Mathematical Modeling of Diabetes Mellitus

A Thesis submitted

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Doctor of Philosophy

In

Mathematics

By

DENGHMINGLIANI ZADENG

Regd. No. : MZU/PhD/298 of 10.06.2009

DEPARTMENT OF MATHEMATICS

SCHOOL OF PHYSICAL SCIENCES

MIZORAM UNIVERSITY,

TANHRIL, AIZAWL- 796004

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THESIS CERTIFICATE

This is to certify that the research thesis entitled ***Mathematical Modeling of Diabetes Mellitus*** submitted by ***Denghmingliani Zadeng*** to Mizoram University, Tanhril, Aizawl, for the award of the degree of Doctor of Philosophy is a bonafide record of research work carried out by him under my supervision. The contents of this thesis, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

Aizawl 796 004

Date:……..

Dr. Jamal Hussain

Research Supervisor

Declaration of the Candidate

I, Denghmingliani Zadeng, a Ph.D Scholar in the Department of Mathematics & Computer Science, Mizoram University, Aizawl, do hereby solemnly declare that the subject matter of my thesis entitled **'MATHEMATICAL MODELING OF DIABETES MELLITUS'** is the bonafide record of the work done by me during my Ph.D. programme. I have duly worked on my Ph.D. thesis under the supervision of Dr. Jamal Hussain, Associate Professor & Head, Department of Mathematics, Mizoram University, Aizawl. This is being submitted to the Mizoram University for the degree of Doctor of Philosophy in Mathematics and that I have not submitted this work to any other University or Institute for any other degree.

Dated:…… (DENGHMINGLIANI ZADENG)

Candidate

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INTRODUCTION

1.1 Mathematical Modeling

Mathematical modeling 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 (Berry and Nyman, 2002; Bukova-Guzel, 2011). It involves solving the mathematical problems and interpreting these solutions 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 situations for evaluation and refinement. The flow-chart for the process of mathematical model is given below:

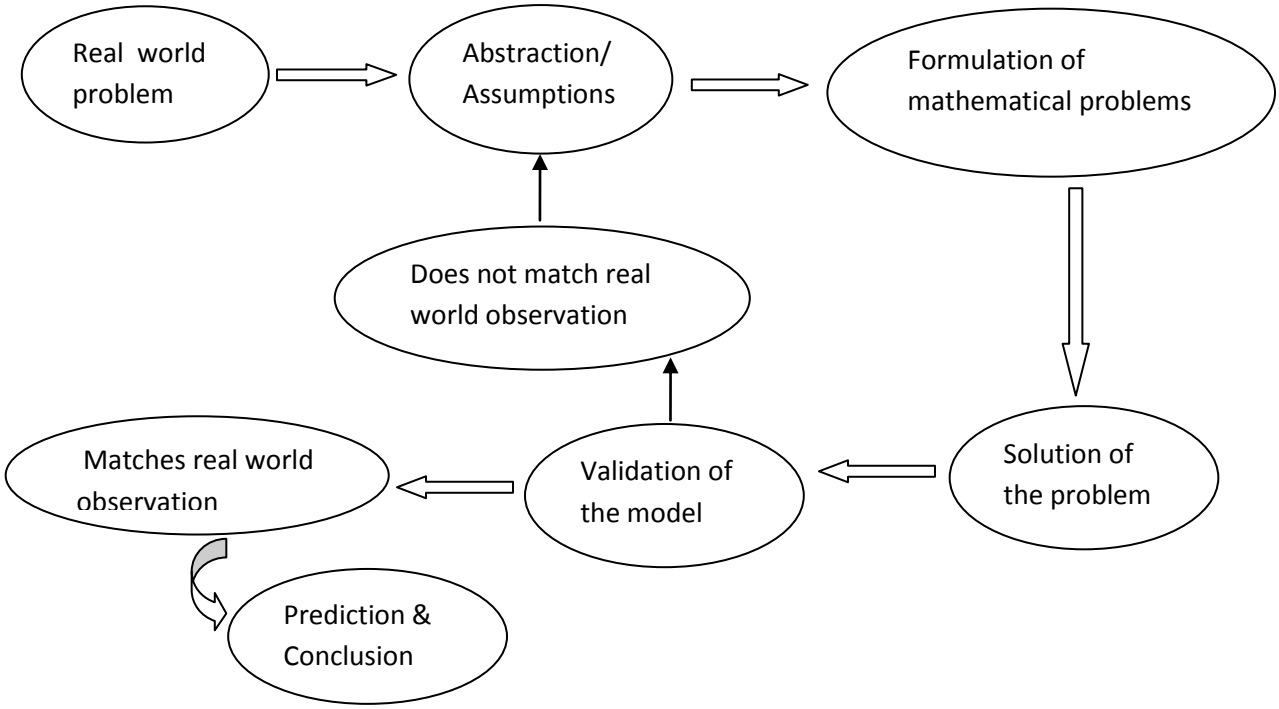

Figure 1.1- Flow chart for the process of mathematical modeling

Mathematical modeling may also be defined as the use of mathematics to describe and explain real world phenomena, investigate important questions about the observed world, test ideas and make predictions about the real world. There is no best model, only better models. It is used in natural sciences such as physics, biology, earth science, meteorology, engineering disciplines such as computer science, artificial intelligence and in the social sciences such as economics, psychology, sociology and political science. A mathematical model may help to explain a system and to study the effects of different components, and to make useful predictions about behavior. Mathematical models can take many forms, including but not limited to dynamical systems, statistical models, differential equations, or game theoretic models. Every branch of knowledge has two aspects, one of which is theoretical, mathematical, statistical and computer-based and the other of which is empirical, experimental and observational. Mathematical modeling is essential to the first of these two aspects. (Kanpur, 1988).

Mathematical modeling may be classified according to the mathematical techniques used in solving them, the purpose we have for the model and according to their nature: linear or non-linear, static or dynamic, deterministic or stochastic, discrete or continuous. Essentially most realistic models are non-linear, dynamic and stochastic although linear, static or deterministic models are easier to handle and also give good approximate results.

1.1.1 Some characteristics of mathematical models:

Some characteristics of mathematical models (Kanpur, 1988) are listed below:

(i) **Realism of models**: We want a mathematical model to be as realistic as possible and to represent reality as close as possible. However, if a model is very realistic, it may not be mathematically tractable. In making a mathematical model, there has to be a trade-off between tractability and reality.

(ii) **Hierarchy of models**: Mathematical models are constantly improved to make them more realistic. Thus for every situation, we get a hierarchy of models, each more realistic than the preceding and each likely to be followed by a better one.

(iii) **Relative precision of models**: Different models differ in their precision and their agreement with observations.

(iv) **Robustness of models:** A mathematical model is said to be robust if small changes in the parameters lead to small changes in the behavior of the model.

(v) **Self-consistency of models:** A mathematical model involves equations and inequations and these must be consistent. Sometimes the inconsistency results from inconsistency of basic assumptions.

(vi) **Oversimplified and overambitious models:** A model may not represent reality because it is oversimplified. On the other hand, a model may be overambitious in the sense that it may involve too many complications and analysis of the results may be tedious and cumbersome.

(vii) **Complexity of models:** This can be increased by subdividing variables, by taking more variables and by considering more details. Increase of complexity may not always lead to increase of insight.

(viii) **Models can lead to new experiments, new concepts and new mathematics:** Comparison of predictions with observations reveals the need for new experiments to collect needed data. Mathematical models can lead to development of new concepts.

(ix) **A model may be good, adequate, similar to reality for one purpose and not for another:** We need different models for explaining different aspects of the same situation or even for different ranges of the variables. Search for a unified model continues.

(x) **Models may lead to expected or unexpected predictions:** Usually models give predictions expected on common sense considerations, but the model predictions are more quantitative in nature. Sometimes they give unexpected predictions and may lead to innovations, breakthroughs or deep thinking about assumptions. Sometimes models give predictions completely at variance with observations and these models need to be revised drastically.

(xi) **A model is not good or bad; it does or does not fit:** Models may lead to elegant mathematical results, but only those models which can explain, predict or control situations are acceptable. A model may fit one situation very well but may be a hopeless fit for another.

(xii) **Modeling creates clear thinking:** Before making a mathematical model, one has to be clear about the structure and characteristics of the situation.

(xiii) **Sticking to one model may prevent insight:** A model helps thinking, but it can also direct thinking in one narrow channel only. Sometimes insight is obtained by breaking from traditional models and designing entirely new models with new concepts.

(xiv) **Inadequate models are also useful:** Since they lead us to search for aspects which may have been neglected at first. Failures can be preludes to successes if the reasons for failure can be identified.

(xv) **Non-feedback models are improper:** A model must include the possibility of its improvement in light of the experimental or observational data.

(xvi) **Partial modeling for subsystems:** Sometimes it is more convenient to make partial models for subsystems, test their validity and then integrate these partial models into a complete model. Sometimes existing models are combined to give models for bigger systems.

(xvii) **Modeling in terms of modules:** Models for small modules may be constructed and may be combined in different ways to get models for a large number of systems.

(xviii) **Imperfections of models and cost of modeling:** No model is perfect and every model can be improved. However such improvements may cost time and money. The improvement in the model must justify the investment made in the process.

(xix) **State variables and relations:** For making a mathematical model, one has to first identify the state variables and then specify the relations between them.

(xx) **Estimation of parameters:** Every model contains some parameters and these have to be estimated. The model must itself suggest experiment or observations and the method of calculation of these parameters.

(xxi) **Validation by independent data:** Sometimes parameters are estimated with the help of some data and the same data are used to validate the model. This is illegitimate. Independent data should be used to validate the model.

(xxii) **New models to simplify existing complicated models:** We start with simple models, introduce more and more variables and more functions to make the models more realistic and more complicated and with the additional insights obtained, we should again be able to simplify the complex models.

(xxiii) **Modeling=Mathematics + Discipline:** To make a mathematical model of a situation, one must know both mathematics and the situation in which the situation arises. Discipline insight must both precede and follow mathematical modeling.

(xxiv) **Transferability of mathematical models:** A mathematical model for one field may be equally valid for another field and may be validly transferred to another field but great care must be exercised in this process.

(xxv) **Prediction-validation-iteration cycle:** A mathematical model predicts conclusions which are then compared with observations. Usually there are some discrepancies. To remove such discrepancies, the model is then improved and again predictions and validations are made and this iteration is repeated till a satisfactory model is obtained.

(xxvi) **Models for strategic and tactical thinking:** Models may be constructed for determining guidelines for particular situations or they may be for determining an overall strategy applicable to a variety of situations**.**

(xxvii) **Constraints of additivity and normality:** Models which are linear, additive and in which the probability distribution follows the normal distribution are relatively simpler, but relatively more realistic models have to be free from constraints.

(xxviii) **Mathematical modeling and mathematical techniques:** Emphasis in applied mathematics has often been on mathematical techniques but the heart of applied mathematics is mathematical modeling.

(xxix) **Ideology and Unity:** Mathematical modeling gives new ideology and unity to applied mathematics. Thus operations research and fluid dynamics differ in their subject matter as well as in techniques but mathematical modeling is common to both.

(xxx) **Non-uniqueness of models:** A situation need not have only one model and the existence of one model for it should not inhibit search for better and different models.

(xxxi) **Dictionary of mathematical models:** It is unlikely that we shall ever have a complete dictionary of mathematical models but familiarity with existing models will always be useful. New situations will always demand construction of new models.

(xxxii) **No prefabrication of models:** There will always be large number of mathematical structures without corresponding physical models and there will always be physical situations without good mathematical models. Search has to go on in both directions.

(xxxiii) **Mathematical modeling is an art:** It requires experience, insight and understanding.

(xxxiv) **Criteria for successful models:** These include good agreement between predictions and observations, of drawing further valid conclusions, simplicity of the model and its precision.

(xxxv) **Generality and applicability of models:** There are some models which are applicable to a wide variety of situations, while there are others which are applicable to specific situations only.

(xxxvi) **Unity of disciplines through mathematical modeling:** When a number of different situations are represented by the same mathematical model, it reveals a certain identity of structures of these situations. It can lead to certain economy of efforts and can reveal a certain underlying unity between different disciplines.

Many researchers (Dubey and Hussain, 2004; Dubey and Hussain, 2006; Dubey *et al*., 2011; Schlessinger and Eddy, 2002; Boutayeb and Kerfati, 1994; Brandeau, 2005; Eddy and Schlessinger, 2003; Freedman and Shukla, 1991) have used Mathematical Models to understand and predict the behavior of Biological Systems.

1.2 Diabetes and its symptoms

Diabetes Mellitus, commonly known as diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels known as hyperglycemia. Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the beta cells of the pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action in the body. This term is used to describe a disease characterized by chronic high blood plasma glucose concentration and other disturbances of carbohydrate and

lipid metabolisms which are often associated with the development of specific microvascular and macrovascular complications. The most affected parts of such a patient are the eye and kidney as well as other vascular and coronary tissues (Mbah, 2011).

During digestion, carbohydrates are broken down mainly into a simple sugar called glucose. When glucose enters the bloodstream, the pancreas goes into red alert. It secretes insulin into the blood, then the liver and muscles immediately remove glucose from the blood, when it fails to do so then diabetes occurs. Diabetes Mellitus are classified into many types and this classification is based on the classification of the group of disorders which constitute the disease, that is, it is based on the pathogenesis of the disease. One of the most acceptable methods of classification of this disease is based on the verification method. It is classified into three major subclasses: type 1 diabetes (T1DM), type 2 diabetes (T2DM) and others (International Diabetes Federation, www.idf.org/what-diabetes). There are many different kinds of diabetes with different causes and treatments. The most common are type 1 diabetes and type 2 diabetes.

In type 1, diabetes occurs due to a diminished product of insulin. It is the 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. It affects mostly children or young adults. People with type 1 need daily insulin injections to survive and lead normal lives.

In type 2, diabetes occurs due to a resistance to the effects of insulin. It is known as adult-onset or non-insulin-dependent diabetes mellitus (NIDDM). Type 2 diabetes results when the muscle, liver and other tissues stop reacting to insulin. The pancreas tries to compensate by producing additional insulin, but in some people this compensation is insufficient. The blood sugar stays high and if this increase is not treated, the beta-cells die or become dysfunctional over time and the pancreas stops producing insulin. Type 2 diabetes is the most common type and is associated with both genetics and lifestyle – junk food, obesity and lack of exercise. Environmental exposures might have contribute to recent increases in the rate of type 2 diabetes. A positive correlation has been found between the concentration of urine of bisphenol A, a constituent of polycarbonate plastic from some producers, and the incidence of type 2 diabetes.

