Project Report

On

STUDY ON MATHEMATICAL MODELLING OF DIABETES MELLITUS

Submitted

in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE

in

MATHEMATICS

by

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(Register No. SM20MAT008)

(2020-2022)

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APRIL 2022

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CERTIFICATE

This is to certify that the dissertation entitled, **A STUDY ON MATHEMATICAL MODELLING OF DIABETES MELLITUS is a bonafide** record of the work done by Ms. **KRISHNAPRIYA SUNILKUMAR** under **my guidance as partial fulfillment of the award of the degree of Master of Science in Mathematics** at St. Teresa's College (Autonomous), Ernakulam af**filiated to Mahatma Gandhi University, Kottayam.** No part of this **work has been** submitted for any other degree elsewhere.

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DECLARATION

I hereby declare that the work presented in this project is based on the original work done by me under the guidance of **NISHA OOMMEN**, Assistant Professor, Department of Mathematics, St. Teresa's College(Autonomous), Ernakulam and has not been included in any other project submitted previously for the award of any degree.

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ACKNOWLEDGEMENTS

I express my deep sense of gratitude to NISHA OOMMEN, Assistant Professor of department of Mathematics, St. Teresa's College, Ernakulam for her valuable guidance, constant suggestion and encouragement throughout my course of the project.

I am also extremely grateful to our HOD Dr. URSALA PAUL for her continuous support and all the teachers of our department who provided us with the necessities for the completion of the project.

I also wish to thank my group members and all others who have given me the moral support and helped me to complete my project and made this venture a success. Above all, I thank God almighty and my parents for giving me the blessings to take over this project.

Krishnapriya.

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Date: 26/05/2022. **SM20MAT008**

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Chapter 1

INTRODUCTION AND HISTORY OF DIABETES

1.1 INTRODUCTION

Diabetes mellitus commonly known as diabetes is a disease in glucose-insulin endocrine metabolic system.Glucose metabolism is intensively investigated by using mathematical models. Mathematical modelling become the most powerful tool in the dynamic behaviour of non-infectious diseases.
Modelling is referred as a method of simulating real life situations with mathematical equations to forecast their future behaviour. Mathematical models are used to understand and predict the behaviour of biological systems. Glucose- insulin regulation dynamic model is useful for developing treatment strategies. Mathematical modelling plays an important role in the process of description, prediction and evaluation of diabetes mellitus.

A realistic representation of the long-term physiologic adaptation is necessary for evaluating diabetes, prevention or disease modification therapies. This project is study on different models for detecting diabetes mellitus.

Differential equations involving time delay are an exciting form of differential equations having various kind of applications, specifically in

the biological and medical worlds. The ultimate aim of developing models of diabetes is to understand the dynamics and use that knowledge to efficiently for its control and treatment. Mathematical modelling tightly linked to experiments had a greater impact in our understanding of diabetes.

1.2 Ancient times to 20th century

Aretaeus of cappadocia in the 2ND century AD was the first who used the term "DIABETES" from the Greek word for a siphon ,because the fluid does not remain in the body ,but uses the man's body as a channel whereby to leave it.The Hindu physicians, Charak and Sushrut who wrote between 400 and 500 BC were probably the first to recognise the sweetness of diabetic urine. Charak and Sushrut noted that the disease was mostly in those who were overweight and who indulged in sweet and fatty foods.

physical exercise and liberal quantities of vegetables were the mainstays of treatment in the obese,while lean people,in whom the disease was regarded as more serious were given a nourishing diet. The first description of HYPERGLYCEMIA was in a paper published in 1776. The term DIABETES is the shortened version of full name DIABETES MELLITUS. It was known in 17Th century as the "pissing evil".

The term DIABETES was probably coined by APPOLONIUS OF MEMPHIS around 250 BC.Diabetes is first recorded in English in the form diabetes ,in a medical text written around 1425.It was in 1675 that Thomas Willis added the word mellitus to the word Diabetes. where Mellitus means honey.This was because of the sweet taste had been noticed in urine by the ancient Greek,Chinese, Egyptians,Indians an Persians as is evident from their literature.In 1776, Mathew Dob-son confirmed that the sweet taste of urine of diabetics was due to the ex-

cess of a kind of sugar in the urine and blood of people with Diabetes.In ancient time of medieval ages diabetes was usually a death sentence.

SUSHRUTA an Indian healer identified diabetes and classified it as "MADHUMEHA". The ancient Indians tested for diabetes and by looking at whether ants were attracted to a person's urine. In 1910 , Edward Albert found that diabetes resulted from the lack of insulin.
He termed the chemical regulating blood sugar as insulin from the Latin "insula" meaning island ,in reference to the insulin producing islets of Langerhans in the pancreas.

1.3 Discovery of insulin

Many attempts were made between 1889 to 1921 to isolate the elusive internal secretion of the pancreas.These largely failed because the extracts were inactive or had unacceptable side effects.

In 1921 Sir Frederick Grant Banting and Charles Herbert Best demonstrate that they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs. This led to the availability of an effective treatment for diabetes in 1922.

