-insulin model.

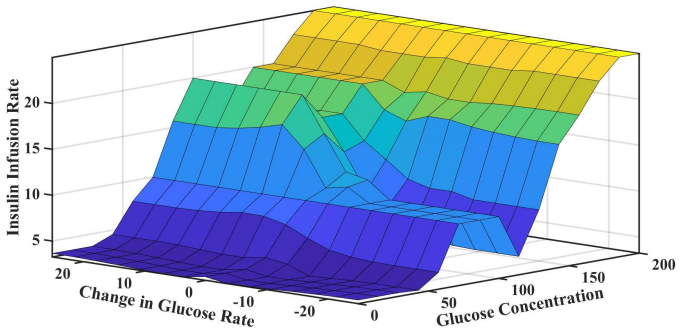

Figure 6.3: Control action surface

Parameter	Values
k_p	0.865
k_i	-0.000005
k_d	0.0009

Table 6.4: Parameter values of PID controller

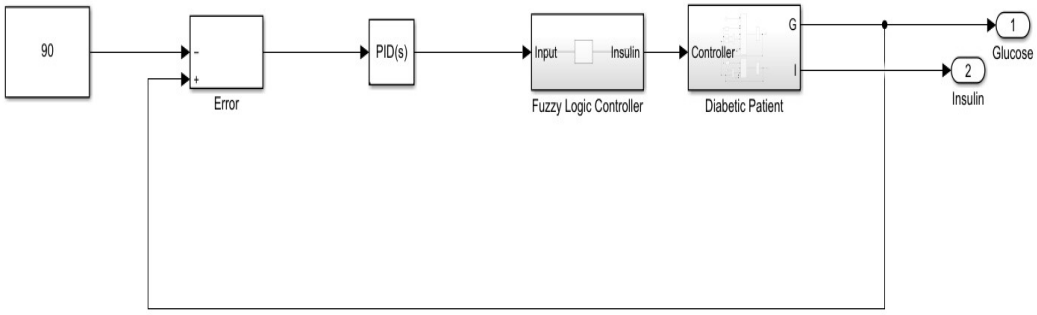

Figure 6.4: Type 1 diabetes simulink model to explore PID-Fuzzy control strategy for insulin infusion

6.5 Numerical Simulations

This section contains the results of numerically solution of the optimality system (6.2.1). The effect of the suggested PID-FLC on the two primary situations for diabetic patients addressed in this part are: i) Maintaining the sugar level for the entire day, and ii) Model's parameter uncertainty. Furthermore, we also showed the glucose-insulin dynamic for normal and diabetic people.

Fig 6.5 depicts glucose-insulin dynamic of normal and diabetic individual.

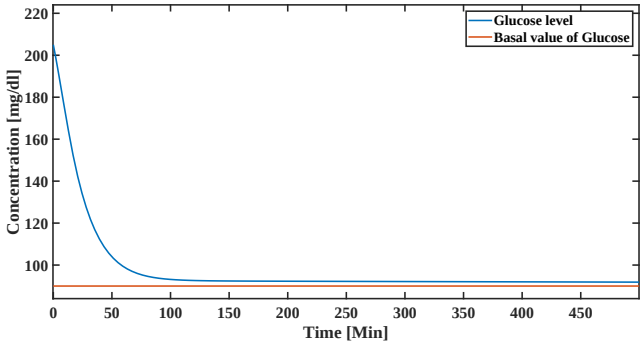

Figure 6.5(a). Glucose concentration of normal individual

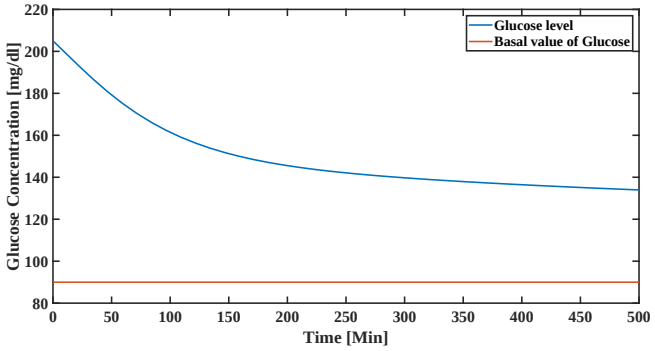

Figure 6.5(b). Glucose concentration of diabetes individual

Figure 6.5: Glucose - Insulin dynamic behavior of people

The Fig 6.6 represent the phase portrait of normal and diabetic people which show the model forms the stable node.

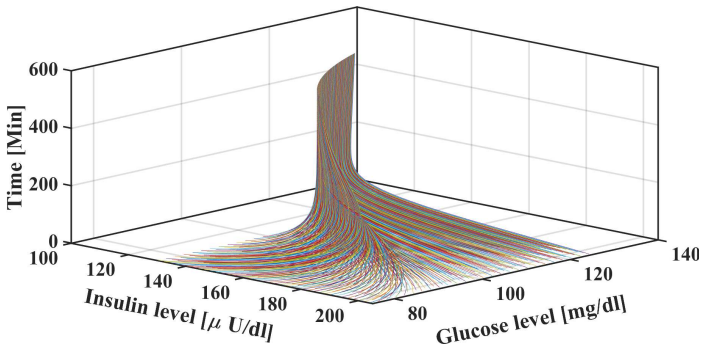

Figure 6.6(a). Glucose concentration of normal individual

6.5.1 Monitoring the patient's routine for one full day

The patient's sugar level was monitored for 24 hours using two simulation tests. We assume that virtual patients had the meal at three separate time for slots in the First Test's named as day shift. In the second test, known as the night shift, we assumed that patients had not eaten anything in the previous 8 hours. The next subsections go

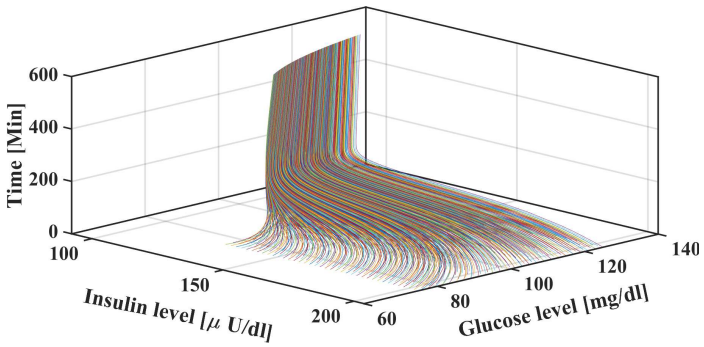

Figure 6.6(b). Glucose concentration of diabetes individual

Figure 6.6: Phase Portraits of individual

over the specifics of each experimental setup.

Case scenario : day shift of diabetic person

It was a day protocol test. The simulation was performed for 16 hours. Initially, we assumed the blood glucose level of a patient in morning 08:00 is 130 mg/dl. The virtual diabetic patient has consumed 32.5g of Carbohydrates (CHO) during breakfast at 09:30 am, 57g CHO during lunch at 01:00 pm and 86.5g CHO at 11:00 pm during dinner. The duration for the consumption of food was considered as 10 minutes. The table given below shows the meal consumption of patient at different time slots[159].

Meal	Time	g CHO	mol CHO
Breakfast	09:30 am	32.50	1.12
Lunch	01:00 pm	57.00	1.96
Dinner	11:00 pm	86.50	2.98

Table 6.5: Scheduled of meal consumption

On simulation of model with above data set several results have been drawn. Fig 6.7 shows the blood glucose level after applying the PID, fuzzy and PID-fuzzy control techniques. The simulation was started at time t = 0, and this time the sugar level was 130 mg/dl. The artificial pancreas began to release insulin after the consumption of meal. At time t = 100, 300 and 900 minutes, without the presence of controller, the sugar levels reached 250 mg/dl, 410 mg/dl and 650 mg/dl respectively during the food consumption. Following 2 hours of meal consumption, glucose level in body was 109 mg/dl, 108 mg/dl, and 93 mg/dl after implementation of PID, FLC and PID-FLC

controllers, respectively. The proposed PID-FLC has maintained the sugar concentration of diabetic patients at safe range in day shift. Fig 6.8 depicts the model's phase

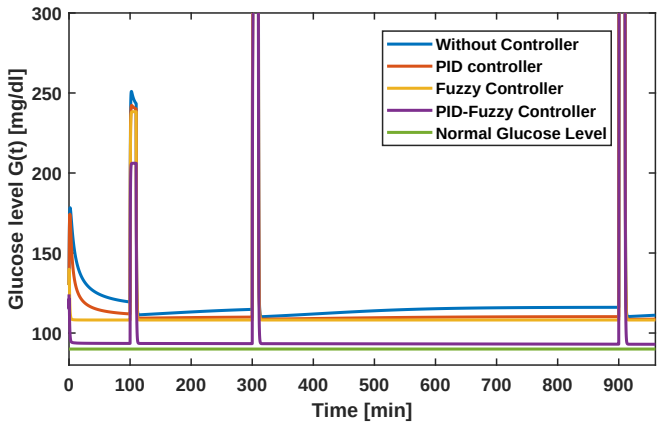

Figure 6.7: Patient's glucose concentration during day shift with implementation of different controller

portraits, which illustrate that the model is stable in the presence of a controller for a day shift protocol.