Gestational Diabetes Mellitus (GDM) is 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. Risk to the baby includes macrosomia (high birth weight), congenital cardiac and central nervous system anomalies and skeletal muscle malformations.

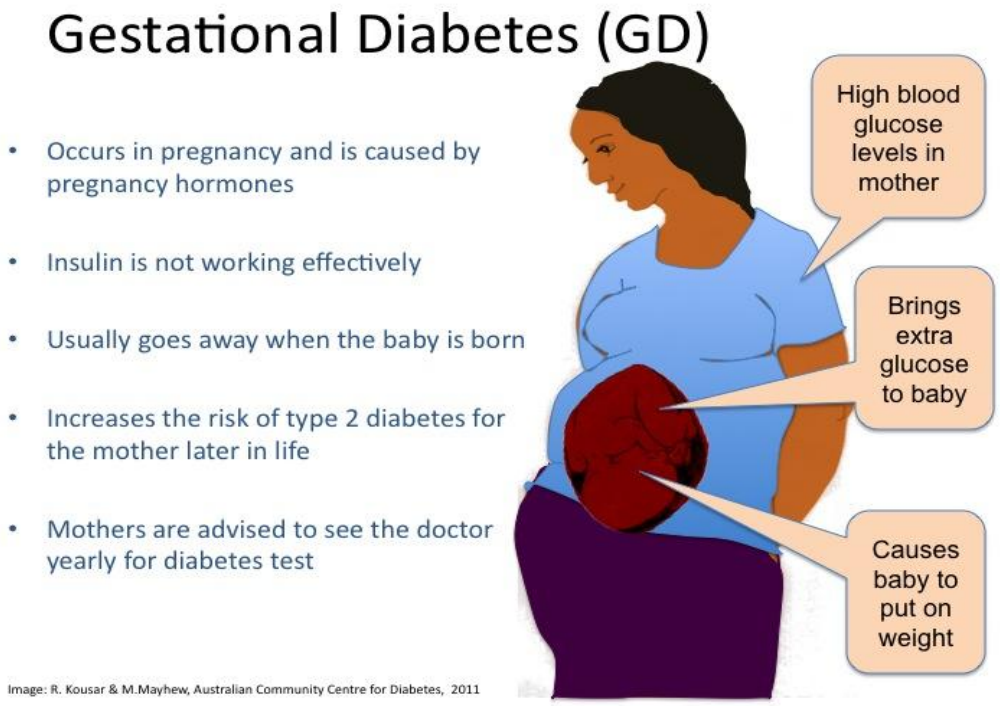

Figure 1.2- Gestational Diabetes

The main symptoms of diabetes are frequent urination (polyuria), increased thirst (polydipsia) and increased appetite (polyphagia). Symptoms may develop quite rapidly within weeks or months in type 1 diabetes, particularly in children. Type 1 diabetes may cause a rapid weight loss despite normal or even increased eating and irreducible mental fatigue. (Medicinenet.com, 2014).

Diabetic ketoacidosis (DKA), usually caused by type 1 diabetes is an extreme state of metabolic dysregulation characterized by the smell of acetone on the patient's breath, a rapid, deep breathing known as Kussmaul breathing, nausea, vomiting and abdominal pain, and altered states of consciousness or arousal such as hostility and mania or, equally confusion and

lethargy. In severe DKA, coma may follow, progressing to death. DKA is a medical emergency and requires immediate hospitalization.

Hyperosmolar nonketotic state is mainly the result of dehydration due to loss of body water and is more commonly found in type 2 diabetes.

There has been found to be strong implications of an association between Alzheimer's disease and diabetes (Rovner, 2009). 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. Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in blurred vision, hence people with diabetes have a higher risk of blindness and other vision problems. Diabetes can damage the kidneys and may lead to kidney failure. Diabetes can cause damage to the nerves that run through the body. Nerve damage, infections of the feet (foot ulcers), and problems with blood flow to the feet can be caused by diabetes. Diabetes can cause skin problems, such as infections, sores, and itching. Skin problems are sometimes a first sign that someone has diabetes. Diabetes can lead to problems with teeth and gums, called gingivitis and periodontitis (www.medicalnewstoday.com/info/diabetes/).

Figure 1.3 Foot Ulcer due to Diabetes

1.3 Diagnosis of Diabetes Mellitus

The most commonly used tests for detecting diabetes are

1) HbA1c test, also called the haemoglobin A1c or glycohaemoglobin test
2) Fasting plasma glucose (FPG) test
3) Oral glucose tolerance test (OGTT)

Another blood test, the random plasma glucose (RPG) test, is sometimes used to diagnose diabetes during a regular health checkup. If the RPG measures 200 micrograms per deciliter or above, and the individual also shows symptoms of diabetes, then a health care provider may diagnose diabetes (World Health Organization, 2013).

The following table provides the blood test levels for diagnosis of diabetes for non-pregnant adults and diagnosis of prediabetes. (mg=milligram, dl=deciliter).

Condition	A1c (percent)	Fasting plasma glucose (mg/dl)	Oral Glucose Tolerance Test (mg/dl)
Normal	About 5	99 or below	139 or below
Pre-diabetic	5.7 to 6.4	100 to 125	140 to 199
Diabetic	6.5 or above	126 or above	200 or above

Table 1.1 – Blood test levels for diabetes

There are many ways of diagnosing diabetes mellitus although an internationally accepted method, the glucose tolerance test (GTT), is always preferred. However, when diabetes mellitus is detected, further tests need to be carried out to know whether it is IDDM or NIDDM. This method is still not foolproof since it is usually based on abnormal carbohydrate tolerance and again this disease occurs even in conditions beside sugar diabetes. Thus, to clearly demonstrate that a given case is caused by abnormal carbohydrate tolerance, an abnormal standard oral glucose tolerance test has to be demonstrated and further shown that no other factor contributed to this abnormal result. The severity of carbohydrate intolerance is instantly revealed by the level of the fasting blood sugar. The severity of the disease can thus be determined depending on this categorization as illustrated in the table below:

SEVERITY	RANGE OF FASTING BLOOD SUGAR
Normal person	60-100mg/dl
Mildly diabetic person	60-105 mg/dl
Moderately diabetic person	106-200 mg/dl
Severely diabetic person	Above 200 mg/dl

Table 1.2 –Severity of diabetes

As can be seen from the above table, the abnormal oral glucose tolerance curve of mild diabetes is indistinguishable from those found in many non-diabetic conditions. Hence, to correctly interpret a given tolerance curve, awareness of the patient's metabolic make-up is required. In analysis of the blood for its glucose level, the following facts must be determined:

1) The actual method used by name

2) Whether it measures true sugar

3) Whether the blood being used is whole blood, plasma or serum, and

4) The fasting glucose levels for normal person when any of these blood sample types are used.

The knowledge of these facts is important because fasting glucose levels are not same in the above three samples and again, the methods in use have also varying fasting blood glucose levels. An example is illustrated by the table below:

True Sugar after Overnight Fast:

Clinical Status	Whole Blood	Plasma or Serum
Normal	60-100mg/dl	70-115mg/dl
Mild Diabetes	60-105mg/dl	70-120mg/dl
Moderate Diabetes	106-200mg/dl	121-230mg/dl
Severe Diabetes	Above 200mg/dl	Above 230 mg/dl

Table 1.3 – Whole blood vs. plasma

However, the recommendations by the American National Diabetes data group criterion is that diagnosis of diabetes requires fasting plasma glucose level of 140mg/dl or the

fasting blood glucose level of 126mg/dl (ref. table 1.1), although the renal glucose threshold rises with increase in age. Hence, there are cases of blood glucose being as high as 200mg/dl though the patient is not diabetic. This indicates that the age of the individual in question need to be taken into consideration when diagnosing diabetes. In diagnostic procedure, it is recommended that when feasible, the blood should be taken from an antecubital vein within seconds of placing the tourniquet so as to avoid falsely high or low blood sugar level. The sample should be analysed preferably on the same day. If the sample has to be taken from the capillaries, this has to be from the heel, earlobe or fingertip and this is equivalent to arterial blood sample. The capillary and venous blood levels are same after an overnight fasting. The capillary blood sugar is usually higher for the first two hours after meals since the tissues utilises postprandial hyperglycaemia. Also the plasma glucose levels are shown (as in table 1.3) to be usually higher than those of the whole blood for an overnight fast. However, the plasma glucose level is preferred in determining the level of diabetes instead of the whole blood, for the following reasons:

1) Changes in plasma glucose level more accurately reflect the absorption, production and uptake of glucose than the whole blood whose value is affected by dead space of red cell solids.
2) The plasma value is independent of the hematocrit where as the whole blood glucose rises by 3-4 mg/dl for every 10% fall in hematocrit and vice versa
3) Plasma is more suitable than whole blood for analysis by the automated methods that are now replacing the manual methods in laboratories.

There are many methods used in the determination of the blood glucose level among which are Folin-Wu, Soinogyi-Nelson, Hoffman, Benedict, Hagedorn-Jensen, Folin-Malmros and Glucose-Oxidase. In determining this glucose level, they all use two basic reactions, namely chemical reduction of the Copper or Ferricyanide by glucose or the interaction between glucose and the glucose oxidase which is an enzyme that reacts only with the specific form of the glucose found in the body fluids. The Folin-Wu method, even though clinically disqualified, is being widely used in the diagnosis of diabetes. The details on the methods and also other factors contributing to diagnostic results are found in Ellenberg and Rifkin (1983).

1.4 Status of Diabetes

The global prevalence of type 2 diabetes has shown a trend of rapid growth over the past few decades and concerns grow over this increase (Santora, 2009). According to the National Health and Nutrition Examination Survey, U.S. (NHANES 2005-2006) more than 40 per cent of U.S. adults have diabetes or pre-diabetes (Cowie *et al*., 2009). According to statistics of International Diabetes Federation (IDF), two individuals develop diabetes every 10 second worldwide (IDF, 2007), and two individuals die of diabetes-related conditions every 10 second worldwide. Diabetes therefore has become a very serious public health problem with a heavy socio-economic burden to each country. Asia is the world's most populated area and over 56 per cent of the world's population lives in the continent (U.S. Census Bureau, 2010). As Asia is hit hardest with diabetes, any subtle changes of diabetes mellitus occurrence can have a great influence on the overall global trends. And the effect of diabetes control in Asia

may have an important impact on the global response to diabetes-related stress (Wenying, 2010).

1.4.1 Diabetes around the world

Diabetes Mellitus has become a global epidemic, rising at an alarming rate throughout the world, due to increases in life expectancy, obesity and sedentary lifestyles. In 2014, the International Diabetes Federation estimated that approximately 387 million people around the world have diabetes. The figure is expected to rise to 592 million by the year 2035 accounting to 10 % of the world's population. 80% of diabetic patients live in low- and middle-income countries. One person dies from diabetes every seven seconds, which amounts to 1.5 million annual deaths (International Diabetes Federation, 2014).

As the number of people with diabetes grows worldwide, the disease takes an ever-increasing proportion of national health care budgets. Without primary prevention, the diabetes epidemic will continue to grow. Even worse, diabetes is projected to become one of the world's main disablers and killers within the next twenty-five years. As per the National Diabetes Statistics Report, 2014 (released June 10,2014), in the United States alone, the total estimated cost of diagnosed diabetes in 2012 is $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity (American Diabetes Association, http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html).

The top 10 countries/territories of number of people with diabetes in the age ranged between 20-79 years, according to the IDF in 2013 is given in the following table:

Country/Territory	Number of people with diabetes (in millions)
China	98.4
India	65.1
USA	24.4
Brazil	11.9
Russian Federation	10.9
Mexico	8.7
Indonesia	8.5
Germany	7.6
Egypt	7.5
Japan	7.2

Table 1.4 – Diabetic population around the world

World Diabetes Day (WDD) is celebrated every year on November 14. The World Diabetes Day campaign is led by the International Diabetes Federation (IDF) and its member associations. It engages millions of people worldwide in diabetes advocacy and awareness. World Diabetes Day was created in 1991 by the International Diabetes Federation and the World Health Organization in response to growing concerns about the escalating health threat that diabetes now poses. World Diabetes Day became an official United Nations Day in 2007 with the passage of United Nation Resolution 61/225. The campaign draws attention to issues of paramount importance to the diabetes world and keeps diabetes firmly in the public spotlight.

Figure 1.4- World Diabetes Day

Each year World Diabetes Day is centered on a theme related to diabetes. Topics covered in the past have included diabetes and human rights, diabetes and lifestyle, and the costs of diabetes. World Diabetes Day is a campaign that features a new theme chosen by the International Diabetes Federation each year to address issues facing the global diabetes community. While the themed campaigns last the whole year, the day itself is celebrated on November 14, to mark the birthday of Frederick Banting who, along with Charles Best, first conceived the idea which led to the discovery of insulin in 1921. In 2007-2008, the theme was 'Diabetes in Children and Adolescents', and in 2009-2013, the theme was 'Diabetes Education and Prevention'. The current theme (2014-2016) is 'Healthy Living and Diabetes'.

World Diabetes Day is celebrated worldwide by the over 200 member associations of the International Diabetes Federation in more than 160 countries and territories, all Member States of the United Nations, as well as by other associations and organizations, companies, healthcare professionals and people living with diabetes and their families.

The global diabetes community including International Diabetes Federation member associations, diabetes organizations, NGOs, health departments, civil society, individuals and companies develop an extensive range of activities, tailored to a variety of groups. Activities organized each year include radio and television programs, sports events, free screenings for diabetes and its complications, public information meetings, poster and leaflet campaigns, diabetes workshops and exhibitions, press conferences, newspaper and magazine articles, events for children and adolescents, monument lightings, human blue circles, walks, runs, cycle race and political events.

1.4.2 Diabetes in India

In India alone, approximately 65.1 million diabetes patients have been identified according to The Indian Council of Medical Research (ICMR). Only China, with 98.4 million cases has more diabetes patients globally. (The Hindu, Coimbatore, Jan 27, 2014).