IN 1936 Sir Harold Percival differentiated TYPE 1 and TYPE 2 diabetes as different entities. In 1982 the first bio synthetic human insulin - HUMULIN that is identical in chemical structure to human insulin and can be mass produced was approved to market in several countries.

Chapter 2

MATHEMATICAL MODELLING

Mathematical modelling is defined as the translation of real-life problems into mathematical problems, formulating mathematical models necessary for solving a problem and interpretation of the results. It involves solving the mathematical problems and interpreting solution in the language of the real world, validating the conclusions by comparing them with the situation, and then either improving the model or, if it is acceptable, and applying the model to similar situation for evaluation and refinement.

Mathematical modelling defined as the use of mathematics to describe and explain about the real-life situations and for investigate the important questions about the observed conditions.It is used in natural sciences , Physics, biology, earth science, meteorology and in social sciences ,Economics, psychology, sociology, and political science

A mathematical model help to explain a system and to make useful predictions. Mathematical models can take any forms including dynamical systems, statistical models and differential equations.Mathematical modeling may be classified in to theoretical models and empirical models

2.1 Empirical models

Based on data gathered by original experiments or observations.Empirical models are supported by experimental data.Data obtained from experiments are correlated to obtain the derived quantities. A common disadvantage of empirical models is that experimental data are always needed and in most cases,they are applicable only for the modeled experiment under a particular operating condition.Empirical models are not able to predict beyond a particular operating range or designed experiment .

2.2 Theoretical models

Analyzes and makes connections between empirical studies to define or advance a theoretic position.Theoretic models are useful,they cover a wide range of situations and predict extremely well over a very wide range of factor levels. When we have theoretical models then we are in an ideal position.But every theoretical models are based on certain assumptions.If these assumptions are not met then the model may fail to predict correctly.

2.3 Models according to their nature

LINEAR OR NON-LINEAR
STATIC OR DYNAMIC
DETERMINISTIC OR STOCHASTIC
DISCRETE OR CONTINUOUS

Most realistic models are non-linear, dynamic and stochastic. Linear, static or deterministic models are easier and give good approximate results.

2.4 Characteristics of mathematical modelling

*** REALISM OF MODELS:**

Mathematical model to be realistic, represents reality as close as possible.

*** RELATIVE PRECISION OF MODELS:**

Different models differ in

their precision and their agreement with observations.

*** SELF- CONSISTENCY OF MODELS:**

A mathematical model involves equations and in-equations and these must be consistent.

*** COMPLEXITY OF MODELS:**

This can be increased by subdividing variables, by taking more variables and more details.

*** CLEAR THINKING:**

making models one has to be clear about the structure and characteristic of the situation.

*** IDEOLOGY AND UNITY:**

Mathematical modelling gives new ideology and unity to applied mathematics.

Models describe our beliefs about how the world functions. In mathematical modelling we translate those beliefs into the language of mathematics.

It help us to formulate ideas and It has well-defined rules for manipulations.

Chapter 3

DIABETES MELLITUS

Diabetes mellitus commonly known as diabetes is a syndrome of disordered metabolism. It is due to a combination of hereditary and environmental causes. Results in abnormal high blood sugar level known as hyperglycemia. Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body.

Diabetes refers to the group of diseases that leads to high blood glucose levels due to the defects in insulin secretion or insulin action in the body.The most affected parts of such a patient are the eye and kidney. During digestion carbohydrates are broken down into a simple sugar called glucose. When glucose enters the blood stream, the pancreas secretes insulin into blood. Then the liver and muscles immediately remove glucose from the blood.When it fails to do so then diabetes occurs.

Diabetes mellitus is a significant disorder of the metabolism. It causes abnormalities in the metabolism of carbohydrates, fats and proteins.Diabetes is a serious health problem that growing around the world because of several factors including

INCREASING POPULATION DENSITY
URBANISATION
PREVALENCE OF OBESITY
LOW PHYSICAL ACTIVITY

Mathematical modelling plays an important role in the process of description, prediction and evaluation of diabetes mellitus.

A clear description of the main two types of diabetes appeared at the end of 19Th century.

Diabetes mellitus is mainly classified into 2 types: type 1 and type 2 diabetes. There were many other phenotype including gestational ,pancreatic,endocrine,insulin resistant .

3.1 Type1 Diabetes Mellitus

Diabetes occurs due to a diminished product of insulin. So called juvenile onset or insulin-dependent diabetes mellitus (IDDM).

It is an autoimmune disease, in which the victim's own antibodies destroy the insulin-secreting beta-cells in the pancreas.After the initial stages insulin is required for survival.It affects mostly children or young adults mainly non obese and generally under the age of 30 years.As with autoimmune diabetes,however there is clear loss of beta cell function as measured by low or absent c-peptide secretion.

People with type 1 need daily insulin injections to survive and lead normal lives.

3.2 Type2 Diabetes Mellitus

Diabetes occurs due to a diminished product of insulin. So called juvenile onset or insulin-dependent diabetes mellitus (IDDM).