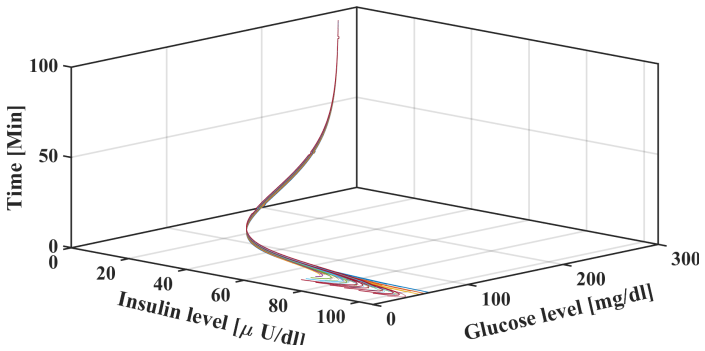

Figure 6.8: Phase portrait of model with PID-FLC controller in day shift

Case scenario : night shift of diabetic person

It was an in-night protocol test. The simulation was performed for 8 hour. Fig 6.9 shows the glucose concentration of the diabetic patients during night shift. The initial value of glucose level was 130 mg/dl. After 2 minute, the glucose concentration started to rise. Without applying the proposed controller, the level of glucose in diabetic patient was 178 mg/dl at time t = 2 minute. At the same time, the glucose level was 174, 137, and 120 mg/dl after implement the PID, fuzzy and PID-FLC controllers, respectively. Two hours later, PID, fuzzy, and PID-fuzzy controllers maintained the glucose concentration at values 118, 108 and 93 mg/dl respectively for diabetic

patients. The proposed PID-FLC supervisor has maintained the glucose level at 93 mg/dl during night shift.

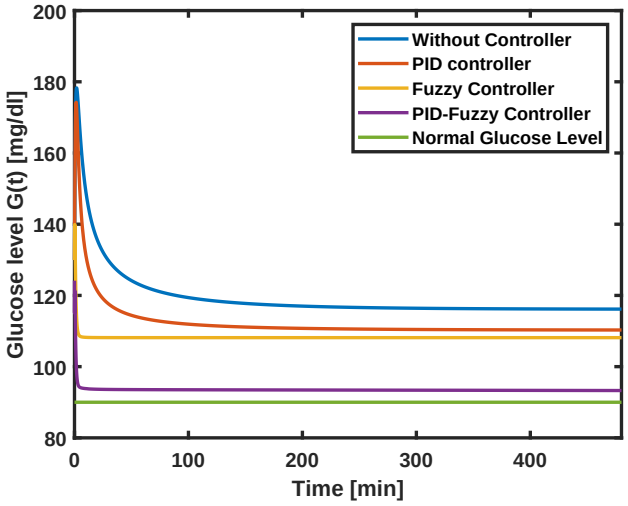

Figure 6.9: Patient's glucose concentration during night shift with implementation of different controller

The model's phase portraits are shown in Fig 6.10, which show that it is stable in the presence of a controller for a night shift protocol.

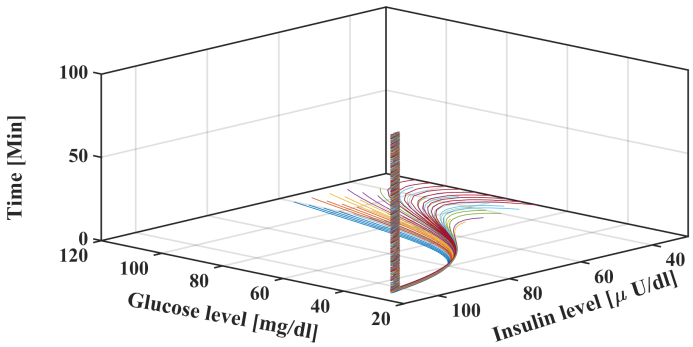

Figure 6.10: Phase portrait of model with PID-FLC controller in night shift

6.5.2 Controller robustness

We had considered ± 20% error in insulin clearance rate. The clearance rate of insulin is defined as the measurement of insulin degradation relative to the amount of delivered insulin. High clearance rate of insulin means that a large amount of insulin is not used to help the absorption of glucose molecules into the body. Thus, we assumed the insulin clearance rate is d = 0.0076. In the context of robustness

test, we had taken 80% and 120%, amount of insulin clearance rate. The closed-loop robust performance of the proposed PID-FLC system is shown in Fig 6.11(a) and Fig 6.11(b). It can be seen that excellent comparative results have been attained resulting increased blood sugar level in the body between with and without meal consumption by the patient.

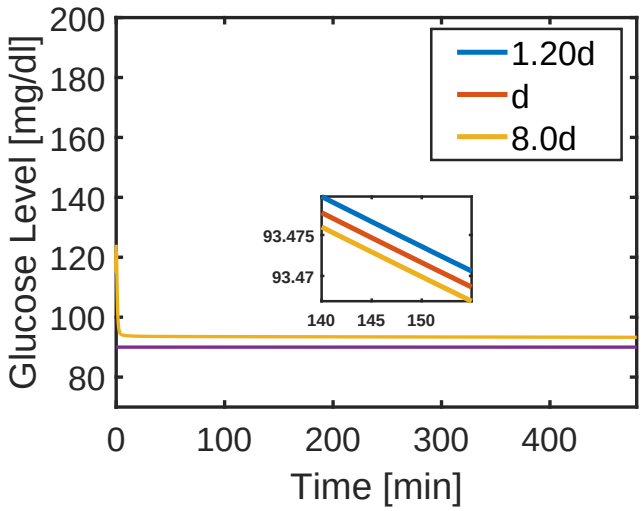

Figure 6.11(a). Glucose level during the night shift in the presence of PID-FLC

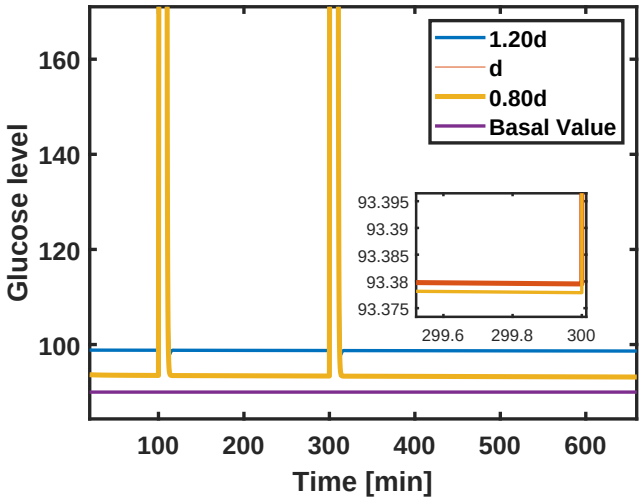

Figure 6.11(b). Glucose level during the day shift in the presence of PID-FLC

Figure 6.11: Glucose level of diabetic patients with ±20% error in insulin clearance rate parameter

6.5.3 Sensor noise

Here, measurement noise's impact is taken into account. A band-limited white Gaussian noise has noise power equal to 0.1. Following that, a group of simula-

tion results for the PID-fuzzy controller that include scenarios (meal intake and sensor noise) are shown in Fig 6.12.