Diabetes has emerged as a major healthcare problem in India. By 2030, India is predicted to have the largest number of diabetes patients in the world. The International Journal of Diabetes in Developing Countries says that there is an alarming rise in the prevalence of diabetes, which has gone beyond epidemic form to a pandemic one. The economic burden due to diabetes in India is among the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. WHO estimates that mortality from diabetes, heart disease and stroke cost about $210 billion in India in the year 2005. Much of the heart disease and stroke

in these estimated were linked to diabetes. WHO estimates that diabetes, heart disease and stroke together will cost about $333.6 billion over the next 10 years in India alone. These estimates are based on lost productivity, resulting primarily from premature death (Neogi, 2007). The diabetes population and the related costs are expected to at least double in the next 25 years. Without significant changes in public or private strategies, this population and cost growth are expected to add a significant strain to an overburdened health care system. (Huang *et al*., 2009).

In India alone, approximately 65.1 million diabetes patients have been identified in 2013, compared to 50.8 million in 2010 according to The Indian Council of Medical Research (ICMR). An estimate shows that nearly 1 million Indians die due to diabetes every year (Gale 2010. Only China, with 98.4 million cases has more diabetes patients globally. (The Hindu, Coimbatore, Jan 27, 2014). By 2030, India is predicted to have the largest number of diabetes patients in the world. Obesity is reaching epidemic proportions among India's middle-class children and adolescents, as young people choose Western fast food over traditional cuisine. Doctors in India are fitting gastric bands on children as young as 13 (http://www.idf.org/BRIDGES/map/india).

1.4.3 Diabetes in Mizoram

Dr. Rosangluaia, Principal Investigator headed the project titled ICMR- India diabetes (INDIAB) Study (North East Component) Mizoram State under Indian Council of Medical Research which commenced on 20th November, 2011. Their primary objectives were

to determine the prevalence of diabetes mellitus and prediabetes (impaired fasting glucose (IFG)/ impaired glucose tolerance (IGT)) in Mizoram and to compare the prevalence of diabetes and pre-diabetes in urban areas and rural areas in Mizoram. Their secondary objectives were to determine the prevalence of hypertension and dyslipidemia in urban and rural areas in Mizoram, to determine the prevalence of coronary artery disease among subjects with and without diabetes and to assess the level of diabetes control among self reported diabetic subjects in urban and rural Mizoram. (ICMR-India Diabetes (INDIAB), Mizoram Report, 2012).

The ICMR-INDIAB (North-East Component) reports on the results obtained from the state of Mizoram of North East region of India. A stratified multi-stage sampling design was used to survey individuals aged $\geq$ 20 years with the primary objective to determine the prevalence of diabetes and prediabetes in North East India. Of the 4112 individuals selected for the study, 4079 (99.1%) individuals participated. The weighted prevalence of diabetes (both known and newly diagnosed) in Mizoram was 5.7% and that of prediabetes was 5.8%. In terms of glycemic control, urban areas of Mizoram had good glycemic control. Nearly 89.5% of urban residents and 71.5% of the rural residents in Mizoram reported that they knew about a condition called diabetes. They summarized that the prevalence of diabetes was higher in urban areas as compared to rural areas. It was observed that the overall ratio of newly diagnosed to known diabetes was 1:1, while in urban areas it was 1:0.9 and 1:1.5 in rural areas. In terms of glycemic control, 23% of self-reported diabetic subjects in Mizoram has poor glycemic control compared to 18.9% in urban areas.

1.5 Methodology

Mathematical models for the dynamics of glucose-insulin are formulated where less significant components are ignored. The importance of the components is evaluated by the relative effect of system components on its dynamics. Solutions of the mathematical problems are achieved, after which interpretation is done by relating model components and model behavior to components, characteristics and behavior of real systems. The models are then validated by using data from various sources as well as by giving arbitrary values to the parameters. The models can be used to explain the dynamics of the disease, predictions about the rate of increase or decrease of the disease can be made.

The two main methods used in our work for stability analysis are:

1. *The method of characteristic roots:* The asymptotic stability of a system depends on the eigenvalues of a Jacobian matrix of first order derivatives of interaction-functions called the variational matrix. As this Jacobian is determined by Taylor expansion of the interaction-functions and neglecting higher order terms, this method studies only the local stability of the system in the neighbourhood of its equilibrium state. Gershgorin's theorem (Lancaster and Tismanetsky, 1985) and Routh-Hurwitz criterion (Sanchetz, 1968) are very useful in the study of local stability of wide range systems in homogeneous environments. This method establishes stability only relative to small perturbations of the initial state. Hence it is called local stability.

2. Lyapunov's Direct Method: Real systems are often subjected to large perturbations of the initial state and system dynamics. The most powerful analytical method for studying stability to finite perturbations of the initial state of an ecosystem model is the direct method of Lyapunov (La Salle and Lefschetz, 1961; Rao, 1981). This method requires the construction of certain functions called Lyapunov functions. For a physical system, the direct method of Lyapunov generalizes the principle that a system which continually dissipates energy until it attains an equilibrium is stable.

1.6 Literature review

The incidence and prevalence of diabetes are increasing all over the world. Complications of diabetes constitute a burden for the individuals and the society as a whole. The literature dealing with mathematical modeling for diabetes is abundant though still not adequate. During the last decades, a variety of models have been devoted to different aspects of diabetes, including glucose and insulin dynamics, management and complications preventions, cost and cost-effectiveness of strategies and epidemiology of diabetes in general. Several research papers are published regularly on mathematical models used for specific aspects of diabetes.

The majority of mathematical models proposed in the literature were devoted to the dynamics of glucose-insulin, including Intra Venous Glucose Tolerance Test (IVGTT), Oral Glucose Test (OGT), Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT). One of the earliest work was done by Himsworth and Kerr (1939) where they introduced the first

approach to measure the insulin sensitivity *in vivo*. Mathematical models were used to estimate the glucose disappearance and insulin-glucose dynamics in general. Bolie (1961) is also one of the pioneer in this field, formulating a simple model using ordinary differential equations.

The real start of modeling the glucose-insulin dynamics is thought to begin with the so-called "minimal model" proposed by Bergman *et al*. (1979) in the late seventies. This model is one of the most widely used model in physiological research on the metabolism of glucose. The model is regarded to be composed of two separate parts and some of the mathematical results produced by this model are not realistic. Bergman continued to work on mathematical modeling of glucose regulation (Bergman et al.,1985; Bergman 1997; Bergman and Ader 2000; Bergman 200;1 Bergman 2002).

Lehmann *et al*. (1994) described a prototype computer system utilizing a model of carbohydrate metabolism linked to an expert system. The prototype which integrated quantitative and quantitative computational methodologies is used to predict blood glucose profiles and adjust insulin doses in insulin-dependent (type 1) diabetic subjects. They described a feedback loop insulin-dosage optimization procedure which allows quantitative advice to be generated. They also discussed possible clinical applications for the system, which is intended for educational use and clinically as a research tool to try and attain normal glycaemia.

Tai (1994) developed a mathematical model for the determination of total areas under glucose tolerance and other metabolic curves. The Tai model allowed flexibility in experimental conditions, which means, in the case of the glucose-response curve, samples can

be taken with differing time intervals and total area under the curve can still be determined with precision.

Rao *et al*. (1997) reviewed a general mathematical model which incorporates beta-cell kinetics and a gastrointestinal absorption term for glucose into a glucose-insulin feedback system. Their model comprised of a set of four nonlinear coupled, ordinary differential equations. Their numerical simulations led to time variations of plasma glucose and insulin levels that are consistent with clinical observations in normal groups. The result they obtained after suitable changes in some of the parameters were in agreement with the clinical profiles and laboratory data in all the clinical categories of diabetes mellitus, viz., insulin-dependent diabetes mellitus, non-insulin dependent diabetes mellitus, and malnutrition related diabetes mellitus, in response to a glucose challenge. Linear stability in each case gave an indication of the metabolic factor(s) responsible for the particular disorder.

Following the minimal model, De Gaetano and Arino (2000) proposed an aggregated delay differential model called the "dynamic model" which solves the problems found in the minimal model. The dynamic model was also observed to have positive, bounded solutions and to be globally asymptotically stable around the pre-injection equilibrium blood glucose and insulin concentrations.

A more general model was proposed by Li *et al.* (2001). They noted that while the dynamical model solves the problems of the minimal model, it implicitly or explicitly made a few assumptions that may not be necessary or realistic. They generalized the mathematical model to allow more general functions and an alternate way of incorporating time delay. Their

work showed that the dynamic model does provide qualitatively robust dynamics for the purpose of clinical application. Their result indicates that diabetic patients can exhibit intrinsic glucose oscillation.

Taking into account the cost of monitoring and treating diabetes, Derouich and Boutayeb (2002) have used a mathematical model to illustrate the role of physical activity in improving insulin sensitivity and regulating blood glucose concentrations in normal, non-insulin-dependent diabetes and insulin-dependent diabetes people with and without physical effort. Simulations were carried out with different values of parameters and graphs were depicted to compare the behavior of blood glucose in NIDD, IDD 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 NIDD patient, it was found that physical exercise improves insulin sensitivity, lowers the average blood glucose concentration and may improve weight reduction. For IDD patient, physical exercise should be taken with precaution and insulin and diet properly adjusted according to the patient's predisposition. They illustrated the effect of exercise on the dynamics of insulin and glucose in order to confirm the role of physical activity as a prevention for people ar risk, to stress the benefit that can be gained by NIDD from improving insulin sensitivity and compensating its eventual partial lack, and to reassure IDD people that no exclusion is made provided a good combination is found to balance between insulin doses, carbohydrates and physical intensity.

Mathematical models in the study of glucose metabolism, insulin secretion and the insulin-glucose interactions have a longstanding tradition. Mari (2002) reviewed the recent

advances in this area, with particular emphasis on the methods for the assessment of insulin sensitivity and insulin secretion. He concluded that mathematical models in this area continue to evolve toward more accurate and clinically applicable approaches, and should be considered as a useful resource for clinical investigators. He also concluded that models have a potentially important role for understanding the mechanisms governing the insulin-glucose regulation system.

In type 2 diabetes, the risk of retinopathy, and of retinal photocoagulation, rises with time after diagnosis of diabetes. Stevens *et al*. (2002) established that mathematical modeling showed that ageing effect is attributable to the rise in glycaemia with time since diagnosis of diabetes. Mathematical models were fitted to data from 3648 patients from the UK Prospective Diabetes Study (UKPDS).

Eddy and Schlessinger (2003) built a mathematical model that replicates the pathophysiology of diabetes at a high level of biological and clinical detail and that can be tested by simulating clinical trials using an object-oriented approach, differential equations and a construct they called “features”. Their model included the pertinent organ systems, more than 50 continuously interacting biological variables, and the major symptoms, tests, treatments, and outcomes. Their model is continuous in time and represented biological variables continuously.

Mukhopadhyay *et al*. (2004) recalled that the dynamical model has been shown to allow simultaneous estimation of both insulin secretion and glucose uptake parameters. They

proposed an extension by introducing a generic weight function in the delay integral kernel for the pancreatic response to glucose.

The incidence of type 2 diabetes is increasing rapidly, but clinically maintenance of normoglycemia remains challenging. The systematic, multifactorial character of diabetes is a key reason its treatment is so difficult. In the past 30 years or so, a number of mathematical and computational models have been developed to study diabetes. These models offer promise in identifying the underlying disease pathophysiology in individual patients and in understanding the general pathophysiology characterizing the disease in large populations. To exploit these models most effectively, it is necessary to understand both the strengths and limitations of each model. Kansal (2004) reviewed a selection of the models available for the study of diabetes, with a particular focus on the types of problems for which each model is well suited and the limitations that restrict how each model can be used.

Boutayeb *et al.* (2004) used ordinary differential equations and numerical approximations to monitor the size of populations of diabetes with and without complications.

The Euglucemic Hyperinsulinemic Clamp (EHC) is the most widely used experimental procedure for the determination of insulin sensitivity and in its usual form the patient is followed under insulinization for two hours. Pichhini *et al.* (2005) fitted a mathematical model of EHC, incorporating delays, to the fitted data, and the insulin resistance behavior of obese subjects was assessed analytically. They found that obese subjects has significantly less effective suppression of hepatic glucose output and higher pancreatic insulin

secretion than lean subjects. They also found that tissue insulin resistance appeared to be higher in the obese group, but this difference did not reach statistical significance.

Maree *et al.* (2006) mathematically modeled competition of IRGP (islet-specific-glucose-6-phosephate catalytic subunit-related protein)- reactive T-cell clones during spontaneous disease, and in response to peptide treatment. Based on realistic T-cell activation, proliferation and differentiation of parameter values, their model showed that progression of spontaneous disease is characterized by (i) initial expansion of all (IGRP) 206-214-reactive T-cell clones (irrespective of avidity) and (ii) slow replacement of T-cell clones recognizing peptide/MHC with low avidity by their high-avidity counterparts. Their model helped in understanding the paradoxical outcomes of IGRP-based peptide treatment experiments and it furthermore, predicted that slight deviations in dose or peptide avidity can lead to treatment failure or disease progression.

Makroglou *et al.* (2006) gave an overview of some of the mathematical models appearing in the literature for use in the glucose-insulin regulatory system in relation to diabetes, enhanced with a survey on available software. The models are in the form of ordinary differential, partial differential, delay differential and integro-differential equations. They also presented some computational results.

Li *et al.* (2006) proposed a mathematical model to study the glucose-insulin regulatory system with two explicit time delays applying the mass conservation law. They noticed many unique features of this two delay model. They suspected that one of the possible

many causes of ultradian insulin secretion oscillations is the time delay of the insulin secretion simulated by the elevated glucose concentration.

Li and Kuang (2007) made an attempt to better understand the glucose-insulin regulatory system with the help of a mathematical model of delay differential equations with two discrete time delays. Their results confirms most current existing physiological observations and reveal more insightful informations.

Adewal *et al*. (2007) presented a new generalized mathematical model for the study of diabetes mellitus. Their model took into account all glucose intake and insulin injected (administered) as a function of the molecular weight of carbohydrate and protein intake, respectively. They used the model to monitor the blood plasma glucose level in non-diabetic and suspected diabetic subjects. They recommended their model for the study of diabetes mellitus since the molecular weight of carbohydrate (glucose) and protein (insulin) could be easily calculated.