It is an autoimmune disease, in which the victim's own antibodies destroy the insulin-secreting beta-cells in the pancreas.After the initial stages insulin is required for survival.It affects mostly children or young adults mainly non obese and generally under the age of 30 years.As with autoimmune diabetes,however there is clear loss of beta cell function as measured by low or absent c-peptide secretion.

People with type 1 need daily insulin injections to survive and lead normal lives.

3.3 Gestational Diabetes

Another type of diabetes which resembles type 2 diabetes in every aspect, involving a combination of relatively inadequate insulin secretion and responsiveness.It occurs in 2%-5% of all pregnancies and may improve or disappear after delivery.

Untreated gestational diabetes can damage the health of the fetus or mother.

Occurs in pregnancy and caused by pregnancy hormones

Usually goes away when baby is born

Insulin is not working effectively

Increases the risk of type 2 diabetes for mother later in life

Mothers are advised to see the doctor yearly for diabetes test

The main symptom of diabetes are frequent urination (poly urea), increased thirst and increased appetite.

Symptoms may develop quite rapidly within weeks or months in type 1 diabetes.

There has been strong implications of an association between Alzheimer's disease and diabetes.People with type 2 diabetes face a 50%-100% higher risk of developing Alzheimer's disease than non-diabetics.

People with diabetes have a higher risk for heart attack and stroke.

High blood glucose level causes glucose absorption which leads to change in the shape of the lenses of the eyes results in blurred vision.People with diabetes has a higher risk of blindness and other vision problems.

Diabetes can damage the kidneys. Nerve damage, infectious of the feet are caused by diabetes Diabetes can cause skin problems. Skin problems are sometimes first sign that someone has diabetes. Diabetes can lead to problems with teeth and gums.

3.4 Diabetic foot

Foot disease affects nearly 6% of people with diabetes and includes infection,ulceration or destruction of tissues of the foot.It can impair patients quality of life and affect social participation and livelihood.

Uncontrolled diabetes contributes to the development of nephropathy and peripheral arterial disease by complex metabolic pathways.Diabetes also leads to leads to the destruction of bones,joints and soft tissues most commonly in the ankle and foot.

Diabetic foot can be prevented with good glycaemic control , regular foot assessment ,appropriate footwear and by patient education

3.5 Diagnosis of Diabetes Mellitus

Diabetes mellitus is a disease which is characterised by too high sugar levels in the blood and urine. It is usually diagnosed by means of glucose tolerance test(GTT).

Diagnosis now depend on glucose measurement with some using glucose tolerance test.There were no standard criteria for these initially,although glucose levels were clearly above normal.Diagnosis usually occurred after clinical development of the disease with the combination of symptoms with raised glucose in the blood.

The most widely used tests for detecting diabetes are,

GLYCO-HAEMOGLOBIN TEST OR HbA1 TEST

FASTING PLASMA GLUCOSE (FPG) TEST

ORAL GLUCOSE TOLERANCE TEST (OGTT)

RANDOM PLASMA GLUCOSE (RPG)

3.6 Glucose tolerance test

There are many ways of diagnosing diabetes mellitus although an internationally accepted method is the glucose tolerance test.When diabetes mellitus is detected further tests need to be carried out to know whether it is IDDM or NIDDM It is usually based on abnormal carbohydrate tolerance and again this my favorite. Disease occur even in the conditions beside sugar diabetes.Thus,to clearly demonstrate that a given case is caused by abnormal carbohydrate an OGTT has to be demonstrated.The severity of the carbohydrate intolerance is instantly revealed by the level of the fasting blood sugar.

RPG test is sometimes used to diagnose diabetes during a regular health checkup.If RPG measures 200 micro grams per deciliter above then the individuals shows symptoms of diabetes.

3.7 Use of HbA1 Diagnostic Test of Diabetes Mellitus

The introduction of HbA1 as means to test glycemic control has an enormous impact on patient care.It has been proposed many times that it could prove a useful means of diagnosing diabetes as it requires neither fasting nor an OGTT.It also represents glycemic status over weeks and gives real certainty that a person is indeed hyperglycemia.It also subjected to fewer errors within an individual patient although it can obviously be affected by conditions such as anemia's and hemoglobinopathies.

But the test was not sufficiently standardized,the quality of assays was variable,the test is expensive and it is not available at all in many parts of the world.

CONDITION	FASTING PLASMA GLUCOSE (mg/dl)	ORAL GLUCOSE TOLERANCE TEST (mg/dl)
NORMAL	99 OR BELOW	139 OR BELOW
PRE- DIABETIC	100 TO 125	140 TO 199
DIABETIC	126 OR ABOVE	200 OR ABOVE

3.8 Problems with glucose Test

Measurement of glucose does have problems.Accuracy and precision are not problems .The assays measured reducing sugars are not specific.Enzyme assays have largely negated this problem.Accuracy and precision are not problems in well run laboratories with appropriate quality .They are efficient if carefully used ,properly controlled and calibrated but the coefficient of variation can be often be as high 20 % which make them unsuitable for diagnostic purposes. The another problem is, unless blood is separated immediately after withdrawal from the subject there is a steady loss of glucose even when fluoride or other preservatives are present. This can range from 5 to 20%.