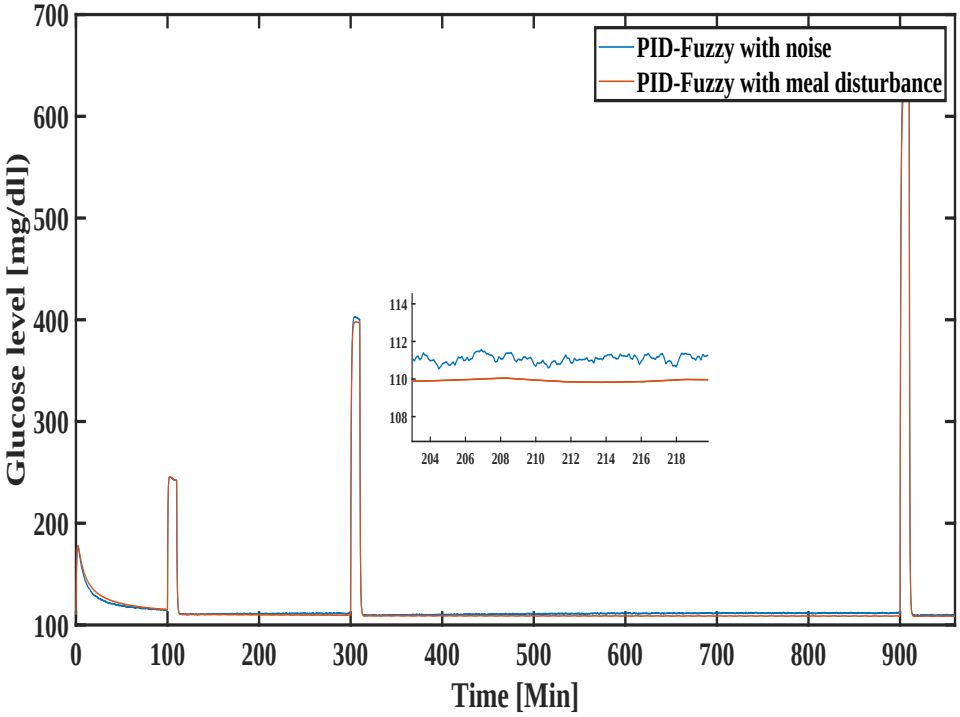

Figure 6.12: Blood glucose profile of PID-Fuzzy controller against noise effect

6.6 Results and Discussion

Two shifts were considered, the day shift of 16 hours and the night shift of 8 hours. During the day shift, it was observed that patients consume meals at different times (meal disturbance), and the proposed controller successfully kept their glucose levels at 93 mg/dl after two hours of consumption of meal . In the night shift, patients did not have meal disturbance, and the proposed controller was able to maintain the glucose levels at 93 mg/dl. The uncertainty in the clearance rate parameter can cause hyperglycemia or hypoglycemia due to inappropriate handling of insulin delivery. The proposed controller was able to handle both states effectively and keep the blood glucose concentration within the normal range. Finally, the effect of measurement noise was tested by exposing the glucose-insulin model to white Gaussian noise, and the proposed controller still maintained the blood glucose level within the normal

range.

6.7 Conclusion and Future Scope

In this study, an ordinary differential equation model was analyzed to develop a closed-loop control system for type 1 diabetes patients using fuzzy logic control. The proposed model, which is suitable for an automated insulin administration system, was improved from Bergman's model by appropriate inclusion of related parameters. The stability of the unique equilibrium point was proven using the Jacobian linearization method. A Mamdani-type fuzzy scheme was used to design a PID-Fuzzy controller that incorporates patient treatment knowledge. The proposed controller has the ability to handle dynamic uncertainties in the model, such as parameter fluctuations and meal disturbances. Simulation results showed that the controller can maintain stable blood glucose levels near 93 mg/dl during both day and night shifts, despite meal disturbances. The high efficiency of the controller under various clinical experimental setups suggests its suitability for feasible applications such as insulin infusion micropumps and artificial pancreas.

Chapter 7

Conclusion and Future Scope

7.1 Conclusion

The application of controllers in mathematical modeling for the management of diabetes has demonstrated potential as an innovative and effective approach to glucose control. By incorporating continuous glucose monitoring data and insulin delivery systems, mathematical models can predict glucose levels and determine optimal insulin dosing in real-time. This has the potential to greatly improve glucose control and reduce the risk of hypoglycemia and other diabetes-related complications. Studies have shown that mathematical models incorporating controllers can lead to improved glucose control, with a decrease in average glucose levels, hemoglobin A1c, and hypoglycemic episodes. In addition, these models have been shown to provide patients with improved quality of life and satisfaction with their treatment. Despite these promising results, there are still challenges that need to be addressed. One of the main challenges is the accuracy of the mathematical models, as they are dependent on the quality of the CGM data and the ability of the algorithm to predict glucose levels. In addition, the cost of controllers and the need for technical expertise to operate them remain barriers to widespread adoption.

7.2 Future Scope

The future of the application of controllers in mathematical modeling for the management of diabetes holds much promise. There are a number of areas where further research and development is needed to improve the performance of these models and make them more widely available to patients. Some of these areas include:

- Improved accuracy: Further research is needed to improve the accuracy of the mathematical models, including the development of new algorithms that take into account individual patient characteristics and preferences.
- Integration with other medical devices: Integrating mathematical models with wearable devices, such as fitness trackers and smartwatches, could provide additional data to the algorithms and improve the accuracy of glucose predictions.
- Personalization: Machine learning techniques could be used to personalize mathematical models to each patient's individual needs, resulting in more accurate glucose predictions and improved treatment plans.
- Increased accessibility: Efforts should be made to reduce the cost of controllers and make them more widely available to patients. This could be achieved through partnerships with healthcare providers, government programs, and private insurance companies.
- Real-world implementation: Large-scale implementation studies are needed to evaluate the real-world effectiveness of mathematical models incorporating controllers in improving glucose control and patient outcomes.

In conclusion, the application of controllers in mathematical modeling for the management of diabetes has the potential to revolutionize the way in which diabetes is managed. The future of diabetes management holds much promise with the continued development of these models and the integration of innovative technologies. With the right resources and support, the application of controllers in mathematical

modeling could become a standard of care for diabetes patients, providing them with improved glucose control, reduced risk of complications, and a better quality of life

Bibliography

[1] Abadi, D. N. M., Khooban, M. H., Alfi, A., and Siahi, M. (2014). Design of Optimal Self-Regulation Mamdani-Type Fuzzy Inference Controller for Type I Diabetes Mellitus. *Arabian Journal for Science and Engineering*, 39(2):977–986.

[2] Abbasi, F., Blasey, C., Feldman, D., Caulfield, M. P., Hantash, F. M., and Reaven, G. M. (2015). Low circulating 25-hydroxyvitamin D concentrations are associated with defects in insulin action and insulin secretion in persons with prediabetes. *Journal of Nutrition*, 145(4):714–719.

[3] Ackerman, E., Gatewood, L. C., Rosevear, J. W., and Molnar, G. D. (1965). Model studies of blood-glucose regulation. *The bulletin of mathematical biophysics*, 27(1 Supplement):21–37.

[4] Adams, C. L. and Lasseigne, D. G. (2018). An extensible mathematical model of glucose metabolism. Part I: the basic glucose-insulin-glucagon model, basal conditions and basic dynamics. *Letters in Biomathematics*, 5(1):70–90.

[5] Adamu, I., Haruna, Y., and Garba, E. (2013). A Mathematical Model For Attenuating the Spread Of Diabetes and Its Management In A Population. *Global Journal of Mathematical Sciences*, 12(1):1–14.

[6] Allam, F., Nossair, Z., Gomma, H., Ibrahim, I., and Abdelsalam, M. (2012). Evaluation of Using a Recurrent Neural Network (RNN) and a Fuzzy Logic Controller (FLC) In Closed Loop System to Regulate Blood Glucose for Type-1 Diabetic Patients. *International Journal of Intelligent Systems and Applications*, 4(10):58–71.

[7] Allen, F., Stillman, E., and Fitz, R. (1919). *Total Dietary Regulation in the Treatment of Diabetes.*, volume 25.

[8] Alzahrani, A. and Alanzi, T. (2019). Social media use by people with diabetes in saudi arabia: A survey about purposes, benefits and risks. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 12:2363–2372.

[9] Amuthameena, S. (2016). A novel strategy for blood glucose control in human body using PID-Fuzzy Logic Controller. *Journal of Chemical and Pharmaceutical Sciences*, (8):88–92.

[10] Appuhamy, J. A. N., Kebreab, E., and France, J. (2013). A mathematical model for determining age-specific diabetes incidence and prevalence using body mass index. *Annals of Epidemiology*, 23(5):248–254.

[11] Ashraf, A. and Alvarez, J. A. (2010). Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. *International Journal of Endocrinology*, 2010:18.

[12] Askari, M. R., Hajizadeh, I., Rashid, M., Hobbs, N., Zavala, V. M., and Cinar, A. (2020). Adaptive-learning model predictive control for complex physiological systems: Automated insulin delivery in diabetes. *Annual Reviews in Control*, 50:1–12.

[13] Banerjee, A. T., Mahajan, A., Mathur-Balendra, A., Qureshi, N., Teekah, M., Yogaratnam, S., Prabhakar, P., Ahmed, S., Shah, B. R., Velummailum, R., Price, J. A., de Souza, R. J., and Bajaj, H. S. (2022). Impact of the South Asian Adolescent Diabetes Awareness Program (SAADAP) on diabetes knowledge, risk perception and health behaviour. *Health Education Journal*, 81(1):96–108.

[14] Bansode, B. and Nagarajan, R. (2017). Diabetes: A review of awareness, comorbidities, and quality of life in India. *Journal of Social Health and Diabetes*, 05(02):77–82.