De Gaetano *et al*. (2008) formulated a model of the pancreatic islet compensation, presented its physiological assumptions, established some fundamental qualitative characteristics of its solutions, extensively discussed the numerical values assigned to its parameters, simulated its performance over the span of a lifetime under various conditions, including worsening insulin resistance and primary replication defects. They highlighted the differences with respect to two previously proposed models of diabetic progression, and therefore, they proposed the model as a realistic, robust description of the evolution of the compensation of the glucose-insulin system in healthy and diabetic individuals.

Svitra *et al.* (2009) proposed a mathematical model to study the impact of physical exercises on glycemic regulation. They performed linear, nonlinear and numerical analysis of glycemic regulation and they also applied the simulating modeling program "Model Maker" for modeling. On introducing two external periodical functions defining diet and physical exercise in normal and diabetic cases, their numerical analysis showed that their model reflects glycemia and insulin dynamics of a healthy person and a diabetic person rather exactly. On comparing received numerical solutions of these models with experimental data, a fairly good coincidence of the models and the data was received and this fact allows to apply the investigated model in monitoring complex systems.

Li and Zheng (2010) proposed a more general model following the dynamic model which includes Single Delay Model and one of the models in Li *et al.* (2001) as its special cases. Their model admits globally stable equilibrium under certain conditions of the parameter. Their model is shown to admit oscillating behavior due to the existence of Hopf-bifurcation.

Chen *et al*. (2010) proposed a novel mathematical model to describe the dynamic behavior of plasma glucose and insulin on diabetic subjects where five specific adjustable parameters are defined as the factors of the major physiological functions. Their model is able to represent the dynamics and oscillation behavior of glucose-insulin on diabetes according to the long term clinical data verification. The resulting parameters are found to be helpful in identifying the patient's condition of major physiological function. They expected that their model will be constructive for designing appropriate therapy strategies for diabetic patients.

Sadhya and Kumar (2011) proposed a new mathematical model for the study of diabetes which takes into account all plasma glucose concentration, generalized insulin and plasma insulin concentration. Their model showed the difference of glucose-insulin regulatory system between a normal person and a diabetic person. They found that the glucose concentration of diabetic patient does not come down after a certain time which showed the evidence that the person suffer from diabetes.

Appuhamy *et al.* (2013) proposed a generic mechanistic model considering birth, death, migration, aging, and diabetes incidence dynamics. Diabetes incidence rates were determined using their body mass index (BMI) represented by the Hill equation. Their model successfully predicted the prevalence of diabetes in younger, middle-aged, and older results. They found that diabetes prevalence was positively associated with diabetes occurrence in every age-group, but the associations among younger adults were stronger. Diabetes prevalence was found to be more sensitive to death rates in older adults than in younger adults. Both diabetes incidence and prevalence were strongly sensitive to BMI at younger ages, but sensitivity gradually declined as age progressed. Their model predicts diagnosed diabetes incidence and prevalence reasonably well using the link between BMI and diabetes development risk.

Ajmera *et al.* (2013) studied the existing mathematical models of diabetes for the past five decades and identified the fragile points that are yet to be worked upon for further studies. They found that although modeling studies related to diabetes and its associated complications are abundant, not all aspects of diabetes are mathematically

represented, and of those that are, not all are represented equally and there is need of more mathematical models to represent the existing knowledge of diabetes, such as the link between aging and insulin, obesity factor, eating habits, genetics etc. They highlighted that mathematical modeling tightly linked to experiments had a great impact in their understanding of diabetes and efforts on merging subsystem models could pave the way toward discovering the entire regulatory network.

Samanta *et al*. (2013) proposed and analyzed a mathematical model to assess the effect of awareness programs by media on the prevalence of infectious diseases and revealed that the rate of executing awareness programs has a substantial effects over the system and sustained oscillation may arise with increasing its value above a threshold. The biologically feasible equilibria and their stability properties are analysed and discussed. They observed that if the awareness of the local prevalence of a disease is not covered by the media or local health authorities, it is more likely to be raised by the acts of informal information spread. If information is disseminated properly in the population, people adapt their behavior as a result of their awareness of the disease.

Singh (2014) formulated a mathematical model to describe the performance of Blood Glucose Regulating System (BRGS) during Glucose Tolerance Test (GTT). He concluded that a value of less than four hours for t_0 , the corresponding period to the natural frequency of the system indicated normalcy while appreciably more than four hours implied mild diabetes. He also observed that sociological factors play an important role in BRGS.

Yang *et al.* (2014) proposed a novel piecewise glucose-insulin models with a threshold window for diabetes mellitus. They studied the relation between regular equilibria and a pseudo-equilibria of the glucose-insulin regulatory system and established the sufficient and necessary conditions for the global stability of regular equilibria and the pseudo-equilibria by using qualitative analysis techniques of non-smooth Filippov dynamic systems. Their result indicates that blood glucose level can be maintained within a normal range using piecewise glucose-insulin models with a single threshold or a threshold window. Their findings suggest that it is critical to individualize insulin therapy for each patient separately, based on initial blood glucose levels.

1.7 Thesis objectives

The objectives of my PhD thesis is focused on studying the physiological behavior of diabetes, in particular type 2 diabetes, through mathematical modeling and computer simulation in order to evaluate the medical condition of diabetic patients and to find suitable and optimal methods to control their blood glucose level. The focus also lies in studying the population of diabetic patients, with and without complications. Developing a mathematical model for diabetes mellitus can be performed either by constructing a new model or by improving an existing model.

[1]CHAPTER 2

A MODEL OF GLUCOSE-INSULIN INTERACTION

2.1 Introduction

Diabetes mellitus, commonly known as diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels known as hyperglycemia. Glucose concentration in the blood of a normal person lies in the range of 80-110mg/dl (Norman and Litwack, 1997). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin produced in the beta cells of the pancreas. Diabetes has become an epidemic with considerable complications such as retinopathy, nephropathy, peripheral neuropathy and blindness (Derouich and Boutayeb, 2002). The number of diabetics in the world is increasing every year. International Diabetes Federation estimates that 387 million people around the world have diabetes corresponding to 6.4% of the adult's population. The figure is expected to hit the 592 million people in 2035 (http:/www.idf.org).

The study of glucose-insulin interaction dates back as early as the sixties (Bolie, 1961) and since then has been studied extensively by many researchers (Sluiter *et al*. 1976; Sluiter *et al*. 1976; Toffolo *et al*., 1980; Charette *et al*., 1989; Srinivasan, 1970; Cobelli *et al*.,

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1982; Cobelli and Thomaseth, 1985; Bergman *et al*., 1985; Cobelli and Thomaseth, 1987; Cobelli et al., 1998; Fisher and Teo, 1989; Berger and Rodbard, 1989; Fisher, 1991; Sturis and Polonsky, 1991; Lehmann and Deutsch, 1992; Kuang, 1993; Hethcote, 1994, 2000; Hashiguchi *et al*., 1994; Quon *et al*., 1994; Thomaseth *et al*., 1996; Meilunas, 1998; Parker, 1999; Bergman and Ader, 2000; Topp *et al*., 2000; Tolic *et al*., 2000; Breda *et al*., 2001; Korchinsky, 2001; Mari *et al*., 2001; Srinivasan *et al*., 2002; Khan, 2003, 2005; Man *et al*., 2004; Brubaker *et al*., 2007).

The most widely used model in the study of diabetes is the minimal model which is used in the interpretation of the intravenous glucose tolerance test (IVGTT) (Bergman *et al*., 1979). This model consists of three equations which may be considered to be divided into two separate parts. The model was formulated as:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b, \qquad G(0) = p_0$$

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

$$\frac{dI(t)}{dt} = p_4(G(t) - p_5)^+ t - p_6(I(t) - I_b), \; I(0) = p_7 + I_b$$

Where $(G(t) - p_5)^+ = \begin{cases} G(t) - p_5, & \text{if } G(t) > p_5 \\ 0, & \text{if } G(t) \leq p_5 \end{cases}$, and

$p_0, p_1, p_2, p_3, p_4, p_5, p_6, p_7$ are parameters.

In order to overcome the difficulties of the coupled minimal model and to remove the artificial non-observable variatble $X(t)$, Gaetano and Arino (2000) have proposed the following dynamical model:

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7, \qquad G(0) = G_b + b_0$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s) ds\,, \qquad I(0) = I_b + b_3 b_0$$

With $G(t) = G_b \; for - b_5 \leq t < 0$. $b_0, b_1, b_2, b_3, b_4, b_5, b_6, b_7$ are the parameters.

Following the dynamic model, several authors (Mukhopadhyay *et al*, 2004); Chen *et al*., 2010; Giang *et al*., 2008; Li and Kuang, 2007; Li *et al.*, 2006; Li *et al.*, 2001; Li and Zheng, 2010; Panunzi *et al.*, 2007) have proposed more popular, general and realistic models with results consistent with physiology. The modelling of the glucose-insulin system has become an interesting topic and several models have been proposed and studied with the purpose of understanding the system better, investigating possible pathways to diabetes as well as providing better insulin administration practices. Many models have been presented as described in a survey by Makroglou *et al.* (2006) as well as in the review by Boutayeb and Chetouani (2006).

In this chapter, a mathematical model of diabetes mellitus is analyzed, which is concerned with the regulation process of glucose in the body by the pancreatic insulin. This chapter considers the disappearance of glucose due to insulin action (insulin-dependent) as well as the disappearance of glucose due to tissue uptake such as the brain and nerve cells

(insulin-independent) and rise in glucose level due to infusion through meal intake, oral glucose intake, continuous enteral nutrition absorption and constant infusion (Li *et al.*, 2006).

2.2 Interaction of glucose and insulin

This chapter is based on the mechanism and the effect of the interaction of the glucose and insulin levels in the human system with particular interest on the diabetic patients. The study is carried by using mathematical models which are built on the knowledge of glucose and insulin.

2.2.1 Glucose and its biosynthesis

Human food substances are mostly product of photosynthesis by plants of which carbohydrate is one of the end products. Thus, green plants in the presence of sunlight use water and carbon dioxide to produce carbohydrates. It is in this form that much of the glucose in the human system is derived since the carbohydrates when taken as food undergoes digestion in the stomach/intestines and thus broken down into monosaccharides, polysaccharides and disaccharides. Glucose molecules incidentally are monosaccharide and it is in this form that the body makes use of the carbohydrates. Examples of food substances rich in carbohydrates are rice, yam, cassava and corn. After digestion of the carbohydrates and the subsequent breakdown to the various forms, the glucose diffuses from the digestive system into the blood. The blood then conveys it to the requiring cells where they will be utilized by a certain mechanism. Principally, much of the glucose in the blood passes through the liver before it is taken to the tissues and peripheral cells. When in excess, they are converted to glycogen and stored in the liver by the appropriate enzymes. In extreme cases where the liver

has stored to its maximum capacity, the excess glucose is converted into fats and then taken to the muscles and other tissues for storage.

Conversely, in case of lack of glucose in the blood, these stored fats and glycogen are reconverted back into glucose and sent to the blood for onward transportation to the requiring cells. The maximum quantity of glucose that the liver can store can barely sustain live for 24 hours after which the stored fats and proteins are then being converted to supply the energy needed by the cells. In such a situation, the gate to glucose metabolisms by cells other than the brain cells are shot as the basal level of insulin do not interact further with the glucose. The reason for closing the door to glucose metabolism is that the brain cells needed mainly the glucose for their sustenance while the other cells can make use of the fats and proteins in obtaining the energy they needed.

In general, the daily intake of carbohydrate varies considerably although this ranges from 250-800 g. Most of these carbohydrates come in the form of plant polysaccharides, starch and with small amount of disaccharides (table sugar) and lactose (milk sugar). Carbohydrates are compounds whose general chemical formula is $(CH_2O)_n$, where n is a positive number.

2.2.2 Blood glucose regulation by the liver and other tissues

The liver is an organ which produces and consumes glucose. It is exposed to insulin concentration in the portal venous blood. The insulin concentration here is 3-10 folds greater than that in the systemic circulation. The liver alone is the sole site of the blood gluco-regulation action of the glucagon. When we consider the regulation of the blood glucose level by the liver, we consider the period following an overnight fast and preceding the ingestion of

the first meal of the day. This period is generally referred to as post absorptive state. After the overnight fast, the concentration of hormones (insulin and glucagon) and substrates (glucose, amino acids, fatty acids) usually return to the baseline concentrations which we call the basal levels. The reduction of insulin to the basal level (10-20 μ U/m) results in virtually total cessation of glucose uptake by the insulin-dependent tissues such as resting muscles, adipose tissues and the liver though its uptake is continued by the non-insulin-dependent tissues such as the brain, the formed elements of the body and the renal medulla at a combined rate of about 2-3 mg/kg/mm. Under this state, the maintenance of the blood glucose is realised by the hepatic release of glucose at rates equal to the tissue demand and utilization. This addition process is made up of glycogenolysis (synthesis of glucose from the glycogen) and gluconeogenosis (the synthesis of glucose from the pyruvate, lactate, glycerol and amino acids). It is estimated that about 70-75% of hepatic glucose release is as a result of glycogenolysis while the remaining 25% is due to gluconeogenesis (Vallence-Owen, 1975). In as much as the fall in plasma glucose give rise to hepatic glucose output, the relative contributions from glycogenolysis and gluconeogenosis are influence by the following:

1) Total glycogen stored in the liver which is usually not less than 70g and about 450g in a 70kg man.

2) Stored protein-derived amino acids

The daily glucose requirement by the brain is about 150g so that if the liver store 70g daily, then this stored glucose will get depleted in less than 24 hour period of fasting. When this stored glycogen is depleted, the splanchnic uptake of alanine gets stimulated. This stimulation have been shown to be a consequence of starvation, the kidney becomes an

important source of glucose synthesis and at such a time, this accounts for approximately half of the total glucose release into the blood stream. This is suspected to have come from the conversion of nitrogen substances that would have been excreted in the urine since experiment has shown a reduction in the urinary nitrogen excreted (10-12g a day or even less) after some long period of starvation. For such long period of starvation, glucose utilization has reduced to as much as 50%. This is because at such periods, the brain used Ketone acid as its main oxidation fuel in place of glucose.