There are also potential problems with the subject tested.Fasting glucose is reasonably reproducible but can be influenced by drugs or coexisting conditions or the patient may not have fasted appropriately.

Chapter 4

DIABETES MODELS

4.1 Introduction

The dynamics of glucose and insulin has been studied and mathematically modeled by many researchers over several decades. Diabetes is a chronic disease that occurs when the beta cells in the Langerhans islets of the pancreas does not produce enough insulin or when the body cannot effectively utilize the insulin it produces. Hyperglycemia is a common consequence of uncontrolled diabetes and over time may prove to be fatal. According to International Diabetes Federation 4.6 million people in the age of 20-79 years died from diabetes in 2011, 347 million people have diabetes worldwide and 3.4 million people have died due to this killer disease.

Countries with the highest number of deaths due to diabetes include India, China, United States of America and the Russian Federation. 48% of deaths due to diabetes are in people under the age of 60. Since more than 80% of diabetes deaths were reported to occur in low-income and middle-income countries. Healthy diet, regular exercise and maintaining a normal body weight have been recommended to diabetic patients for a long time, whose costs are minimal. Regular activity reduces the risks of occurrence of Non-insulin Dependent Diabetes Mellitus (NIDDM). This effect is more prominent in people at risk that is the people with obesity, hypertension and family history.

However, NIDDM affects people over the age of 40, for whom rigorous exercise may not be suitable, especially for those with complications such as retinopathy, neuropathy, hypertension or heart problems. Insulin Dependent Diabetes Mellitus (IDDM) affects younger people who are more physically active and glycemia may be controlled with insulin and exercise but with caution so as to avoid both hyperglycemia and hypoglycemia.

Taking into account the cost of monitoring and treating diabetes, Derouich and Boutayeb (2002) have used a simple mathematical model to illustrate the role of physical activity in improving insulin sensitivity and regulating blood glucose concentrations. Simulations were carried out with different values of parameters and graphs were depicted to compare the behavior of blood glucose in NIDDM, IDDM and normal people. They have recommended the regular practice of physical activity to diabetic as well as non-diabetic people especially to those who are at risk. For NIDDM patient, it was found that physical exercise improves insulin sensitivity, lowers the average blood glucose concentration and may improve weight reduction. For IDDM patient, physical exercise should be taken with precaution and insulin and diet properly adjusted according to the patient's predisposition.

4.2 Ackerman's diabetes model

PRELIMINARIES

G = GLUCOSE CONCENTRATION

H = NET HORMONE CONCENTRATION

The hormone INSULIN decreases the blood glucose concentration G and increases the hormone concentration H

The model is described analytically by the equation,

$$\frac{dG}{dt} = F_1(G, H) + J(t)$$

———**(1)**

$$\frac{dH}{dt} = F_2(G, H)$$

———**(2)**

The dependence of F_1 and F_2 on G and H are determined by the value both G and h.

The function j(t) is the external rate at which the blood glucose concentration being increased such as stress, life style and dietary choices. We assume that G and H achieved at optimal value $G_o and H_o$ by the time fasting patient arrived at the hospital.

$F_1(G_o, H_o) = 0$
$F_2(G_o, H_o) = 0$

Since we are interested here in the derivation of G and H from there optimal value, we make the substitution,
$G–G_o = g$
$H–H_o = h$
Then,

$$\frac{dg}{dt} = F_1(G_0 + g, H_0 + h) + J(t)$$

$$\frac{dh}{dt} = F_2(G_0 + g, H_0 + h)$$

Observe that,

$$F_1(G_0+g, H_0+h) = F_1(G_0, H_0) + \frac{\partial F_1(G_0, H_0)}{\partial G}g + \frac{\partial F_1(G_0, H_0)}{\partial H}h + e_1$$

$$F_2(G_0+g, H_0+h) = F_2(G_0, H_0) + \frac{\partial F_2(G_0, H_0)}{\partial G}g + \frac{\partial F_2(G_0, H_0)}{\partial H}h + e_2$$

e_1 and e_2 are very small comparing to g and hence assuming that g and h deviate only slightly from G_0 and H_0
Therefore neglecting the terms e_1 and e_2

$$\frac{dg}{dt} = \frac{\partial F_1(G_0, H_0)}{\partial G}g + \frac{\partial F_1(G_0, H_0)}{\partial H}h + J(t)$$

———(3)

$$\frac{dh}{dt} = \frac{\partial F_2(G_0, H_0)}{\partial G}g + \frac{\partial F_2(G_0, H_0)}{\partial H}h$$

———(4)

We can determine the signs of ,

$\frac{\partial F_1(G_0,H_0)}{\partial G}$ **,** $\frac{\partial F_1(G_0,H_0)}{\partial H}$ **and** $\frac{\partial F_2(G_0,H_0)}{\partial G}$ **,** $\frac{\partial F_2(G_0,H_0)}{\partial H}$

Therefore, the blood glucose concentration will be decreased through tissue uptake of glucose and storing the excess glucose in the liver in the form of glucagon. Consequently,

$\frac{\partial F_1(G_0,H_0)}{\partial G} \rightarrow$ **must be negative**
$\frac{\partial F_2(G_0,H_0)}{\partial H} \rightarrow$ **must be negative**

Since a positive value of H tend to decrease blood glucose levels by facilitating tissue uptake of glucose and increases at the rate at which

glucose is converted into glycogen.