[15] Basha, A. A. and Vivekanandan, S. (2017). Evolution of diabetic control identification in lieu of continuous glucose monitoring technology- a review. *International Journal of Applied Engineering Research*, 12(16):6102–6107.

[16] Bell, D. S. (1992). Exercise for patients with diabetes: Benefits, risks, precautions. *Postgraduate Medicine*, 92(1).

[17] Bennett, D. L. and Gourley, S. A. (2004). Asymptotic properties of a delay differential equation model for the interaction of glucose with plasma and interstitial insulin. *Applied Mathematics and Computation*, 151(1):189–207.

[18] Bergman, R. N. (2005). Minimal model: Perspective from 2005. In *Hormone Research*, volume 64, pages 8–15. Karger Publishers.

[19] Bergman, R. N., Finegood, D. T., and Ader, M. (1985). Assessment of insulin sensitivity in vivo. *Endocrine Reviews*, 6(1):45–86.

[20] Bergman, R. N., Ider, Y. Z., Bowden, C. R., and Cobelli, C. (1979). Quantitative estimation of insulin sensitivity. *American Journal of Physiology Endocrinology Metabolism and Gastrointestinal Physiology*, 5(6):667–681.

[21] Bergman, R. N., Phillips, L. S., and Cobelli, C. (1981). Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. *Journal of Clinical Investigation*, 68(6):1456–1467.

[22] Bergman, R. N., Prager, R., Volund, A., and Olefsky, J. M. (1987). Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *Journal of Clinical Investigation*, 79(3):790–800.

[23] Bernal, E., Lagunes, M. L., Castillo, O., Soria, J., and Valdez, F. (2021). Optimization of Type-2 Fuzzy Logic Controller Design Using the GSO and FA Algorithms. *International Journal of Fuzzy Systems*, 23(1):42–57.

[24] Birjandi, S. Z., Sani, S. K. H., and Pariz, N. (2022). Insulin infusion rate control in type 1 diabetes patients using information-theoretic model predictive control. *Biomedical Signal Processing and Control*, 76:103635.

[25] Boli, V. W. (1961). Coefficients of normal blood glucose regulation. *Journal of applied physiology*, 16:783–788.

[26] Bordenave, S., Brandou, F., Manetta, J., Fédou, C., Mercier, J., and Brun, J. F. (2008). Effects of acute exercise on insulin sensitivity, glucose effectiveness and disposition index in type 2 diabetic patients. *Diabetes and Metabolism*, 34(3):250–257.

[27] Borzouei, S. and Soltanian, A. R. (2018). Application of an artificial neural network model for diagnosing type 2 diabetes mellitus and determining the relative importance of risk factors. *Epidemiology and health*, 40:e2018007.

[28] Boutayeb, A. and Chetouani, A. (2007). A population model of diabetes and pre-diabetes. *International Journal of Computer Mathematics*, 84(1):57–66.

[29] Boutayeb, A., Chetouani, A., Achouyab, A., and Twizell, E. H. (2006). A non-linear population model of diabetes mellitus. *Journal of Applied Mathematics and Computing*, 21(1-2):127–139.

[30] Brown, L. and Edelman, E. R. (2015). Optimal Control of Blood Glucose : The Diabetic Patient or the. *Sci Transl Med*, 2(27).

[31] Campos-Delgado, D. U., Hernández-Ordoñez, M., Femat, R., and Gordillo-Moscoso, A. (2006). Fuzzy-based controller for glucose regulation in type-1 diabetic patients by subcutaneous route. *IEEE Transactions on Biomedical Engineering*, 53(11):2201–2210.

[32] Catalogna, M., Cohen, E., Fishman, S., Halpern, Z., Nevo, U., and Ben-Jacob, E. (2012). Artificial Neural Networks Based Controller for Glucose Monitoring during Clamp Test. *PLoS ONE*, 7(8).

[33] Caumo, A., Giacca, A., Morgese, M., Pozza, G., Micossi, P., and Cobelli, C. (1991). Minimal Models of Glucose Disappearance: Lessons from the Labelled IVGTT. *Diabetic Medicine*, 8(9):822–832.

[34] Chatterji, P., Joo, H., and Lahiri, K. (2012). Beware of being unaware: Racial/ethnic disparities in chronic illness in the USA. *Health Economics (United Kingdom)*, 21(9):1040–1060.

[35] Chee, F., Savkin, A. V., Fernando, T. L., and Nahavandi, S. (2005). Optimal HâĹđ insulin injection control for blood glucose regulation in diabetic patients. *IEEE Transactions on Biomedical Engineering*, 52(10):1625–1631.

[36] Chen, J., Cao, K., Sun, Y., Xiao, Y., and Su, X. (2008). Continuous drug infusion for diabetes therapy: A closed-loop control system design. *Eurasip Journal on Wireless Communications and Networking*, 2008:1–10.

[37] Christie, D., Strange, V., Allen, E., Oliver, S., Wong, I. C., Smith, F., Cairns, J., Thompson, R., Hindmarsh, P., O'Neill, S., Bull, C., Viner, R., and Elbourne, D. (2009). Maximising engagement, motivation and long term change in a structured intensive education programme in diabetes for children, young people and their families: Child and Adolescent Structured Competencies Approach to Diabetes Education (CASCADE). *BMC Pediatrics*, 9(57):57.

[38] Coates, P. A., Luzio, S. D., and Owens, D. R. (1995). Minimal Model Analysis of the Insulin-Modified Comparison of Estimates of Insulin Sensitivity From Frequently Sampled Intravenous Glucose Tolerance Test and the Isoglycemic Hyperinsulinemic Clamp in Subjects With NIDDM. *Diabetes*, 44(JUNE):631–635.

[39] Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., Chasan-Taber, L., Albright, A. L., and Braun, B. (2010). Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. 33(12):e147.

[40] Contreras-Bolívar, V., García-Fontana, B., García-Fontana, C., and Muñoz-Torres, M. (2021). Mechanisms involved in the relationship between vitamin D and insulin resistance: impact on clinical practice. *Nutrients*, 13(10).

[41] Dalla Man, C., Breton, M. D., and Cobelli, C. (2009). Physical activity into the meal glucose-insulin model of type 1 diabetes: In silico studies. *Journal of Diabetes Science and Technology*, 3(1):56–67.

[42] Dalla Man, C., Caumo, A., Basu, R., Rizza, R., Toffolo, G., and Cobelli, C. (2004). Minimal model estimation of glucose absorption and insulin sensitivity from oral test: Validation with a tracer method. *American Journal of Physiology - Endocrinology and Metabolism*, 287(450).

[43] Dalla Man, C., Caumo, A., and Cobelli, C. (2002). The oral glucose minimal model: Estimation of insulin sensitivity from a meal test. *IEEE Transactions on Biomedical Engineering*, 49(5):419–429.

[44] Datta, B. N. (1999). Stability and inertia. *Linear Algebra and Its Applications*, 302:563–600.

[45] De Gaetano, A. and Arino, O. (2000). Mathematical modelling of the intravenous glucose tolerance test. *Journal of Mathematical Biology*, 40(2):136–168.

[46] De Gaetano, A., Hardy, T., Beck, B., Abu-Raddad, E., Palumbo, P., Bue-Valleskey, J., and Pørksen, N. (2008). Mathematical models of diabetes progression. *American Journal of Physiology - Endocrinology and Metabolism*, 295(6):1462–1479.

[47] Deepa, M., Bhansali, A., Anjana, R., Pradeepa, R., Joshi, S., Joshi, P., Dhandhania, V., Rao, P., Subashini, R., Unnikrishnan, R., Shukla, D., Madhu, S., Das, A., Mohan, V., and Kaur, T. (2014). Knowledge and awareness of diabetes in urban and rural India: The Indian Council of Medical Research India Diabetes Study (Phase I): Indian Council of Medical Research India Diabetes 4. *Indian Journal of Endocrinology and Metabolism*, 18(3):379–385.

[48] DeFronzo, R. A., Hendler, R., and Simonson, D. (1982). Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes*, 31(9):795–801.

[DeFronzo et al.] DeFronzo, R. A., Tobin, J. D., and Andres, R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. *American Journal of Physiology Endocrinology Metabolism and Gastrointestinal Physiology*, 6(3):214–223.

[50] Derouich, M. and Boutayeb, A. (2002). The effect of physical exercise on the dynamics of glucose and insulin. *Journal of Biomechanics*, 35(7):911–917.

[51] Derouich, M., Boutayeb, A., Boutayeb, W., and Lamlili, M. (2014). Optimal control approach to the dynamics of a population of diabetics. *Applied Mathematical Sciences*, 8(53-56):2773–2782.

[52] DHHS (2020). National Diabetes Statistics Report, 2020. Technical report.