Also one of the functions of the liver is the conversion of the excess glucose to glycogen which is the storage form. However, this action is possible in the presence of insulin and hence, the recognition of liver as the site for the glucose-insulin interaction. Also the peripheral muscles and adipose tissues take part in the disposal of oral glucose.

The level of glucose in the systemic circulation (blood plasma) measures the amount of glucose that escapes from the splanchnic bed. Also the basal rate of glucose utilization represents consumption by non-insulin-dependent tissues particularly, the brain and blood cellular elements. Fellig *et al.* (1975) showed that only about 15% of the ingested glucose load is available for disposal by the peripheral insulin-dependent tissues. They further showed the disposal of the 100g ingested glucose over a 3-hour period as depicted in the following table:

Ingested glucose	Disposal
Glucose remaining in glucose space (Unmetabolised)	Less than 5%
Increased peripheral glucose utilization (Insulin-dependent)	15%
Glycogen-spacing (non-insulin dependent peripheral uptake)	25%
Hepatic retention	55%
Hepatic disposal, glycogen synthesis, triglyceride formation, glysolysis	Less than 5%

Table 2.1 – Disposal of glucose

Fats are produced in the liver of which only some small amount is stored there and others are released into the blood and taken to the adipose tissues for storage. The catabolism of adipose-tissues triacylglycerol to liberate fatty acids into the blood which are picked by all these tissues (excluding the nervous system) enter the Krebs cycle and are oxidised to release the required energy by the cells. This helps in the reservation of the glucose for the brain cells and the nervous system.

2.2.3 Mechanism of entry of glucose into the cells

The study of cell structure shows that the cells are separated from the extra-cellular fluids by the surface membrane called the plasma membrane. This membrane provides barrier to the movement of molecules in and out of the cells and equally provided scaffolding to which

the cell compartment anchors. Movement of molecules across cell membranes is not constant and this regulates the cell functions. On the outer surface of the plasma membrane are located the receptors to hormones and chemical messengers so that the plasma membrane acts as a signal-receiving device for the detection of chemical signals that regulate the cell activities. These receptors are proteins. Also in the plasma membrane are the junctions which serve as channels for cell to cell communication. Certain enzymes also anchor on the cell membranes rather than dissolving in the intra-cellular fluid so that chemical reactions occur only in association with particular organelle. This is because mediating reactions are either bound to the membranes of the organelle or, are located within the organelle and thus unable to penetrate the surrounding membrane.

In general, the cell membranes are composed of bimolecular lipid matrix in which proteins are embedded. The lipids and proteins are present in approximately equal proportions. The lipids form the barriers to movement of molecules through the membrane while the protein provide selective means for transfer of certain molecules through the barrier and constitutes the binding sites with enzymes associated with the membrane. Majority of the membrane lipids are phospholipids which are amphitatic molecules having a charged region at one end (negatively charged phosphate group which is usually attached to another small group) while the other end is neutral and consists of two long chain fatty acids (Vander *et al.,* 1980).

When glucose is obtained as one of the products of digestion, it is absorbed into the blood from where it diffuses into the extracellular spaces surrounding the cells. Since diffusion is an extremely slow process, the blood circulation helps in taking the glucose very close to the cells so that the time needed for receiving nutrients is minimised. Though the sugar (glucose)

diffuses into the extra-cellular surrounding of the cell from the blood, it does not actually diffuse into the cells. The movement of these glucose molecules into the cells requires a special mechanism that is built into the cell membrane structures. This special mechanism through which the glucose molecules move into the cells is called the mediated transport mechanism. In this mechanism, the glucose molecules bind to the specific protein on the membrane surface and this leads to their movement through the membrane. The membrane actually determines which molecules should enter the cell by mediated transport or diffusion. The major characteristics of mediated transport are specificity, saturation and competition. In mediated transport, the flux constant changes in the extracellular nutrient concentration unlike in diffusion, although there is maximum rate that the nutrient can enter the cell by this means.

The transporters are carrier proteins and they facilitate the transport of these glucose molecules from the extracellular spaces to the intracellular space of the cells. About six of such carrier proteins have been identified. However, not all of the glucose transporters are responsive to insulin stimulation. There are protein receptors on the cell membranes which receive those glucose molecules when the transporter brings them. These receptors are evenly distributed in the membrane when not influence by insulin. However, the mechanism by which these carrier proteins enable the solute to pass through the molecules is not quite known though it is thought to involve conformational changes in the carrier molecules resulting from the binding action of the solute.

For IDDM patient, this process still holds but at a reduced level due to non-availability of sufficient insulin in the blood plasma.

2.2.4 Insulin and its biosynthesis

Insulin is a protein hormone secreted by the islets of Langerhans clusters of endocrine cells in the pancreas. This hormone has wide spectrum of activities among which is the enhancement of the conversion of glucose to glycogen which is the storable form of glucose in the body. There are three distinct types of the islets namely: the alpha, beta and gamma cells. The alpha cells secretes the glucagon, the beta cells secretes the insulin while the gamma cells secretes the peptides named somatotastin. Insulin act directly or indirectly on most tissues of the body though it has no action in the brain cells (Vander *et al*., 1980). The presence of insulin induces on its target cells an alteration of either the membrane transport or the enzyme function.

On biosynthesis of insulin, this takes place in the beta cells in the islet of Langerhans of the pancreas. The study of the process involved and controlling the biosynthesis, storage and release of insulin was done by studying the insulin-producing tumours and insulinomas that abound in the pancreas. Steiner and Oyer (1967), Steiner (1967) through their studies showed that there is a precursor insulin called the proinsulin in insulin biosynthesis. It has also been shown that photeolytic conversion of this precursor to the hormone insulin prior to its storage takes place in the beta cells. In the proper sense of it, insulin synthesis begins at the ribosomes bound to the endoplasmic reticulum (Sorenson *et al*., 1970). This synthesis has been shown to be enhanced by the presence of glucose. The presence of glucose leads to proinsulin production and this is concentrated at the golgi body cisternae where it is packaged in the secretory granules, though some remains in the cytoplasmic microvesicles. This is the stage where the proinsulin is converted to insulin and C-peptides (Steiner *et al*., 1974). For the

conversion of the proinsulin to insulin, two types of proteolytic activities are necessary: a tryptic-like activity to cleave at the dipeptides located at the ends of the C-peptides and caboxypeptidase B activity- to remove the arginine dipeptide from the carboxyl end of the B-chain leaving the B-30 residue intact. Research has also shown that although enzymes are thought of to be responsible for the conversion of proinsulin to insulin, only one such enzyme have so far been discovered and this takes place in the secretory granules. This suggests that the more mature a granule is, the less it will contain proinsulin since newly formed granules contain mainly proinsulin. The proteolytic conversion of proinsulin to insulin is strictly an intracellular process and this is not inhibited by cyclohaximide or other inhibitors of protein synthesis, indicating that transformation of proinsulin to insulin is not necessarily due to continuous protein synthesis.

2.2.5 Insulin release

Glucose presence is not the only pre-eminent stimulus for insulin secretion. It is also one of the major regulators of insulin biosynthesis. The stimulation of the cells for insulin synthesis and release by the presence of glucose is thought of as being a kind of signal by the glucose or one of its metabolites. It has been shown that replica stimulation of insulin synthesis and release is possible in a low calcium medium though the extrusion of granules is inhibited under these conditions. Another stimulant for the release of insulin is the sugar called manose. Similarly, the glucose metabolites formed in the liver and the blood/tissue insulin level are thought of to influence insulin secretion. Lacy *et al.* (1968), Howell and Lacy (1971), Malaise *et al*., (1972), Gomez-Acebo and Hermida (1973) showed that insulin release is by the process

of exocytosis which is the movement of the secretory granules to the cell membrane where it fuses with it and then the extrusion of their contents to the extracellular fluid. While the above mentioned factors initiate insulin release, there are other factors that inhibit the release. These are mannoheptulose, absence of external Ca^{2+} (blocks secretory responses to all agents except Ba^{2+}) and other chemicals. On timely release of insulin, it is seen that its secretory response to glucose stimulation is biphasic where increased glucose concentration elicits within 0.5-1 minute, a rapid rise in the rate of the release, which returns to the basal level within 5-10 minutes and this is followed by a more gradual increasing rise in the rate of insulin (Grodsky, 1972).

Similar biphasic release was seen when insulin release was stimulated by more of tolbutamide. These observations thus suggest the storage of insulin in two compartments- the smaller being particularly laible to stimulants so that the limited phase of the insulin release is the emptying of this liable compartment while the second phase release is from the larger storage compartment (Grodsky, 1972).

Insulin produced by the islet of Langerhans of the pancreas is usually stored in case of need by the body mechanisms. In a normal person, the average basal insulin level in the blood is about 20 μ U/ml (Arnold, 1966). The daily insulin requirement is about 30-50 μ U while about 200 units are stored in the pancreas (Campbell *et al*., 1977). As mentioned earlier, the produced proinsulin are stored in the secretory granules and thus are ever ready for release.

However, in the case of insulin-dependent diabetes mellitus (IDDM), the available insulin to the cells for usage is very low so that amount released when the glucose

concentration increases is low. It might also be that when the levels is a bit high, there may be poor cell response to this insulin even at high level of blood plasma glucose.

When the insulin is being used, the replacement is possible by conversion of the produced proinsulin although it has been shown that the replacement is not of linear relationship. This means that the amount of insulin degraded is not at all times equal to the amount produced. Hence for long period of glucose charge, only the recently produced insulin are being released. Hence, continued glucose charge may eventually result in high blood plasma glucose level since quantity of insulin produced and releasable may not be even enough to take care of this high level.

2.2.6 Insulin degradation

Since insulin is a hormone, it has to be degraded like any other hormone. Apart from its degradation as it helps in the conversion of the excess glucose to glycogen, it is being used for other activities and these activities degrade it. It has been shown that the level of degradation of insulin vary from person to person and from male to female. Even in women, pregnant women degrades insulin more than the non-pregnant ones. In our model, we assume an average degradation.

In general, insulin degradation occurs in two ways: reduction and proteolytic. The reduction process is encountered when insulin takes part in reaction or used up by cells as they act as enzymes in reactions in the body (Mirsky and Broh-Kahn, 1949). This activity therefore reduces the amount of the insulin available for further reactions. Also certain enzymes in the body inactivate the biological activity of insulin. Such enzymes are called ‘insulinase’ and they

are considered to be proteolytic in nature. An example of such enzyme is 'protein-disulphide-reductase (glucathione)'. It inactivates insulin by catalysing the reduction of the disulphate bonds of insulin and thus splitting of the insulin molecules. Tomizawa and Varandani (1965), Varandani and Nafz (1970) and Varandani, Nafz and Chandler (1975) have isolated the glucathione in the liver, kidney and the leukocytes respectively. This glucathione also inactivates proinsulin and at the same time the reactivation of reduced and randomly oxidised proinsulin (Varandani and Nafz, 1969). However, excess inactivation of the insulin is controlled by another enzyme called the glucagon. Other growth hormones also contribute in the control of insulin degradation. These enzymes help in the adjustment in the rate of insulin degradation to changing rate of insulin secretion and requirements.

2.2.7 Mechanism of insulin action on glucose level in blood.

It is known that the increase in the plasma glucose concentration induces insulin release and this released insulin in turn helps in reducing the level of glucose in the same plasma. As the glucose concentration increases in the blood plasma, the pancreas is activated to release insulin. As this insulin is released into the extracellular fluid in the pancreas by exocytosis, it diffuses out to join the blood stream and therefore taken along to the appropriate sites, most especially the liver for the required actions. At the liver, it diffuses into the extracellular fluids surrounding the liver cells where the insulin binds with the appropriate protein on the plasma membrane and get aggregated thereby clearing the inhibiting actions of these receptors to glucose transporters, which are also protein-like. Thus, insulin binds with these receptors either in the phosphorylated form or the unphosphorylated form. This

autophosphorylation of the insulin is what causes the aggregation of the protein-receptors on the plasma membrane (Qoun & Campfield, 1991) which are evenly distributed at the membrane surface when not activated by glucose charge (Gavin *et al.,* 1974; Lonnroth & Smith, 1983; Koskamos & Roth, 1980). This might mean that the level of entry of glucose into the cell depend on the insulin action since the area of the plasma membrane to be cleared of the inhibiting actions of the plasma membrane-protein depends on the insulin and its binding actions (Jarett and Smith, 1979). This action so treated is for the case of a normal person with normal insulin release and high glucose concentration in the blood plasma. However, if the individual is fasting, we have just the basal level of the insulin as required in the body. This insulin level is such that it does not act on the glucose being converted from glycogen to glucose in the liver. Hence, we may say that if the glucose level in the blood plasma is of basal value, then the gateway to insulin action on plasma glucose level gets shut.

For the diabetic patient (IDDM), the binding action of the receptor-proteins is impaired. This impaired action negatively affects the amount of glucose that enters the cells and thus the high concentration of glucose in the blood plasma. Also in IDDM patient, there is reduction in production and release of insulin although the amount released follows the above described process in reducing the blood plasma level.

Going by the result that insulin infusion into an IDDM patient corrects the high blood plasma glucose concentration, one may be tempted to say that the reduction in the available quantity of insulin affects the plasma membrane action on the glucose transporters.

2.3 Modeling the glucose-regulatory system

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(glucose) levels falls 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 oxidation. Elevated glucose concentrations of glucose in blood stimulate the release of insulin, and insulin acts on cells throughout the body to stimulate uptake, storage and utilization of glucose.

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

$$\dot{x} = -a_1 x - a_2 xy + a_3$$

$$\dot{y} = b_1 x - b_2 y \qquad \ldots\ldots\ldots\ldots \qquad (2.1)$$

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

x represents glucose concentration

y represents 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

2.4 Linearization of the model

Consider the critical point of the system (2.1)

$$\dot{x} = 0 \Rightarrow -a_1 x - a_2 xy + a_3 = 0 = f(x, y)$$

$$\dot{y} = 0 \Rightarrow b_1 x - b_2 y = 0 = g(x, y) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2.2)$$

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

Solving (2.2), we get

$$x^* = \frac{-a_1 b_2 + \sqrt{(a_1 b_2)^2 + 4a_2 b_2 a_3 b_1}}{2b_1 a_2}$$

$$y^* = \frac{-a_1 b_2 + \sqrt{(a_1 b_2)^2 + 4a_2 b_2 a_3 b_1}}{2b_2 a_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2.3)$$

We are interested in the interior-equilibrium point (x^*, y^*) which always exist since all the parameters are considered positive.