$\frac{\partial F_2(G_0,H_0)}{\partial G} \rightarrow$ **must be positive**
$\frac{\partial F_2(G_0,H_0)}{\partial H} \rightarrow$ **must be negative**
Since a positive value of G causes the endocrine gland to secrete those hormones which tend to increase the H. Therefore, the concentration of hormone in the blood decreases through hormone metabolism.
Then (3) and (4) become

$$\frac{dg}{dt} = -m_1 g - m_2 h + J(t)$$

——**(5)**

$$\frac{dh}{dt} = -m_3 h + m_4 g$$

——**(6)**

$m_1, m_2, m_3 and m_4$ **are positive constants**
(5) and (6) are two first order differential equation for g and h However, we only measure the concentration of glucose in the blood we can remove the variable h.
Differentiating (5)

$$\frac{d^2 g}{dt^2} = -m_1 \frac{dg}{dt} - m_2 \frac{dh}{dt} + \frac{dJ}{dt}$$

Substituting from (6)

$$\frac{d^2 g}{dt^2} = m_1 \frac{dg}{dt} - m_2 m_3 h - m_2 m_4 g + \frac{dJ}{dt}$$

——**(7)**

(5) becomes,

$$m_2 h = -[\frac{dg}{dt}] - m_1 g + J(t)$$

Consequently j(t) satisfies the second order differential equation

$$\frac{d^2g}{dt^2} + (m_1 + m_3)\frac{dg}{dt} + (m_2m_3 + m_2m_4)g = m_3J + \frac{dJ}{dt}$$

We rewrite the equation by,

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + \omega_0^2 g = S(t)$$

,
where $\alpha = \frac{m_1+m_3}{2}$ **,**
$\omega_0^2 = m_1m_3 + m_2m_4$**,**
$\mathbf{S(t)=m_3}J + \frac{dJ}{dt}$

Right side of (8) is identically zero for a very short time interval in which the glucose load is being ingested. Now let t=0 be the time at which the glucose load has been completely ingested.

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + \omega_0^2 g = 0$$

——(9)

This equation has positive coefficients. Hence g(t) approaches zero as t approaches infinity. Therefore, the model certainly confirms to reality in predicting that the blood glucose concentration tends to return eventually to its optimal concentration. The solution g(t) of (9) are of three different types on depending that,

$\alpha^2 - \omega_0^2 \rightarrow$ **Positive, negative or Zero**

we will assume that $\alpha^2 - \omega_0^2$ **is negative rather two cases are treated in a similar manner if** $\alpha^2 - \omega_0^2 < 0$**, Then the (9) has complex roots. It is easily verified in this case that every solution of g(t) of (9) is in the**

form,

$$g(t) = Ae^{-(\alpha t)} * cos(\omega t - \delta)$$

; $\omega^2 = \omega_0^2 - \alpha^2$ **——(8)**

Consequently,

$$G(t) = G_0 + Ae^{-(\alpha t)} * cos(\omega t - \delta)$$

——(11)

(11) contains four unknowns $\mathbf{G}_o, A, \alpha, \omega_0, \delta$

4.3 population model of diabetes

THE MODEL OF DEROUICH AND BOUTAYEB (2002)

Due to the complications of Diabetes, it needs costly and prolonged treatment and care, affecting individuals, families and the whole society. the studies estimate that the treatment of a diabetic patient with complication is 2 to five times higher than for a diabetic without complication. But the burden of diabetes goes beyond the limit of economic problems. the burden of diabetes can be reduced by controlling the number of people evolving from the stage of pre-diabetic to the stage of diabetes with and without complications.
The model by DEROUICH AND BOUTAYEB proposes an optimal control approach modeling the dynamics of population with diabetes.

FORMULATION OF DIABETES

we consider the model developed by Boutayeb and chetouani,

$$\frac{dE(t)}{dt} = I - (\mu + \beta_3 + \beta_1)E(t)]$$

$$\frac{dD(t)}{dt} = \beta_1 E(t) - |(\mu + \beta_2)D(t) + \gamma C(t)$$

$$\frac{dC(t)}{dt} = \beta_3 E(t) + \beta_2 D(t) - (\mu + \gamma + v + \delta)C(t)$$

Suppose that C = C(t) and D = D(t) represent the numbers of diabetics with and without complications, respectively.

let N = N(t) = C(t) + D(t) denote the size of the population of diabetics at time t .

Let I = I(t) denote the incidence of diabetes mellitus.