[53] Djouima, M., Azar, A. T., Drid, S., and Mehdi, D. (2017). Higher Order Sliding Mode Control for Blood Glucose Regulation of Type 1 Diabetic Patients. *International Journal of System Dynamics Applications*, 7(1):65–84.

[54] Drozdov, A. and Khanina, H. (1995). A model for ultradian oscillations of insulin and glucose. *Mathematical and Computer Modelling*, 22(2):23–38.

[55] Dutta, D., Mondal, S. A., Choudhuri, S., Maisnam, I., Hasanoor Reza, A. H., Bhattacharya, B., Chowdhury, S., and Mukhopadhyay, S. (2014). Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: an open label randomized prospective study from Eastern India. *Diabetes Res Clin Pract*, 103(3):e18–e23.

[56] Eknoyan, G. (2006). A history of diabetes mellitus - A disease of the kidneys that became a kidney disease. *Journal of Nephrology*, 19(SUPPL. 10).

[57] Engelborghs, K., Lemaire, V., Bélair, J., and Roose, D. (2001). Numerical bifurcation analysis of delay differential equations arising from physiological modeling. *Journal of Mathematical Biology*, 42(4):361–385.

[58] Farahmand, B., Dehghani, M., and Vafamand, N. (2019). Fuzzy model-based controller for blood glucose control in type 1 diabetes: An LMI approach. *Biomedical Signal Processing and Control*, 54:101627.

[59] Fereydouneyan, F., Zare, A., and Mehrshad, N. (2011). Using a fuzzy controller optimized by a genetic algorithm to regulate blood glucose level in type 1 diabetes. *Journal of Medical Engineering and Technology*, 35(5):224–230.

[60] Fiala, D., Lomas, K. J., and Stohrer, M. (1999). A computer model of human thermoregulation for a wide range of environmental conditions: The passive system. *Journal of Applied Physiology*, 87(5):1957–1972.

[61] Finegood, D. T., Hramiak, I. M., and Dupre, J. (1990). A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. *Journal of Clinical Endocrinology and Metabolism*, 70(6):1538–1549.

[62] Fisher, M. E. (1991). A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics. *IEEE Transactions on Biomedical Engineering*, 38(1):57–61.

[63] Garcia-Gabin, W., Vehí, J., Bondia, J., Tarín, C., and Calm, R. (2008). Robust Sliding Mode Closed-loop Glucose Control with Meal Compensation in Type 1 Diabetes Mellitus. *IFAC Proceedings Volumes*, 41(2):4240–4245.

[64] Gaz, C., De Gaetano, A., Manes, C., Palumbo, P., Borri, A., and Panunzi, S. (2017). Effective Control of Glycemia using a Simple Discrete-delay Model. In *IFAC-PapersOnLine*, volume 50, pages 13526–13531. Elsevier B.V.

[65] Gerard, K., Donaldson, C., and Maynard, A. K. (1989). The Cost of Diabetes. *Diabetic Medicine*, 6(2):164–170.

[66] Gharghory, S. M. and El-Dib, D. A. (2016). Fuzzy Control System for Regulating the Blood Glucose Level of Diabetes Patients Implemented on FPGA. *Journal of Circuits, Systems and Computers*, 25(12):1650161.

[67] Goghari, Z. S., Vosoughi, R., and Jafari, A. H. (2022). Modelling System of Two Insulin-Glucose Delays to Achieve the Dynamics of Glucose Changes. *Journal of Biomedical Physics and Engineering*, 12(2):189–204.

[68] Goharimanesh, M., Akbari, A. A., Lashkaripour, A., and Akbari, A. A. (2015). A Comparison of Fuzzy Types 1 and 2 in Diabetics Control, Based on Augmented Minimal Model. *Journal of World's Electrical Engineering and Technology*, 4(2):70–75.

[69] Grammatiki, M., Karras, S., and Kotsa, K. (2019). The role of vitamin D in the pathogenesis and treatment of diabetes mellitus: a narrative review. *Hormones*, 18(1):37–48.

[70] Grant, P. (2007). A new approach to diabetic control: Fuzzy logic and insulin pump technology. *Medical Engineering and Physics*, 29(7):824–827.

[71] Grimnes, G., Figenschau, Y., Almås, B., and Jorde, R. (2011). Vitamin D, insulin secretion, sensitivity,and lipids: Results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. *Diabetes*, 60(11):2748–2757.

[72] Hachana, A. and Abdelaziz, M. (2015). H-infinity controller design for blood glucose regulation in diabetes patients in the presence of uncertain parameters. *3rd International Conference on Control, Engineering and Information Technology, CEIT 2015*.

[73] Hamzeh, A., Almhanni, G., Aljaber, Y., Alhasan, R., Alhasan, R., Alsamman, M. I., Alhalabi, N., and Haddeh, Y. (2019). Awareness of diabetes and diabetic retinopathy among a group of diabetic patients in main public hospitals in Damascus, Syria during the Syrian crisis. *BMC Health Services Research*, 19(1):1–10.

[74] Hernández-Ordoñez, M. and Campos-Delgado, D. U. (2008). An extension to the compartmental model of type 1 diabetic patients to reproduce exercise periods with glycogen depletion and replenishment. *Journal of Biomechanics*, 41(4):744–752.

[75] Heydarinejad, H., Delavari, H., and Baleanu, D. (2019). Fuzzy type-2 fractional Backstepping blood glucose control based on sliding mode observer. *International Journal of Dynamics and Control*, 7(1):341–354.

[76] Hoseini, S. A., Aminorroaya, A., Iraj, B., and Amini, M. (2013). The effects of oral vitamin D on insulin resistance in pre-diabetic patients. 18(1):47–51.

[77] Huang, M., Li, J., Song, X., and Guo, H. (2012). Modeling impulsive injections of insulin: Towards artificial pancreas. *SIAM Journal on Applied Mathematics*, 72(5):1524–1548.

[78] Huard, B. and Kirkham, G. (2022). Mathematical modelling of glucose dynamics. *Current Opinion in Endocrine and Metabolic Research*, 25:100379.

[79] Huu, T. T. T., Tran, H. D., Tran, T. N., and Hoang, B. B. (2021). Relationship between vitamin D status and the relevant parameters of glucose in patients with type 2 diabetes. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 14:2489–2494.

[80] Ibbini, M. (2006). A PI-fuzzy logic controller for the regulation of blood glucose level in diabetic patients. *Journal of Medical Engineering and Technology*, 30(2):83–92.

[81] Ibbini, M. S. and Masadeh, M. A. (2005). A fuzzy logic based closed-loop control system for blood glucose level regulation in diabetics. *Journal of Medical Engineering and Technology*, 29(2):64–69.

[82] Jain, V. and Raheja, S. (2015). Improving the Prediction Rate of Diabetes using Fuzzy Expert System. *International Journal of Information Technology and Computer Science*, 7(10):84–91.

[83] Jauslin, P. M., Silber, H. E., Frey, N., Gieschke, R., Simonsson, U. S., Jorga, K., and Karlsson, M. O. (2007). An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics. *Journal of Clinical Pharmacology*, 47(10):1244–1255.

[84] Javier, B. (2011). My β IG Fat Math Model : β -Cell Compensation and Type 2 Diabetes. In *In Conference society for advancement of Hispanic/Chicanos and Native Americans in Science.*, pages 2–35.

[85] Kahar, K. N. B. A. and bin Mamat, M. (2014). Minimal modeling of glucose-insulin interactions: In the intravenous glucose tolerance test. *Applied Mathematical Sciences*, 8(65-68):3273–3281.

[86] Kang, S. L., Hwang, Y. N., Kwon, J. Y., and Kim, S. M. (2022). Effectiveness and safety of a model predictive control (MPC) algorithm for an artificial pancreas system in outpatients with type 1 diabetes (T1D): systematic review and meta-analysis. *Diabetology and Metabolic Syndrome*, 14(1):1–12.

[87] Kardar, L., Fallah, A., Gharibzadeh, S., and Moztarzadeh, F. (2008). Application of fuzzy logic controller for intensive insulin therapy in type 1 diabetic mellitus patients by subcutaneous route. 3(8):712–721.

[88] Karmegam, D. and Mappillairaju, B. (2022). Social media analytics and reachability evaluation - #Diabetes. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, 16(1):102359.

[89] Kayani, M. H. Q., Malik, K. N., Ahmad, S., Khaqan, A., Shuja, S., Qadeer-Ul-Hasan, Malik, S. A., and Riaz, R. A. (2017). A switching based PID technique for blood glucose control. *Biomedical Research (India)*, 28(19):8477–8483.

[90] Kayaniyil, S., Retnakaran, R., Harris, S. B., Vieth, R., Knight, J. A., Gerstein, H. C., Perkins, B. A., Zinman, B., and Hanley, A. J. (2011). Prospective associations of vitamin D with β-cell function and glycemia: The PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. *Diabetes*, 60(11):2947–2953.