Consider the Jacobian matrix of (2.2) given by

$$J = \begin{pmatrix} -a_1 - a_2 y & -a_2 x \\ b_1 & -b_2 \end{pmatrix}$$

At (x^*, y^*),

$$J^* = \begin{pmatrix} -a_1 - a_2 y^* & -a_2 x^* \\ b_1 & -b_2 \end{pmatrix}$$

We now use the transformation $x = X + x^*, y = Y + y^*$ and then linearize the system

$$\begin{pmatrix}\dot{X}\\ \dot{Y}\end{pmatrix} = J^* \begin{pmatrix}X\\ Y\end{pmatrix} = \begin{pmatrix}-a_1 - a_2 y^* & -a_2 x^*\\ b_1 & -b_2\end{pmatrix}\begin{pmatrix}X\\ Y\end{pmatrix}$$

We get the linearized system

$$\dot{X} = -a_1 X - a_2 y^* X - a_2 x^* Y$$

$$\dot{Y} = b_1 X - b_2 Y \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2.4)$$

2.5 Stability Analysis

***Theorem 2.1*:** *The trivial equilibrium point* $(0,0)$ *is locally asymptotically stable.*

Proof: At $(0,0)$

$$J_{(0,0)} = \begin{pmatrix}-a_1 & 0\\ b_1 & -b_2\end{pmatrix}$$

Whose characteristic equation is given by $\lambda^2 + (a_1 + b_2)\lambda + a_1 b_2 = 0$

Where $TrJ_{(0,0)} = -(a_1 + b_2) < 0$ and $detJ_{(0,0)} = a_1 b_2 > 0$, since $a_1 > 0, b_2 > 0$

Therefore by Routh-Hurwitz criteria, the trivial critical point $(0,0)$ is locally aymptotically stable.

Theorem 2.2: *The interior-equilibrium point* (x^*, y^*) *is locally asymptotically stable if*

$$(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y^*)$$

Proof: Consider the Lyapunov function

$$V = \frac{1}{2}(X^2 + Y^2)$$

Hence, $$\dot{V} = -(a_1 + a_2y^*)X^2 + (b_1 - a_2x^*)XY - b_2Y^2$$

$$= -\frac{1}{2}AX^2 + BXY - \frac{1}{2}CY^2$$

Where $$A = 2(a_1 + a_2y^*)$$

$$B = b_1 - a_2x^*$$

$$C = 2b_2$$

The sufficient condition for $\dot{V}$ to be negative definite is that

$$B^2 < AC$$

i.e. $$(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y^*)$$

which is the condition that the parameters must satisfy so that the critical point (x^*, y^*) is locally asymptotically stable.

Lemma 2.1: *The set* $\Omega = \left\{(x, y): 0 \leq x + y \leq \frac{a_3}{\delta} + ce^{-\delta t},\ \delta = min(a_1 - b_1, b_2),\right.$

$\left.c \text{ is a constant}\right\}$ *is a region of attraction for all solutions initiating in the positive quadrant.*

Proof: From our model (2.1), we have

$$\frac{dx}{dt} = -a_1 x - a_2 xy + a_3$$

And $\frac{dy}{dt} = b_1 x - b_2 y$

Therefore, $\frac{d(x+y)}{dt} = -a_1 x - a_2 xy + a_3 + b_1 x - b_2 y$

$$\leq -a_1 x + a_3 + b_1 x - b_2 y$$

$$= -(a_1 - b_1)x + a_3 - b_2 y\}$$

$$\leq -\min\{(a_1 - b_1), b_2\}(x + y) + a_3$$

Let $\delta = \min\{(a_1 - b_1), b_2\}$

Then $\frac{d(x+y)}{dt} \leq -\delta(x + y) + a_3$

Or $\frac{d(x+y)}{\delta(x+y)-a_3} \leq -dt$

Or $\frac{1}{\delta}\log\{\delta(x + y) - a_3\} \leq -t + logc_1$

Or $x + y \leq \frac{a_3}{\delta} + ce^{-\delta t}$, where $c = \frac{c_1}{\delta}$

Theorem 2.3: *The interior-equilibrium point* (x^*, y^*) *is globally asymptotically stable if*

$(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y)$ *where* $y\epsilon\Omega$.

Proof: Consider the Lyapunov function

$$V = \frac{1}{2}(x - x^*)^2 + \frac{1}{2}(y - y^*)^2$$

Then $\dot{V} = (x - x^*)\dot{x} + (y - y^*)\dot{y}$

$$= (x - x^*)(-a_1x - a_2xy + a_3 + a_1x^* + a_2x^*y^* - a_3 + a_2x^*y - a_2x^*y)$$

$$+(y - y^*)(b_1x - b_2y - b_1x^* - b_2y^*)$$

$$= (x - x^*)\{-a_1(x - x^*) - a_2y(x - x^*) - a_2x^*(y - y^*)\}$$

$$+(y - y^*)\{b_1(x - x^*) + b_2(y - y^*)\}$$

$$= (-a_1 - a_2y)(x - x^*)^2 + (-a_2x^* + b_1)(x - x^*)(y - y^*) - b_2(y - y^*)^2$$

$$= -\frac{1}{2}A_{11}(x - x^*)^2 + A_{12}(x - x^*)(y - y^*) - \frac{1}{2}A_{22}(y - y^*)^2$$

Where $A_{11} = 2(a_1 + a_2y)$

$A_{12} = -a_2x^* + b_1$

$A_{22} = 2b_2$

The condition for $\dot{V}$ to be negative definite is that

$${A_{12}}^2 < A_{11}A_{22}$$

i.e., $(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y)$ *where* $y\epsilon\Omega$

Thus, The interior-equilibrium point (x^*, y^*) is globally asymptotically stable if

$(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y)$ where $y\epsilon\Omega$.

2.6 Numerical Simulation

In a clinical experiment conducted and reported by De Gaetano and Arino (2000), ten healthy volunteers (5 males and 5 females) participated, all of whom had no family or personal history of diabetes and other endocrine diseases. They were not on any medication and had maintained constant weight for the six months preceding the experiment. The parameters values for the volunteers are listed in their table 1 (De Gaetano and Arino. 2000). They were able to show that the dynamic model does produce solutions that fit well with the data collected from their experiment. We fit the data from table 1 and found that it fit well with the conditions for existence and the stability of the interior-equilibrium of our system except for their sixth and seventh subjects which was also observed by Li *et al*. (2001). Taking the data of their first subject:

$$a_1 = 0.0226\ ,\ a_2 = 3.80e-08\ , a_3 = 1.56, b_1 = 0.0022\ , b_2 = 0.0437\ .$$

We get $x^* = 69.0261,\ y^* = 3.5540.$

The condition for local stability for (x^*, y^*) is satisfied as

$$(b_1 - a_2x^*)^2 = 5.0505e-06 < 4b_2(a_1 + a_2y^*) = 0.0040$$

For validation of the global stability condition, we consider the case when $t \to 0$, i.e when $y < \frac{a_3}{\delta} + c$. We again consider the particular case $y = \frac{a_3}{\delta} = \frac{1.56}{0.0204} = 76.4706$. We see that the interior-equilibrium point (x^*, y^*) is globally asymptotically stable.

$$(b_1 - a_2x^*)^2 = 5.0505e-06 < 4b_2(a_1 + a_2y^*) = 0.0039$$

Also, graphs are generated for two different values of a_2, the rate constant which represents insulin-dependent glucose disappearance, where the solid lines depict glucose concentration and the dash-dot lines depict insulin concentration. We see that when $a_2 = 0.038$, the curve for glucose cencentration shows that peak glucose concentration is lower (between 25-30 units) as compared to smaller values of $a_2 = 0.000000038$ where glucose concentration level reaches more than 60 units over the same interval of time.

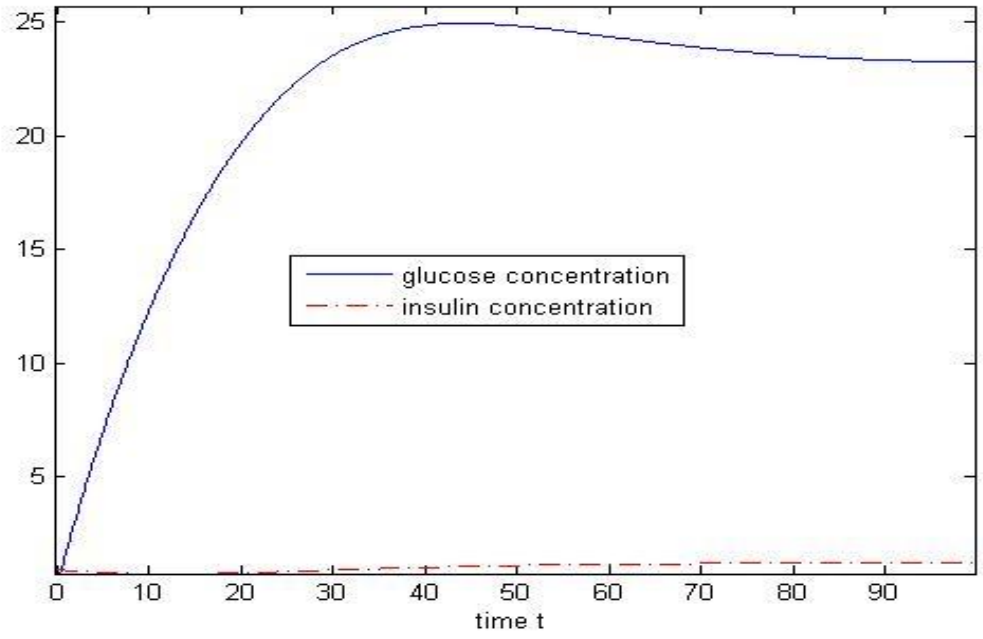

Figure 2.1 - Glucose concentration vs. Insulin concentration when $a_2 = 0.038$

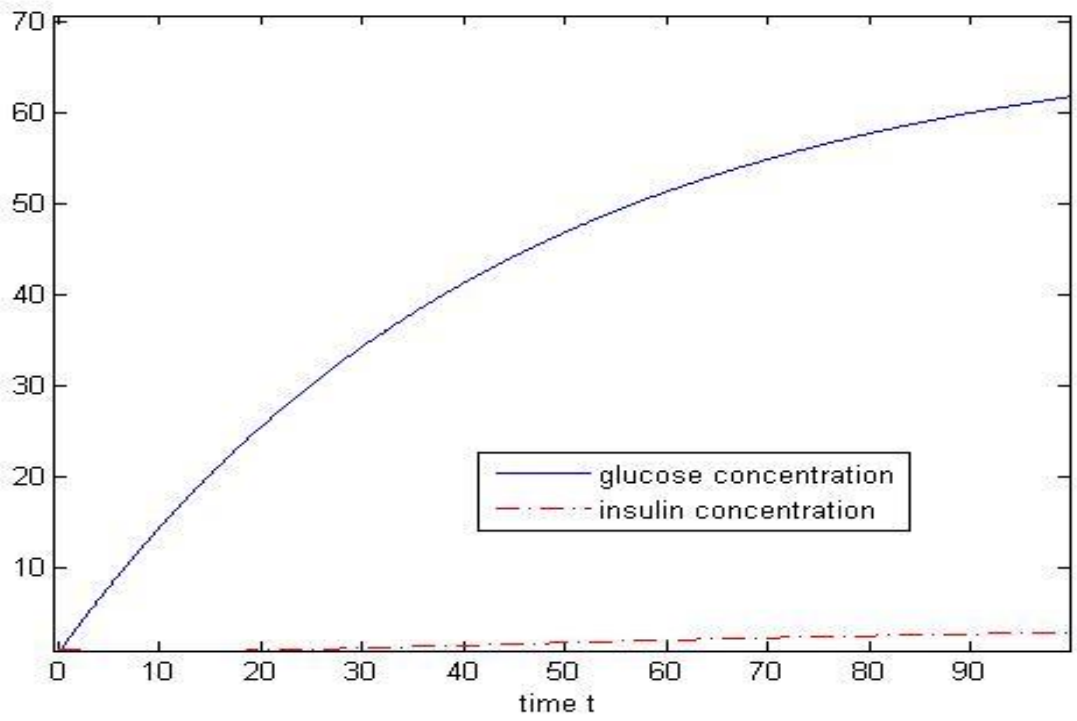

Figure 2.2 - Glucose concentration vs. Insulin concentration when $a_2 = 0.000000038$

2.7 Conclusion

In this chapter, a mathematical model has been proposed and analyzed to study the dynamics of glucose and insulin in the human body. The model was formulated by a system of ordinary differential equations and two cases viz., linear and non-linear cases were considered. Both cases are validated by numerical simulations and the importance of the role of insulin in the disappearance of glucose has been shown by varying the value of a_2, the rate constant representing insulin-dependent glucose disappearance. The model has been analyzed without considering the effect of delay in secretion of insulin from the beta cells in pancreas and the

delayed effect of hepatic glucose production. The interior-equilibrium point is shown to exist and is consistent with the human physiology. The unique interior-equilibrium point has been shown to be locally and globally stable under certain conditions on the system parameters and for a bounded y (insulin concentration), using Lyapunov's method. From the above results, we conclude that the model is physiologically consistent and may be a useful tool for further research on diabetes.

[2]CHAPTER 3

MODELING THE EFFECT OF EXERCISE ON INTERACTIONS OF GLUCOSE AND INSULIN

3.1 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 (http://www.idf.org/diabetesatlas/5e/mortality), 4.6 million people in the age of 20-79 years died from diabetes in 2011, which accounts for 8.2% of the deaths in this age group due to different causes worldwide. In a report by World Health Organization (WHO) in March 2013 (http://www.who.int/mediacentre/factsheets/fs312/en/), 347 million people have diabetes worldwide and 3.4 million people have died due to this killer disease. The mortality rate due to diabetes is expected to grow and WHO projects that diabetes will be the 7^{th} leading cause of death in 2030. 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, a low cost and effective method must be

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formulated to prevent and control the disease. 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) (Wasserman *et al*., 1991; Sigal *et al.*, 1994; Sigal *et al*., 1996). This effect is more prominent in people at risk i.e. 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.