The model parameters to be incorporated are

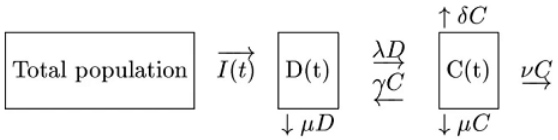
μ - the natural mortality rate

λ - the probability of a diabetic person developing a complication

γ - the rate at which complications are cured

v -the rate at which diabetic patients with complications become severely disabled

δ -the mortality rate due to complications



The diagram shows that I = I(t) cases are diagnosed in a time interval of length 't' and are assumed to have no complications upon diagnosis. In that same time interval, the number of sufferers without complications,

D = D(t), is seen to decrease by the amounts D (natural mortality) and D (sufferers who develop complications), and to increase by the amount C (sufferers whose complications are cured). During this time interval, the number of diabetics with complications is increased by the -mentioned amount C and by the amount C (natural mortality), C (patients who become severely disabled and whose disabilities cannot be cured) and C (those who die from their complications).

E = E(t) Number of pre-diabetic people

D = D(t) numbers of diabetics without complications

C = C(t) numbers of diabetics with complications

N = N(t) = E(t) + C(t) + D(t) denotes the size of the population of diabetics and pre-diabetics at time t

I(t) denotes the incidence of pre-diabetes

μ : natural mortality rate

- **β_1 : the probability of developing diabetes**
- **β_2 : the probability of a diabetic person developing a complication**
- **β_3: the probability of developing diabetes at stage of complications**
- **γ : rate at which complications are cured**
- **v : rate at which patients with complications become severely disabled**
- **δ : mortality rate due to complications,**

$$\frac{dE(t)}{dt} = I - (\mu + (\beta_3 + \beta_1)(1 - u(t)))E(t)$$

$$\frac{dD(t)}{dt} = \beta_1(1 - u(t))E(t) - |(\mu + \beta_2(1 - u(t)))D(t) + \gamma C(t)$$

$$\frac{dC(t)}{dt} = \beta_3(1 - u(t))E(t) + \beta_2(1 - u(t))D(t) - (\mu + \gamma + v + \delta)C(t)$$

4.4 A Mathematical model of glucose insulin reaction

In the glucose regulatory system, the main two players are the pancreatic hormone insulin and glucagon. Insulin and glucagon act together to balance metabolism. The pancreas releases glucagon when blood sugar levels fall too low.

Glucagon causes the liver to convert stored glycogen into glucose, which is released in the bloodstream. Glucagon raises blood glucose levels and insulin organizes the use of fuels for either storage or oxida-

tion. Elevated glucose concentrations of glucose in blood stimulate the release of insulin.

We propose the following general model for the interaction of glucose and insulin.

$\mathbf{x} = \mathbf{-a}_1 x - a_2 xy + a_3$

$\mathbf{y} = \mathbf{b}_1 x - b_2 y$ .....(1)

Where x $\geq$0 , y$\geq$ 0

X = glucose concentration

Y = insulin concentration

a_1 **is the rate constant which represents insulin-independent glucose disappearance**

a_2**is the rate constant which represents insulin-dependent glucose disappearance**

a_3 **is the glucose infusion rate**

b_1 **is the rate constant which represents insulin production due to glucose stimulation**

b_2 **is the rate constant which represents insulin degradation**

LINEARISATION OF THE MODEL

Consider the critical point of the system,

$\mathbf{X = 0} \Rightarrow$ $\mathbf{-a}_1 x – a_2 xy + a_3 = 0 = f(x, y)$

$\mathbf{Y = 0} \Rightarrow$ $\mathbf{b}_1 x – b_2 y = 0 = g(x, y)$ **..... (2)**

The only equilibrium points are (0,0) and (x*, y*)

Solving the equation (2)

$$x* = \frac{-a_1b_2 + \sqrt{(a_1b_2)^2 + 4a_2b_2a_3b_1}}{2b_1a_2}$$

$$y* = \frac{-a_1b_2 + \sqrt{(a_1b_2)^2 + 4a_2b_2a_3b_1}}{2b_2a_2}$$

We are interested in the interior-equilibrium point which always exist since all the parameters are considered positive. consider the Jacobian matrix of (2) given by ,

$$\mathbf{J} = \begin{pmatrix} -a_1 - a_2y & -a_2x \\ b_1 & -b_2 \end{pmatrix}$$

At (x*,y*)

$$\mathbf{J*} = \begin{pmatrix} \mathbf{-a}_1 - a_2y* & -a_2x* \\ b_1 & -b_2 \end{pmatrix}$$

We now use the transformation x = X+x* , y = Y + y*

And then linearise the system,

$$\begin{pmatrix} X^{\cdot} \\ Y^{\cdot} \end{pmatrix} = \mathbf{J}^* \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} -a_1 - a_2y* & -a_2x* \\ b_1 & -b_2 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

We get the linearised equation,

$\mathbf{X}^{\cdot} = -a_1X - a_2y * X - a_2x * Y$

$\mathbf{Y}^{\cdot} = b_1X - b_2Y$ .....(3)

4.5 Modelling the effect of Awareness Programmes by media on the control of Diabetes

Education through media about diabetes and its control can make a huge difference in the current status. Media can bring about awareness among the people on how to prevent and control the disease. Self-care is an integral part of the management of diabetes and people with diabetes build up expertise in self-management through day-to-day living with

the condition.