[91] Khan, M. A. B., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., and Kaabi, J. A. (2020). Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. *Journal of Epidemiology and Global Health*, 10(1):107–111.

[92] Khooban, M. H., Maryam ABADI, D. N., Alfi, A., and Siahi, M. (2013). Swarm optimization tuned mamdani fuzzy controller for diabetes delayed model. *Turkish Journal of Electrical Engineering and Computer Sciences*, 21(SUPPL. 1):2110–2126.

[93] Kienitz, K. H. and Yoneyama, T. (1993). A Robust Controller for Insulin Pumps Based on H-Infinity Theory. *IEEE Transactions on Biomedical Engineering*, 40(11):1133–1137.

[94] Kim, J., Saidel, G. M., and Cabrera, M. E. (2007). Multi-scale computational model of fuel homeostasis during exercise: Effect of hormonal control. *Annals of Biomedical Engineering*, 35(1):69–90.

[95] Kouidere, A., Labzai, A., Ferjouchia, H., Balatif, O., and Rachik, M. (2020a). A New Mathematical Modeling with Optimal Control Strategy for the Dynamics of Population of Diabetics and Its Complications with Effect of Behavioral Factors. *Journal of Applied Mathematics*, 2020:1–12.

[96] Kouidere, A., Labzai, A., Khajji, B., Ferjouchia, H., Balatif, O., Boutayeb, A., and Rachik, M. (2020b). Optimal control strategy with multi-delay in state and control variables of a discrete mathematical modeling for the dynamics of diabetic population. *Communications in Mathematical Biology and Neuroscience*, 2020(0):1–14.

[97] Lam, Z. H., Hwang, K. S., Lee, J. Y., Chase, J. G., and Wake, G. C. (2002). Active insulin infusion using optimal and derivative-weighted control. *Medical Engineering and Physics*, 24(10):663–672.

[98] Lawrence, R. D. (1926). The effect of exercise on insulin action in diabetes. *British Medical Journal*, 1(3406):648–650.

[99] Lee, C. T. C., Harris, S. B., Retnakaran, R., Gerstein, H. C., Perkins, B. A., Zinman, B., and Hanley, A. J. (2014). White blood cell subtypes, insulin resistance and β-cell dysfunction in high-risk individuals - The PROMISE cohort. *Clinical Endocrinology*, 81(4):536–541.

[100] Li, B., Kuang, Y., and Li, J. (2001). Analysis of IVGTT glucose-insulin interaction models with time delay. *Discrete and Continuous Dynamical Systems - Series B*, 1(1):103–124.

[101] Li, J. and Kuang, Y. (2008). Pharmacokinetical models of subcutaneous injection of insulin analogues for type 1 diabetes. *Proceedings of 7th AIMS International Conference*, (October 2007):18–21.

[102] Li, J., Kuang, Y., and Mason, C. C. (2006). Modeling the glucose-insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays. *Journal of Theoretical Biology*, 242(3):722–735.

[103] Li, X., Liu, Y., Zheng, Y., Wang, P., and Zhang, Y. (2018). The effect of vitamin D supplementation on glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. *Nutrients*, 10(3).

[104] Lin, X., Xu, Y., Pan, X., Xu, J., Ding, Y., Sun, X., Song, X., Ren, Y., and Shan, P. F. (2020). Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Scientific Reports*, 10(1):1–11.

[105] Liu, G., Qutub, A. A., Vempati, P., Mac Gabhann, F., and Popel, A. S. (2011). Module-based multiscale simulation of angiogenesis in skeletal muscle. *Theoretical Biology and Medical Modelling*, 8(1):1–26.

[106] Liu, S. W., Huang, H. P., Lin, C. H., and Chien, I. L. (2013). Fuzzy-logic-based supervisor of insulin bolus delivery for patients with type 1 diabetes mellitus. *Industrial and Engineering Chemistry Research*, 52(4):1678–1690.

[107] Lunze, K., Singh, T., Walter, M., Brendel, M. D., and Leonhardt, S. (2013). Blood glucose control algorithms for type 1 diabetic patients: A methodological review. *Biomedical Signal Processing and Control*, 8(2):107–119.

[108] M., S. and V., B. (2019). Correlation between ABO blood groups and body mass index among medical students. Technical Report 10.

[109] Mahikul, W., White, L. J., Poovorawan, K., Soonthornworasiri, N., Sukontamarn, P., Chanthavilay, P., Pan-Ngum, W., and Medley, G. F. (2019). A population dynamic model to assess the diabetes screening and reporting programs and project the burden of undiagnosed diabetes in thailand. *International Journal of Environmental Research and Public Health*, 16(12):2207.

[110] Makroglou, A. and Karaoustas, I. (2011). A review on delay differential equation models in diabetes modeling, II: the insulin therapies and the intracellular activities of β-cells case. *Mathematics and Computers in Simulation*, pages 1–24.

[111] Mancilla, R., Krook, A., Schrauwen, P., and Hesselink, M. K. (2020). Diurnal Regulation of Peripheral Glucose Metabolism: Potential Effects of Exercise Timing. *Obesity*, 28(S1):S38–S45.

[112] Marheineke, N., Cibis, T. M., Schiessl, S., and Pielmeier, U. (2014). Optimal control of glucose balance in ICU patients based on GlucoSafe model. *Journal of Mathematics in Industry*, 4(1):1–13.

[113] Mari, A., Schmitz, O., Gastaldelli, A., Oestergaard, T., Nyholm, B., and Ferrannini, E. (2002). Meal and oral glucose tests for assessment of β-cell function: Modeling analysis in normal subjects. *American Journal of Physiology - Endocrinology and Metabolism*, 283(6 46-6).

[114] Matsuda, M. and DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. *Diabetes Care*, 22(9):1462–1470.

[115] Mauseth, R., Hirsch, I. B., Bollyky, J., Kircher, R., Matheson, D., Sanda, S., and Greenbaum, C. (2013). Use of a “fuzzy logic” controller in a closed-loop artificial pancreas. *Diabetes Technol Therapeut*, 15(8):628–633.

[116] McDonald, C., Dunaif, A., and Finegood, D. T. (2000). Minimal-Model Estimates of Insulin Sensitivity Are Insensitive to Errors in Glucose Effectiveness 1 . *The Journal of Clinical Endocrinology & Metabolism*, 85(7):2504–2508.

[117] McLeod, R., Keshavjee, S., Ahmed, N., Richards, R., Fehlings, M. G., Nathens, A., Rotstein, O. D., and Rutka, J. T. (2022). History of the Department of Surgery at the University of Toronto: celebrating a centennial of progress and innovation. *Canadian Journal of Surgery*, 65(1):56–65.

[118] Menani, K., Mohammadridha, T., Magdelaine, N., Abdelaziz, M., and Moog, C. H. (2017). Positive sliding mode control for blood glucose regulation. *International Journal of Systems Science*, 48(15):3267–3278.

[119] Metwaly, A. M., Ghoneim, M. M., Eissa, I. H., Elsehemy, I. A., Mostafa, A. E., Hegazy, M. M., Afifi, W. M., and Dou, D. (2021). Traditional ancient Egyptian medicine: A review. *Saudi Journal of Biological Sciences*, 28(10):5823–5832.

[120] Mohammadzadeh, A. and Kumbasar, T. (2020). A new fractional-order general type-2 fuzzy predictive control system and its application for glucose level regulation. *Applied Soft Computing Journal*, 91:106241.

[121] Mosavi, A. H., Mohammadzadeh, A., Rathinasamy, S., Zhang, C., Reuter, U., Levente, K., and Adeli, H. (2022). Deep learning fuzzy immersion and invariance control for type-I diabetes. *Computers in Biology and Medicine*, 149(August).

[122] Nakamura, Y., Horie, I., Kanetaka, K., Eguchi, S., Nakamichi, S., Hongo, R., Takashima, M., Kawakami, A., and Abiru, N. (2022). Exenatide challenge in oral glucose tolerance test is insufficient for predictions of glucose metabolism and insulin secretion after sleeve gastrectomy (SG) in obese patients with type 2 dia-

betes: a pilot study to establish a preoperative model to estimat. *Endocrine Journal*, 69(12):1457–1465.

[123] Nath, A. and Dey, R. (2019). Robust observer based control for plasma glucose regulation in type 1 diabetes patient using attractive ellipsoid method. *IET Systems Biology*, 13(2):84–91.

[124] Nazar, C. M. J., Bojerenu, M. M., Safdar, M., and Marwat, J. (2016). Effectiveness of diabetes education and awareness of diabetes mellitus in combating diabetes in the United Kigdom; a literature review. *Journal of nephropharmacology*, 5(2):110–115.