In this chapter, taking into account the effect of physical exercise on the dynamics of glucose and insulin, we propose a mathematical model following the model of Derouich and Boutayeb (2002) and study the stability of the dynamical system of glucose and insulin.

3.1.2 A brief history of mathematical models on diabetes

Mathematical modeling of the dynamics of insulin and glucose dates back as early as 1939 (Himsworth and Kerr, 1939). In the1961, Bolie proposed the simple linear model

$$\frac{dG}{dt} = -a_1 G - a_2 I + p;$$

$$\frac{dG}{dt} = -a_3 G - a_4 I$$

Where *G=G(t)* represents the glucose concentration at time *t*, *I=I(t)* represents insulin concentration at time *t* and $a_1, a_2,\ a_3, a_4, p$ are parameters.

Several authors continued the study (Ackerman *et al.*, 1965; Della *et al*., 1970; G. Serge *et al*., 1973) but the real start of modeling the glucose-insulin dynamics is thought to begin with the so-called minimal model proposed by Bergman (1979). The model was formulated as follows:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b, \qquad G(0) = p_0$$

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

$$\frac{dI(t)}{dt} = p_4(G(t) - p_5)^+ t - p_6(I(t) - I_b), \qquad I(0) = p_7 + I_b$$

Where $(G(t)-p_5)^+ = G(t)-p_5$, if $G(t) > p_5$ and 0 otherwise. X(t) represents an auxiliary function which denotes insulin-excitable tissue glucose uptake activity, G_b and I_b are the subject's baseline glucose and insulin level respectively, $b_i's$ are parameters. The same authors have further published papers which tests and validates the minimal model. Many other authors have revised and modified the minimal model. One such example was the model proposed by De Gaetano and Arino (2000) called the dynamical model which couples the two different parts of the minimal model into one part given by

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7, \qquad G(0) = G_b + b_0$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s)ds\,, \qquad I(0) = I_b + b_3 b_0$$

With $G(t) = G_b \; for - b_5 \leq t < 0$

Following the dynamical model, a more general model was proposed by Li and Kuang (2001). Mukhopadhyay *et al*. (2004) extended the dynamic model to a family of models incorporating a generic non-negative, square integrable normalized kernel. Similar works to obtain a better and accurate model by several authors (Boutayeb *et al.,* 2004; Boutayeb and Chetouani, 2006, Chen *et al*., 2010; Derouich and Boutayeb, 2002; Giang *et al.*, 2008; Kwach *et al.*, 2011; Li and Kuang, 2007; Li *et al.*, 2001; Li and Zheng, 2010; Makroglou *et al.*, 2006; Mukhopadhyay *et al*., 2004; Overgaard *et al*., 2006; Palumbo *et al.*, 2004) can be found in literature.

3.2 The Model

Derouich and Boutayeb have considered the first part of the minimal model for studying the effect of exercise on the dynamics of glucose and insulin which takes the form:

$$\left.\begin{aligned} \frac{dG(t)}{dt} &= -(1+q_2)X(t)G(t) + (p_1+q_1)\big(G_b - G(t)\big) + g(t),\ G(b) = G_b \\ \frac{dX(t)}{dt} &= (p_3+q_3)(I(t)-I_b) - p_2X(t),\ X(0) = X_0, \quad I(0) = I_b \end{aligned}\right\} \quad \text{---- (3.1)}$$

Where, $(I(t) - I_b)$ represents the difference between the plasma insulin concentration and the basal insulin,

$X(t)$ is the interstitial insulin.

$\big(G_b - G(t)\big)$ represents the difference between the basal glucose and the plasma glucose.

p_1 is the insulin-independent rate constant of tissue glucose uptake

p_2 is the rate constant expressing the spontaneous decrease of tissue glucose uptake ability

p_3 is the insulin-dependent increase in tissue glucose uptake ability.

q_1 is the rate constant expressing the effect of physical exercise in accelerating the utilization of glucose by muscles and the liver.

q_2 is the rate constant expressing the effect of physical exercise in increasing the muscular and liver sensibility to the action of insulin

q_3 is the rate constant expressing the effect of physical exercise in increasing the utilization of insulin.

$g(t)$ is the glucose infused at time t.

They have illustrated the importance of the role of physical exercise in the prevention of occurrence of diabetes for people at risk, the benefit that can be gained by NIDDM patients from improving insulin sensitivity and compensating its eventual partial lack and also to reassure IDDM patients that no exclusion is made provided a good combination is found to balance insulin doses, carbohydrates and physical activity. However, they have not considered the stability of the system. In this paper, we propose to study the stability analysis of the same model but considering the infused glucose g(t) to be a constant. The model becomes

$$\left.\begin{aligned} \frac{dG(t)}{dt} &= -(1+q_2)X(t)G(t) + (p_1+q_1)\big(G_b - G(t)\big) + g,\ G(b) = G_b \\ \frac{dX(t)}{dt} &= (p_3+q_3)(I(t)-I_b) - p_2X(t),\ X(0) = X_0, \quad I(0) = I_b \end{aligned}\right\} \quad \text{.....(3.2)}$$

3.3 Stability Analysis

The stationary state of the model is given by

$$X^* = \frac{p_3+q_3}{p_2}(I_e - I_b) \quad \text{..... (3.3)}$$

$$G^* = \frac{(p_1+q_1)G_b+g}{\frac{(1+q_2)(p_3+q_3)(I_e-I_b)}{p_2}+(p_1+q_1)} \text{ ……. (3.4)}$$

Where I_e is the insulinemia at equilibrium and g^* is the infused glucose at equilibrium.

Consider the Jacobian matrix of the model given by

$$J = \begin{pmatrix} -(1+q_2)X & -(p_1+q_1) \\ 0 & -p_2 \end{pmatrix}$$

At equilibrium, we have

$$J^* = \begin{pmatrix} -(1+q_2)X^* & -(p_1+q_1) \\ 0 & -p_2 \end{pmatrix}$$

We use the transformation $X = x + X^*, G = y + G^*$ to linearize the system

$$\begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = J^* \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} -(1+q_2)X^* & -(p_1+q_1) \\ 0 & -p_2 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

We get the linearized system

$$\dot{x} = -(1+q_2)X^*x — (p_1+q_1)y$$

$$\dot{y} = -p_2y \text{ ……(3.5)}$$

Theorem 3.1: *The interior equilibrium point* (G^*, X^*) *is locally asymptotically stable if*

$$c_1^2(p_1+q_1)^2 < 4c_1c_2p_2(1+q_2)X^*$$

Proof: Consider the Lyapunov function

$$V = \frac{1}{2}(c_1x^2 + c_2y^2)$$

Differentiating with respect to time t, we get

$$\dot{V} = c_1x\dot{x} + c_2y\dot{y}$$

$$= c_1x\{-(1 + q_2)X^*x — (p_1 + q_1)y\} + c_2y(- p_2y)$$

$$= -c_1(1 + q_2)X^*x^2 - c_1(p_1 + q_1)xy - c_2p_2y^2$$

$$= -\frac{1}{2}Ax^2 + Bxy - \frac{1}{2}y^2$$

Where $A = 2c_1(1 + q_2)X^*, B = -c_1(p_1 + q_1), C = 2c_2p_2$

The sufficient condition for $\dot{V}$ to be negative definite is that $B^2 < AC$ i.e.

$$c_1^2(p_1 + q_1)^2 < 4c_1c_2p_2(1 + q_2)X^*$$

Which is the condition that the parameters must satisfy so that the critical point (G^*, X^*) is locally asymptotically stable.

Lemma 3.1: *The set* $\Omega = \left\{(G, X): 0 \leq G + X \leq \frac{c_3}{\delta} + c_4e^{-\delta t},\ \ where\ \delta = min(p_1+, p_2), c_3 = (p_1 + q_1)G_b + (p_3 + q_3)(I - I_b) + g\right\}$ *is a region of attraction for all solutions initiating in the positive quadrant.*

Proof: We have

$$\frac{dG}{dt} + \frac{dX}{dt} = -(1 + q_2)XG + (p_1 + q_1)G_b - (p_1 + q_1)G + g + (p_3 + q_3)(I - I_b) - p_2X$$

Or $\frac{d(G+X)}{dt} \leq (p_1 + q_1)G_b - (p_1 + q_1)G + (p_3 + q_3)(I - I_b) - p_2X + g$

Or $\frac{d(G+X)}{dt} \leq (p_1 + q_1)G_b + (p_3 + q_3)(I - I_b) - min\{p_1 + q_1, p_2\}(G + X) + g$

Or $\frac{d(G+X)}{dt} \leq c_3 - \delta(G + X)$, where $c_3 = (p_1 + q_1)G_b + (p_3 + q_3)(I - I_b) + g$

Or $\frac{d(G+X)}{dt} + \delta(G + X) \leq c_3$

Or $\frac{d(G+X)}{dt} \leq -\{\delta(G + X) - c_3\}$

Or $\frac{d(G+X)}{\delta(G+X) - c_3} \leq -dt$

Or $\frac{1}{\delta} log\{\delta(G + X) - c_3\} \leq -t + logc_5$

Or $\delta(G + X) - c_3 \leq c_5 e^{-\delta t}$

Or $(G + X) \leq \frac{c_3}{\delta} + c_4 e^{-\delta t}$, where $c_4 = \frac{c_5}{\delta}$

Theorem 3.2: *The interior equilibrium point* (G^*, X^*) *is globally asymptotically stable if*

$(1+q_2)^2 G^{*2} < 4[(1+q_2)X + p_1 + q_1]p_2$, for $(G, X) \in \Omega$

Proof: Consider the Lyapunov function

$$V = \frac{1}{2}(G - G^*)^2 + \frac{1}{2}(X - X^*)^2$$

Or $\dot{V} = (G - G^*)\dot{G} + (X - X^*)\dot{X}$

Or $\dot{V} = (G - G^*)[-(1+q_2)XG + (\dot{p_1} + q_1)(G_b - G) + g + (1+q_2)X^*G^* - (p_1 + q_1)(G_b - G^*) - g + (1+q_2)XG^* - (1+q_2)XG^*] + (X - X^*)[(p_3 + q_3)(I - I_b) - p_2X - (p_3 + q_3)(I - I_b) + p_2X^*]$

Or $\dot{V} = -(1+q_2)G^*(G - G^*)(X - X^*) - (1+q_2)X(G - G^*)^2 - (p_1 + q_1)(G - G^*)^2 - p_2(X - X^*)^2$

Or $\dot{V} = -[(1+q_2)X + p_1 + q_1](G - G^*)^2 - (1+q_2)G^*(G - G^*)(X - X^*) - p_2(X - X^*)^2$

Or $\dot{V} = -\frac{1}{2}A(G - G^*)^2 + B(G - G^*)(X - X^*) - \frac{1}{2}C(X - X^*)^2$

Where $A = 2[(1+q_2)X + p_1 + q_1], B = -(1+q_2)G^*, C = 2p_2$

Now, $\dot{V}$ is negative definite if $B^2 < AC$ i.e.

$(1+q_2)^2 G^{*2} < 4[(1+q_2)X + p_1 + q_1]p_2$, for $(G, X) \in \Omega$

Which is the condition that the parameters must satisfy so that the interior equilibrium point (G^*, X^*) is globally asymptotically stable.

3.4 Numerical simulation

We consider arbitrary values for the parameters as follows:

$c_1 = 0.5,\ \ c_2 = 0.25,\ \ c_4 = 0.36,\ \ p_1 = 0.0023,\ \ p_2 = 0.0016,\ \ p_3 = 0.076,\ \ q_1 = 0.0012,$ $q_2 = 0.0015, q_3 = 0.0056, I_e = 4.5, I_b = 4.32, I = 4.38, G_b = 80, g = 0.23.$

We then get $c_3 = 0.5149, X^* = 9.18, G^* = 0.0555, \delta = 0.0016$

The condition for local stability is satisfied as

$$c_1^2(p_1 + q_1)^2 = 0.000003062 < 4c_1c_2p_2(1 + q_2)X^* = 0.0074$$

For validating the global stability condition, we consider the case as $t \to 0$ and $c_4 = 0$, that is for $X + G \leq \frac{c_3}{\delta}$, i.e. $X \leq \frac{c_3}{\delta}$. We again consider the particular case when $X = \frac{c_3}{\delta} = 321.8125$. We see that the condition for global stability is also satisfied as

$(1 + q_2)^2 G^{*2} = 0.0120 < 4[(1 + q_2)X + p_1 + q_1]p_2 = 1.1413$, for $X \leq 321.8125$

Again, varying q_2, which is the rate constant expressing the effect of exercise in increasing the muscular and liver sensibility to the action of insulin, say $q_2 = 0.23$, and keeping the values of the rest of the parameters the same, $X^* = 1.4850,\ G^* = 0.0448,$ $\delta = 0.0016.$

The condition for local stability is also satisfied as

$$c_1^2(p_1 + q_1)^2 = 0.0000030025 < 4c_1c_2p_2(1 + q_2)X^* = 0.0015$$

For validating the global stability condition, we again consider the case as $t \to 0$ and $c_4 = 0$, that is for $X + G \leq \frac{c_3}{\delta}$, i.e. $X \leq \frac{c_3}{\delta}$. We again consider the particular case when $X = \frac{c_3}{\delta} = 321.8125$. We see that the condition for global stability is also satisfied as

$(1 + q_2)^2 G^{*2} = 0.0030 < 4[(1 + q_2)X + p_1 + q_1]p_2 = 1.3875$, for $X \leq 321.8125$

As is evident from equation (3.4) for finding the equilibrium level for glucose, we see that as q_2 increases, the glucose level decreases which clearly indicates that physical activity plays an important role in increasing the sensibility of muscles and liver to the action of insulin and thus helps in lowering the glucose level.

The figures illustrated below show that an increase in q_2 i.e., the rate constant expressing the effect of physical exercise in increasing the muscular and liver sensibility to the action of insulin, results in lower glucose level which indicates that physical exercise does help in maintaining lower glucose level. At time t=10, when $q_2 = 0.0015$, glucose concentration lies between 3 and 3.5 units, when $q_2 = 0.15$, glucose concentration is approximately 3 units, when $q_2 = 1.51$, glucose concentration lies between 1.5 and 2 units and when $q_2 = 2.55$, glucose concentration lies between 1.2 and 1.4 units.