The internet has become a valuable resource for people with diabetes. There is also a place for healthcare professionals within these communities and they can learn a lot about their people with diabetes by engaging with these online resources One way for people to gather practical information about managing their condition is from peers using social networks. In addition to the internet, the government is also taking steps to prevent and control diabetes by implementing awareness programs across different regions.

THE MODEL

Let A be the incidence of diabetes in the region under consideration.

Let X denote the population of diabetics who are unaware of the long term complications caused by uncontrolled diabetes

Y denote the aware population.

Let C denote the population of diabetes who have developed complications.

let N denote the total diabetic population

N = X+Y+C

Let M(t) denote the cumulative density of awareness programs existing in the region under consideration at time t. It is assumed that a portion of the population of diabetes with complications after proper control and treatment recover from their complications.

After recovery, a fraction p of recovered patients will become aware and join the aware population whereas the remaining fraction (1-p) again become unaware and negligent over time and join the unaware population. Also, it is assumed that an aware diabetic may still develop complications even with proper control and treatment.

The growth rate of M(t), the cumulative density of awareness programs is directly proportional to the disease induced mortality rate.

The mathematical model is formulated as,

$$\frac{dX}{dt} = A - \beta XC - \lambda XM - \delta X + (1-\rho)\gamma C$$

$$\frac{dY}{dt} = \lambda XM + \rho\gamma C - \delta Y - \rho\beta YC$$

$$\frac{dC}{dt} = \beta XC + \rho\beta YC - \gamma C - \alpha C - \delta C$$

$$\frac{dM}{dt} = \kappa\alpha C - \mu M$$

.....(1)

Where β is the rate of developing complications

ρ is the reduced rate of developing complications due to awareness and its value lies between 0 and 1.

λ is the dissemination rate of awareness

δ is the natural mortality rate

γ is the rate of controlling diabetes so as to avoid complications

α is the disease induced mortality rate

κ is the proportionality constant which governs the implementation of awareness programs $\mu$is the depletion rate of awareness programs due to ineffectiveness, economic constraints

Let the total diabetic population N =X+Y+C

Then we get,

$$\frac{dN}{dt} = A - \delta N - \alpha C$$

THEN THE MODEL BECOMES,

$$\frac{dC}{dt} = \beta(N - (1-\rho)Y - C)C - (\gamma + \alpha + \delta)C$$

$$\frac{dY}{dt} = \lambda(N - Y - C)M + \rho\gamma C - \delta Y - \rho\beta YC$$

$$\frac{dN}{dt} = A - \delta N - \alpha C$$

$$\frac{dM}{dt} = \kappa\alpha C - \mu M$$

4.6 BERGMAN'S MINIMAL MODEL

We can design very complicated models with many parameters, to describe the glucose insulin metabolism. But in many cases a simple model would be sufficient to make a good analysis.

A simple method with few parameters, was introduced in the eighties by Richard Bergman and is called Bergman's minimal model. This model has been modified and examined many times.

Bergman's minimal model is a one compartment model, meaning that the body is described as a compartment/tank with a basal concentration of glucose and insulin. The minimal model actually contains two minimal models.

One describing glucose kinetics, how blood glucose concentration reacts to blood insulin concentration and one describing the insulin kinetics, how blood insulin concentration reacts to blood glucose concentration. The two models respectively take insulin and glucose data as an input. The two models have mostly been used to interpret the kinetics during the IVGTT test, and in their original form they cannot be used to much else. but with small additions or modifications they can also be used to describe meals and exogenous insulin infusion.

THE GLUCOSE MINIMAL MODEL The original glucose minimal model describes how the glucose level behaves according to measured insulin data during an IVGTT. The model is a one compartment model

divided into two parts. The first part is the main part describing the glucose clearance and uptake. The second part describes the delay in the active insulin I2 which is a remote interactor which level affects the uptake of glucose by the tissues and the uptake and production by the liver.

These two parts are described mathematically by two differential equations,

$$\frac{dG(t)}{dt} = -(p_1 + X(t))G(t) + p_1 G_b$$

$$\mathbf{G(0)=G_0} \qquad \text{.....(1)}$$

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

$$\mathbf{X(0)=0} \qquad \mathbf{.....(2)}$$

t = Time G(t) = Blood glucose Concentration G_b = Steady state blood glucose concentration

$I_2(t)$ = Active insulin concentration

X(t)= The effect of Active insulin

I(t) = Blood insulin concentration

I_b = steady state blood insulin concentration

V_G = Volume of the glucose compartment

V_{I2} = Volume of the remote pool

Q_{G1} = flow , Q_{G2} = flow , Q_{I21} = flow , Q_{I22} = flow

W_1 = effect factor

W_2 = effect factor

INSULIN MINIMAL MODEL

Bergman presented the following minimal model of insulin kinetics, represented here by the differential equation:

$$\frac{dI(t)}{dt} = p_6[G(t) - p_5] + t - p_4[I(t) - I_b]$$

$\mathbf{I(0)=I_0}$ (3)

PARAMETERS ARE USED,

I(t) = Blood insulin concentration

I_b = Basal blood insulin concentration

G(t) = Blood glucose concentration

P_5 = Threshold for blood glucose concentration

V_I = Volume of insulin distribution pool

Q_{I1} = flow

Q_{I2} = flow

4.6.1 THE ORIGINAL MODEL

The first coupling proposed is a coupling between the original minimal models, without additions and modifications. From now on this coupled model, will be called the original model.