[125] N'Doye, I., Voos, H., Darouach, M., and Schneider, J. G. (2015). Static output feedback H_∞ control for a fractional-order glucose-insulin system. *International Journal of Control, Automation and Systems*, 13(4):798–807.

[126] Nittala, A., Ghosh, S., Stefanovski, D., Bergman, R., and Wang, X. (2006). Dimensional analysis of MINMOD leads to definition of the disposition index of glucose regulation and improved simulation algorithm. *BioMedical Engineering Online*, 5(1):1–15.

[127] Nizam Ozogur, H., Ozogur, G., and Orman, Z. (2021). Blood glucose level prediction for diabetes based on modified fuzzy time series and particle swarm optimization. *Computational Intelligence*, 37(1):155–175.

[128] Ogurtsova, K., da Rocha Fernandes, J. D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., Cavan, D., Shaw, J. E., and Makaroff, L. E. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Research and Clinical Practice*, 128:40–50.

[129] Oh, S. H., Ku, H., and Park, K. S. (2021). Prevalence and socioeconomic burden of diabetes mellitus in South Korean adults: a population-based study using administrative data. *BMC Public Health*, 21(1):1–13.

[130] Pacini, G. and Bergman, R. N. (1986). MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. *Computer Methods and Programs in Biomedicine*, 23(2):113–122.

[131] Pacini, G., Tonolo, G., Sambataro, M., Maioli, M., Ciccarese, M., Brocco, E., Avogaro, A., and Nosadini, R. (1998). Insulin sensitivity and glucose effectiveness: Minimal model analysis of regular and insulin-modified FSIGT. *American Journal of Physiology - Endocrinology and Metabolism*, 274(4 37-4):E592—-E599.

[132] Palumbo, P., Pepe, P., Panunzi, S., and De Gaetano, A. (2012). Time-Delay Model-Based Control of the Glucose-Insulin System, by Means of a State Observer. *European Journal of Control*, 18(6):591–606.

[133] Panunzi, S., De Gaetano, A., and Mingrone, G. (2010). Advantages of the single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test. *Theoretical Biology and Medical Modelling*, 7(1):1–20.

[134] Parker, R. S., Doyle, F. J., Ward, J. H., and Peppas, N. A. (2000). Robust HâĹđ glucose control in diabetes using a physiological model. *AIChE Journal*, 46(12):2537–2549.

[135] Parsa, N. T., Vali, A. R., and Ghasemi, R. (2014). Back Stepping Sliding Mode Control of Blood Glucose for Type I Diabetes. *International Journal of Medical, Health, Biomedical and Pharmaceutical Engineering*, 8(11):730–734.

[136] Periwal, V., Chow, C. C., Bergman, R. N., Ricks, M., Vega, G. L., and Sumner, A. E. (2008). Evaluation of quantitative models of the effect of insulin on lipolysis and glucose disposal. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 295(4):1089–1096.

[137] Permatasari, A. H., Tjahjana, R. H., and Udjiani, T. (2018). Existence and characterization of optimal control in mathematics model of diabetics population. *Journal of Physics: Conference Series*, 983(1):012069.

[138] Picchini, U., Ditlevsen, S., and De Gaetano, A. (2006). Modeling the euglycemic hyperinsulinemic clamp by stochastic differential equations. *Journal of Mathematical Biology*, 53(5):771–796.

[139] Pramono, A., Jocken, J. W., Blaak, E. E., and van Baak, M. A. (2020). The effect of vitamin D supplementation on insulin sensitivity: A systematic review and meta-analysis. *Diabetes Care*, 43(7):1659–1669.

[140] Rafiq, S. and Jeppesen, P. B. (2018). Is hypovitaminosis D related to incidence of type 2 diabetes and high fasting glucose level in healthy subjects: A systematic review and meta-analysis of observational studies. *Nutrients*, 10(1).

[141] Rathee, S. and Nilam (2015). Quantitative analysis of time delays of glucose - insulin dynamics using artificial pancreas. *Discrete and Continuous Dynamical Systems - Series B*, 20(9):3115–3129.

[142] Rathee, S., Nilam, and Alexander, M. E. (2021). The effects of vitamin D on glucose-insulin dynamics: mathematical model and simulation. *Journal of Diabetes, Metabolic Disorders & Control*, 8(2):105–114.

[143] Reaven, G. M., Bernstein, R., Davis, B., and Olefsky, J. M. (1976). Nonketotic diabetes mellitus: Insulin deficiency or insulin resistance? *The American Journal of Medicine*, 60(1):80–88.

[144] Reddy, G. T. and Khare, N. (2016). FFBAT- Optimized rule based fuzzy logic classifier for diabetes. *International Journal of Engineering Research in Africa*, 24(June):137–152.

[145] Robertson, G., Lehmann, E. D., Sandham, W., and Hamilton, D. (2011). Blood glucose prediction using artificial neural networks trained with the AIDA diabetes simulator: A proof-of-concept pilot study. *Journal of Electrical and Computer Engineering*, 2011.

[146] Rockwell, M., Kraak, V., Hulver, M., and Epling, J. (2018). Clinical management of low vitamin D: A scoping review of physicians' practices. *Nutrients*, 10(4).

[147] Rowley, W. R., Bezold, C., Arikan, Y., Byrne, E., and Krohe, S. (2017). Diabetes 2030: Insights from Yesterday, Today, and Future Trends. *Population Health Management*, 20(1):6–12.

[148] Roy, A. and Parker, R. S. (2007). Dynamic modeling of exercise effects on plasma glucose and insulin levels. In *Journal of Diabetes Science and Technology*, volume 1, pages 338–347.

[149] Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., and Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, 157(107843):107843.

[150] Saiti, K., Macaš, M., Štechová, K., Pithová, P., and Lhotská, L. (2017). A Review of model prediction in diabetes and of designing glucose regulators based on model predictive control for the artificial pancreas. In *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, volume 10443 LNCS, pages 66–81.

[151] Sarah, W. and Gojka, R. (2004). Estimates for the year 2000 and projections for 2030. *World Health*, 27(5):1047.

[152] Sasi, A. Y. B. and Elmalki, M. A. (2013). A Fuzzy Controller for Blood Glucose-Insulin System. *Journal of Signal and Information Processing*, 04(02):111–117.

[153] Segre, G., Turco, G. L., and Vercellone, G. (1973). Modeling blood glucose and insulin kinetics in normal, diabetic and obese subjects. *Diabetes*, 22(2):94–103.

[154] Sharma, R., Mohanty, S., and Basu, A. (2017). Enhancement of Digital PID Controller Performance for Blood Glucose Level of Diabetic Patients using Disparate Tuning Techniques. *Indian Journal of Science and Technology*, 10(17):1–9.

[155] Sherwin, R. S., Kramer, K. J., Tobin, J. D., Insel, P. A., Liljenquist, J. E., Berman, M., and Andres, R. (1974). A model of the kinetics of insulin in man. *Journal of Clinical Investigation*, 53(5):1481–1492.

[156] Shrivastava, S. R. B. L., Shrivastava, P. S., and Ramasamy, J. (2013). Role of self-care in management of diabetes mellitus. *Journal of Diabetes and Metabolic Disorders*, 12(1):1–5.

[157] Silber, H. E., Jauslin, P. M., Frey, N., and Karlsson, M. O. (2007). An integrated model for the glucose-insulin system. In *Basic and Clinical Pharmacology and Toxicology*, volume 106, pages 189–194.

[158] Singh, S., Jajoo, S., Shukla, S., and Acharya, S. (2020). Educating patients of diabetes mellitus for diabetic foot care. *Journal of Family Medicine and Primary Care*, 9(1):367.

[159] Som, A. M., Yusof, N. F. M., Ali, S. A., and Fuzil, N. S. (2019). Meal disturbance effect on blood glucose control for type 1 diabetes using improved Hovorka equations. In *Key Engineering Materials*, volume 797, pages 158–167.

[160] Sorensen, J. T. (1985). *A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes*. PhD thesis.

[161] Soylu, S. and DaniÅ§man, K. (2018). Blood glucose control using an ABC algorithm-based fuzzy-PID controller. *Turkish Journal of Electrical Engineering and Computer Sciences*, 26(1):172–183.

[162] Ståhl, F. and Johansson, R. (2009). Diabetes mellitus modeling and short-term prediction based on blood glucose measurements. *Mathematical Biosciences*, 217(2):101–117.

[163] Steil, G. M., Palerm, C. C., Kurtz, N., Voskanyan, G., Roy, A., Paz, S., and Kandeel, F. R. (2011). The effect of insulin feedback on closed loop glucose control. *Journal of Clinical Endocrinology and Metabolism*, 96(5):1402–1408.

[164] Sturis, J., Polonsky, K. S., Mosekilde, E., and Van Cauter, E. (1991). Computer model for mechanisms underlying ultradian oscillations of insulin and glucose. *American Journal of Physiology - Endocrinology and Metabolism*, 260(5 23-5):801–809.

[165] Sylvester, D. D. and Munje, R. K. (2017). Back Stepping SMC for Blood Glucose Control of Type-1 Diabetes Mellitus Patients. *International Journal of Engineering Technology Science and Research*, 4(5):1–7.

[166] Szablewski, L. (2019). *Blood Glucose Levels*. InTech.

[167] Szymczak-Pajor, I. and Śliwińska, A. (2019). Analysis of association between vitamin d deficiency and insulin resistance. *Nutrients*, 11(4).

[168] Tadić, D., Popović, P., and Dukić, A. (2010). *A fuzzy approach to evaluation and management of therapeutic procedure in diabetes mellitus treatment*, volume 20.

[169] Taghian Dinani, S., Zekri, M., and Nazari, B. (2013). Fuzzy high-order sliding-mode control of blood glucose concentration. *Proceedings of the 3rd International Conference on Computer and Knowledge Engineering, ICCKE 2013*, pages 40–45.

[170] Tai, K., Need, A. G., Horowitz, M., and Chapman, I. M. (2008). Vitamin D, glucose, insulin, and insulin sensitivity. *Nutrition*, 24(3):279–285.

[171] Tan, P. K., Kuppusamy, U. R., Chua, K. H., and Arumugam, B. (2022). Emerging Strategies to Improve the Stability and Bioavailability of Insulin: An Update on Formulations and Delivery Approaches. *Current Drug Delivery*, 20.

[172] Tang, R. and Li, L. (2021). Modulation of Short-Chain Fatty Acids as Potential Therapy Method for Type 2 Diabetes Mellitus. *Canadian Journal of Infectious Diseases and Medical Microbiology*, 2021.

[173] Toffolo, G., Bergman, R. N., Finegood, D. T., Bowden, C. R., and Cobelli, C. (1980). Quantitative estimation of beta cell sensitivity to glucose in the intact organism. A minimal model of insulin kinetics in the dog. *Diabetes*, 29(12):979–990.

[174] Toffolo, G. and Cobelli, C. (2003). The hot IVGTT two-compartment minimal model: An improved version. *American Journal of Physiology - Endocrinology and Metabolism*, 284(2 47-2):317–321.

[175] Tolić, I. M., Mosekilde, E., and Sturis, J. (2000). Modeling the insulin-glucose feedback system: The significance of pulsatile insulin secretion. *Journal of Theoretical Biology*, 207(3):361–375.

[176] Topp, B., Promislow, K., Devries, G., Miura, R. M., and Finegood, D. T. (2000). A model of β-cell mass, insulin, and glucose kinetics: Pathways to diabetes. *Journal of Theoretical Biology*, 206(4):605–619.

[177] Tunç, M., ÅđiÅ§bot, S., and Gülkaya, A. K. (2011). Computational evaluation of the dynamic minimal model for the root causes of hypoglycemia. *Journal of Biomedical Science and Engineering*, 04(05):391–396.

[178] Umaefulam, V. and Premkumar, K. (2020). Impact of mobile health in diabetic retinopathy awareness and eye care behavior among Indigenous women. *mHealth*, 6(14):14–14.

[179] U.S. Department of Health and Human Services (2017). Story of DiscoveryâĂŤArtificial Pancreas for Managing Type 1 Diabetes: Cutting-edge Technology 50 Years in the Making. Technical report.

[180] Vicini, P., Caumo, A., and Cobelli, C. (1997). The hot IVGTT two-compartment minimal model: Indexes of glucose effectiveness and insulin sensitivity. *American Journal of Physiology - Endocrinology and Metabolism*, 273(5 36-5).

[181] Wallace, T. M., Levy, J. C., and Matthews, D. R. (2004). Use and abuse of HOMA modeling. 27(6):1487–1495.

[182] Wang, H., Li, J., and Kuang, Y. (2007). Mathematical modeling and qualitative analysis of insulin therapies. *Mathematical Biosciences*, 210(1):17–33.

[183] Wang, H., Li, J., and Kuang, Y. (2009). Enhanced modelling of the glucoseâĂŞinsulin system and its applications in insulin therapies. *Journal of Biological Dynamics*, 3(1):22–38.

[184] Wasserman, D. H. (2009). Four grams of glucose. *American Journal of Physiology - Endocrinology and Metabolism*, 296(1):11–21.

[185] Watkins, P. J. (1982). What is diabetes? *British Medical Journal*, 284(6330):1690–1692.

[186] Watson, E. M., Chappell, M. J., Ducrozet, F., Poucher, S. M., and Yates, J. W. (2009). *A new general glucose homeostatic model using a proportional-integral-derivative controller*, volume 42. IFAC.

[187] Welch, S., Gebhart, S. S., Bergman, R. N., and Phillips, L. S. (1990). Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. *Journal of Clinical Endocrinology and Metabolism*, 71(6):1508–1518.

[188] Xiao, J., Lv, J., Wang, S., Zhou, Y., Chen, L., Lu, J., Zhang, X., Wang, X., Gu, Y., and Lu, Q. (2021). Association of serum 25-hydroxyvitamin D with metabolic syndrome and type 2 diabetes: a one sample Mendelian randomization study. *BMC geriatrics*, 21(1):391.

[189] Xu, Y., Wang, L., He, J., Bi, Y., Li, M., Wang, T., Wang, L., Jiang, Y., Dai, M., Lu, J., Xu, M., Li, Y., Hu, N., Li, J., Mi, S., Chen, C. S., Li, G., Mu, Y., Zhao, J., Kong, L., Chen, J., Lai, S., Wang, W., Zhao, W., and Ning, G. (2013). Prevalence and control of diabetes in Chinese adults. *Jama*, 310(9):948–958.

[190] Yadav, J., Rani, A., and Singh, V. (2016). Performance Analysis of Fuzzy-PID Controller for Blood Glucose Regulation in Type-1 Diabetic Patients. *Journal of Medical Systems*, 40(12):1–15.

[191] Yasini, S., Naghibi-Sistani, M. B., and Karimpour, A. (2008). Active insulin infusion using fuzzy-based closed-loop control. *Proceedings of 2008 3rd International*

Conference on Intelligent System and Knowledge Engineering, ISKE 2008, pages 429–434.

[192] Zimmet, P. Z. (2017). Diabetes and its drivers: The largest epidemic in human history? *Clinical Diabetes and Endocrinology*, 3(1):1–8.

Publications

1. **Ankit Sharma**, Harendra Pal Singh and Nilam; *A methodical survey of mathematical model-based control techniques based on open and closed loop control approach for diabetes management*, International Journal of Biomathematics (**SCI**), issue. **07**, vol. 15 (2022), ***Impact Factor* - 2.129**, DOI: https://doi.org/10.1142/S1793524522500516

2. **Ankit Sharma**, Harendra Pal Singh and Nillam; *Physical Exercise: Effective Aspect in Diabetes Management*, Advances in Intelligent Systems and Computing, pp 261-273, vol 1440 (2023), DOI: https://doi.org/10.1007/978-981-19-9906-2_22.

3. **Ankit Sharma**, Nilam and Harendra pal Singh; *Vitamin D: The Miracle Nutrient for Preventing and Managing Diabetes* (communicated).

4. **Ankit Sharma**, Nilam and Harendra pal Singh; *An Effective Fuzzy Logic Controller to Determine the Optimal Awareness Percentage for Diabetes Progression* (communicated).

5. **Ankit Sharma**, Nilam and Harendra Pal Singh; *Computer-controlled diabetes disease diagnosis technique based on fuzzy inference structure for insulin dependent patients*, Applied Intelligence (**SCI**), vol. 53 (2018). ***Impact Factor* - 5.019**, DOI: https://doi.org/10.1007/s10489-022-03416-4

6. **Ankit Sharma**, Nilam and Harendra Pal Singh; *An Optimal PID-Fuzzy Logic Insulin Infusion Mechanism for Type I Diabetes in the advancement of Artificial Pancreas* (communicated).

List of Conferences

1. **Ankit Sharma**, Harendra Pal Singh and Nilam; *Role of Control Algorithm in Managment of Diabetes*, presented at International Conference on Recent Advances in Pure and Applied Mathematics held at DTU Delhi, India, October 23-25, 2018.

2. **Ankit Sharma**, Nilam and Hrendra Pal Singh; *Physical Exercise: Effective Aspect in Diabetes Management*, presented at 3^{rd} International Conference on Mathematical Modeling,Computational Intelligence Techniques and Renewable Energy (MMCITRE - 2022). March 04-06, 2022.