The model is represented by the following differential equations:

$$\frac{dG(t)}{dt} = -(p_1 + X(t))G(t) + p_1 G_b$$

$\mathbf{G(0)=G_0}$ (1)

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

X(0)=0 **(2)**

$$\frac{dI(t)}{dt} = p_6[G(t) - p_5] + t - p_4[I(t) - I_b]$$

$\mathbf{I(0)=I_0}$ (3)

G(t) = Blood glucose concentration

X(t) =The effect of active insulin

I(t) = Blood insulin concentration

G_b**= Basal blood glucose concentration**

I_b**=Basal blood insulin concentration**

P_1 **= Glucose clearance rate independent of insulin**

P_2 **=Rate of clearance of active insulin**

p_3 **= Increase in uptake ability caused by insulin**

p_4 **=decay rate of blood insulin.**

$p_5 = Thetargetglucoselevel$

p_6**=Rate of pancreatic release after glucose bolus**

4.6.2 MODIFIED MODEL

The second coupling proposed is a coupling between the minimal models with modifications and additions.

This coupled model will be referred to as the modified model. This model contains the following differential equations:

$$\frac{dG(t)}{dt} = -(p_1 + X(t)G(t)) + p_1 G_b + D(t)$$

$\mathbf{G(0)=G_0}$

$\frac{dX(t)}{dt} - p_2 X(t) + p_3(I(t) - I_b)$ $\qquad$ $\mathbf{X(0)=X_0}$

$\frac{dI(t)}{dt} = -p_4 I(t) + \frac{U(t)}{V_I}$ $\qquad$ $\mathbf{I(0)=I_0}$

$\frac{dD(t)}{dt} = -drate.D(t)$ $\qquad$ $\mathbf{D(0)=D_0}$

$\frac{dG_(sc)(t)}{dt} = \frac{G(t)-G_(sc)(t)}{5} - R_u tin$ $\qquad$ $\mathbf{G}_(sc)(0) = G_0 - 5.R_u tin$

G(t) = Blood glucose concentration

X(t) = The effect of active insulin

I(t) = Blood insulin concentration

D(t) = Meal disturbance function

G_{sc}**(t) = Subcutaneous glucose concentration**

U(t) = exogenous insulin

G_b **=Basal blood glucose concentration**

I_b **= Basal blood insulin concentration**

V_1 **= Volume of insulin distribution pool**

p_1**= Glucose clearance rate independent of insulin**

p_2 **= Rate of clearance of active insulin (decrease of uptake)**

p_3 **= Increase in uptake ability caused by insulin.**

p_4**= decay rate of blood insulin.**

This model could be used to simulate the glucose-insulin system for a type 1 diabetic on treatment. The model is not attached to a single type of test. Thus, it has more possibilities concerning simulations of meal disturbance and insulin injections. It can be used to test model predictive controllers. And this could make it a tool in the search of an artificial pancreas. This model also adopts the problem with the glucose minimal model.

Chapter 5

CONCLUSION

Research work is focused on the dynamics of glucose and insulin in the human body. Mathematical models are proposed and analyzed to understand the disease better with a view to contribute in the reduction of the incidence of the diabetes mellitus as well the occurrence of complications due to the disease. This work is conducted keeping in mind that immediate action is needed to stem the tide of diabetes and to introduce cost-effective treatment strategies to reverse this trend

The dynamics on the interaction of insulin and glucose in the body is studied and mathematical models are developed to represent the system. A general non-linear mathematical model is developed using ordinary differential equations.

The model is concerned with the regulation process of glucose in the body by the pancreatic insulin.

The model is then analyzed for stability in the small as well as in the large sense. The system is locally asymptotically stable under certain conditions on the parameters. A mathematical model is developed which takes an alternate form of the model proposed by Derouich and Boutayeb (2002) where we considered the infused glucose to be constant. Stability analyses are carried out and the interior-equilibrium point is found to be locally as well as globally asymptotically stable. We conclude that both the mathematical models are physiologically consistent and may represent a useful tool for further research on dia-

betes.

A mathematical model on the population of diabetic patients is developed where the population is categorized into two namely, diabetics without complications and diabetics with complications. Diabetes is sweeping the world as a global epidemic and death rate due to diabetes is growing at an alarming rate. Controllable factors which cause diabetes such as unhealthy eating habits, obesity and inactive lifestyles should be given importance and the need for awareness of the negative impact of such factors cannot be neglected. Further research is needed so as to alleviate the cost and burden of this disease.

In this project the construction of a mathematical model describing the whole blood glucose-insulin system was tried. Two models were derived. They were both based upon the two minimal models of Bergman's minimal model, these two minimal models carried some problems.

The modified model, like the original model, adopted the problem of the glucose minimal model, and among other things this made it difficult to simulate a type 1 diabetic without treatment.

The final results shows that the system of glucose insulin is better described by nonlinear Bergman's model.

Chapter 6

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