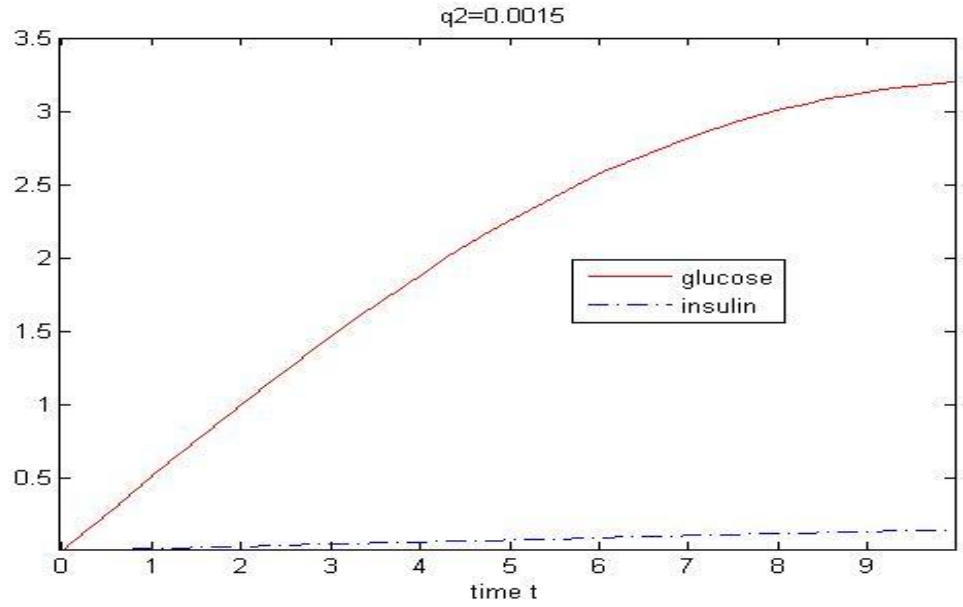

Figure 3.1 - Glucose concentration vs. insulin concentration when $q_2 = 0.0015$

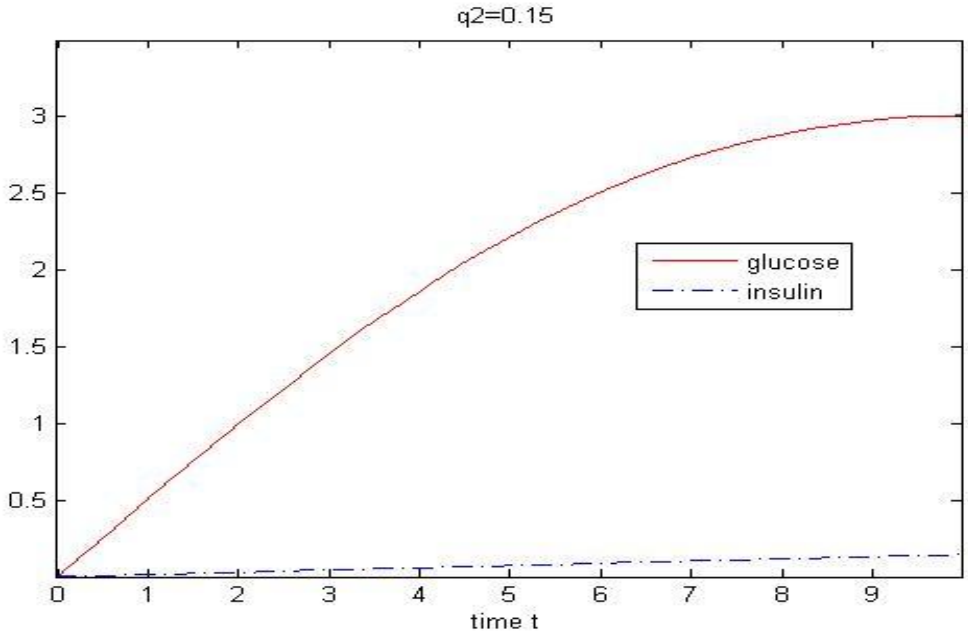

Figure 3.2 - Glucose concentration vs. insulin concentration when $q_2 = 0.15$

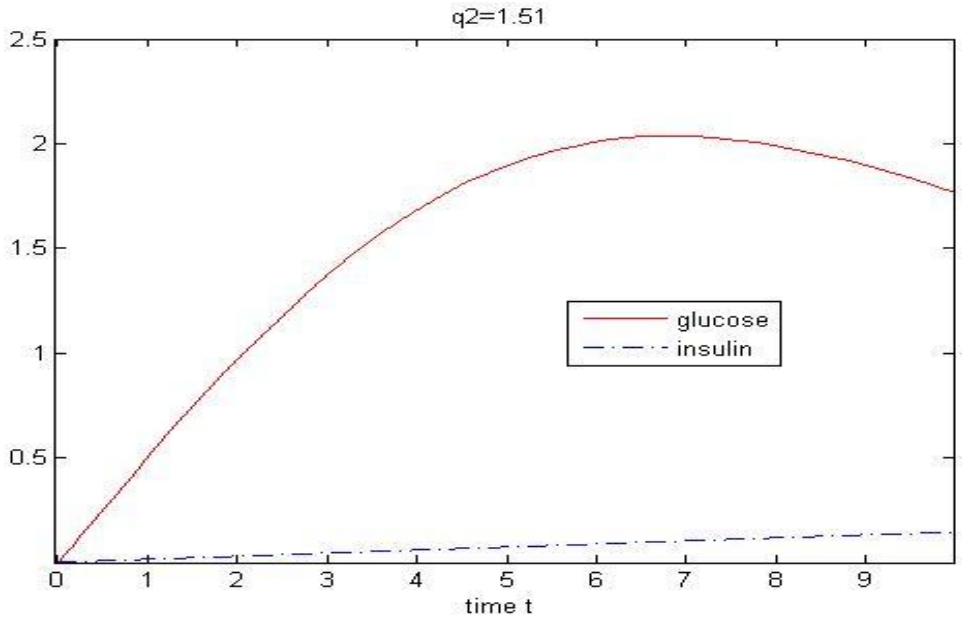

Figure 3.3 - Glucose concentration vs. insulin concentration when $q_2 = 1.51$

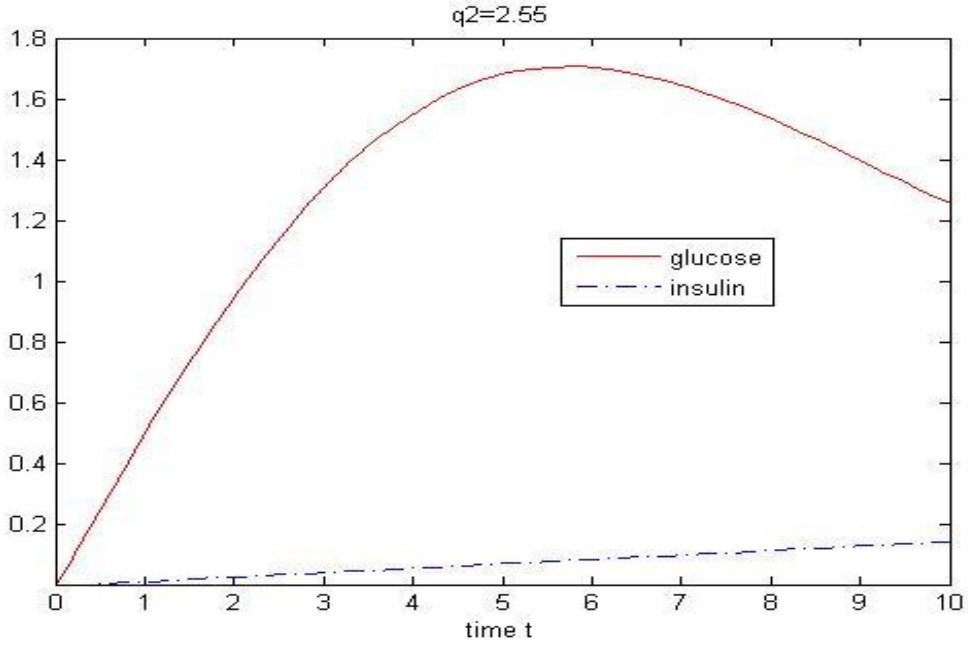

Figure 3.4 - Glucose concentration vs. insulin concentration when $q_2 = 2.55$

3.5 Conclusion

The complex equilibrium between insulin and blood glucose depends on the extremely delicate balance of anabolism and catabolism that occur throughout the body in response to changes in the level of calorie intake, food composition, and the level of physical activity. In the present work, we have considered the effect of physical exercise on this delicate equilibrium between insulin and glucose. It is seen that physical exercise does help in lowering the level of blood glucose. The effect of exercise in increasing the sensibility of muscles and liver to the action of insulin is simulated numerically and is seen than as the rate constant expressing the effect of physical exercise in increasing the muscular and liver sensibility to the action of insulin increases, the glucose level drops down accordingly. We have found that the positive equilibrium of the system is locally as well as globally asymptotically stable for the region of attraction Ω, under certain conditions on the parameters. From the above results, we conclude that the model is physiologically consistent and may represent a useful tool for further research on diabetes.

CHAPTER 4

POPULATION MODEL OF DIABETES MELLITUS: THE LINEAR AND NON-LINEAR CASE

4.1 Introduction

Diabetes Mellitus has become a global epidemic, rising at an alarming rate throughout the world, due to increases in life expectancy, obesity and sedentary lifestyles. In 2013, the International Diabetes Federation estimated that approximately 382 million people around the world has diabetes. The figure is expected to rise to 592 million by the year 2035 accounting to 10 % of the world's population. 80% of diabetic patients live in low- and middle-income countries. One person dies from diabetes every seven seconds, which amounts to 1.5 million annual deaths. In India alone, approximately 65.1 million diabetes patients have been identified according to The Indian Council of Medical Research (ICMR). Only China, with 98.4 million cases has more diabetes patients globally. (The Hindu, Coimbatore, Jan 27, 2014). By 2030, India is predicted to have the largest number of diabetes patients in the world.

People with diabetes, especially those without proper treatments usually develop complications later on such as heart diseases, eye complications, nerve damage, kidney diseases, skin complications and dental diseases. (www.diabetes.org., American Diabetes Association).

Boutayeb *et al.* (2006) have studied the population of diabetes and have proposed a mathematical model to represent the diabetic population. Their model is

$$\dot{D}(t) = I - (\lambda + \mu)D(t) + \gamma C(t)$$

$$\dot{C}(t) = \lambda D(t) - (\gamma + \mu + \delta + \nu)C(t)$$

Where D(t) represents the population of diabetics without complications

C(t) represents the population of diabetics with complications

I is the incidence of diabetes

λ is the probability of developing complications

μ is the natural mortality rate

γ is the rate at which complications are cured

δ is the mortality rate due to complications

ν is the rate at which people with complications become severely disabled

Boutayeb also worked on more mathematical models of diabetic population (Boutayeb and Kerfati, 1994; Boutayeb and Derouich, 2002; Boutayeb and Twizell, 2004; Boutayeb and Chetouani, 2003; Boutayeb and Boutayeb, 2005; Boutayeb 2006; Boutayeb *et al*. 2006).

In this chapter, we take into account that type 2 diabetes is caused by hereditary factors, inactive lifestyles and improper diet (National Diebetes Clearing House). We introduce a parameter α which incorporates these factors to the incidence of diabetes.

4.2 The Mathematical Model

Let the total diabetic population at time t be denoted by N(t), which is then again sub-divided into two categories ; diabetics without complications D(t) and diabetics with complications C(t). Hence, N(t)=D(t)+C(t). Let λ denote the probability that a diabetic patient will develop complications. The parameters to be considered are α, the rate at which diabetics occur, μ, the rate of natural mortality, γ, the rate at which complications are cured and δ, the mortality rate caused by complications.

The rates of change of D(T) and C(T) are given by the following differential equations:

$$\frac{dD(t)}{dt} = \dot{D}(t) = \alpha D(t) - (\lambda + \mu)D(t) + \gamma C(t)$$

$$\frac{dC(t)}{dt} = \dot{C}(t) = \lambda D(t) - \theta C(t) \quad \text{..... (4.1)}$$

Where $\theta = \gamma + \mu + \delta$

Now, since N(t)=D(t)+C(t), we get the IVP,

$$\dot{C}(t) = -(\lambda + \theta)C(t) + \lambda N(t), t > 0, C(0) = C_0$$

$$\dot{N}(t) = (\alpha - \mu)N(t) - (\alpha + \delta)C(t), t > 0, N(0) = N_0 \text{ .....(4.2)}$$

where C_0 and N_0 are the initial values of C(t) and N(t) respectively and

$$\theta = \gamma + \mu + \delta$$

4.3 The Linear System

In this case, we consider λ, the probability of a diabetic patient developing complications to be a constant i.e.

$$\lambda = \frac{C_0}{N_0} \qquad \text{.....} \qquad (4.3)$$

Let

$$\dot{C}(t) \equiv f(C,N) = -(\lambda+\theta)C(t) + \lambda N(t), t > 0, C(0) = C_0$$

$$\dot{N}(t) \equiv g(C,N) = (\alpha-\mu)N(t) - (\alpha+\delta)C(t), t > 0, N(0) = N_0 \quad \text{.....(4.4)}$$

The critical points of the IVP (3.2) arise when both f and g vanish simultaneously. In such a case, we get the non-trivial critical point as

$$(C^*, N^*) \equiv \left(\frac{\lambda\{\lambda(\mu+\delta) - (\alpha-\mu)\theta\}}{(\lambda+\theta)^2}, \frac{\lambda(\mu+\delta) - (\alpha-\mu)\theta}{\lambda+\theta} \right)$$

4.3.1 Stability Analysis of the non-trivial critical point (C^*, N^*)

Theorem 4.1: *The non-trivial critical point* (C^*, N^*) *is locally asymptotically stable if*

$\alpha < 2\mu + \lambda + \delta + \gamma$ *and* $\lambda(\mu+\delta) > (\alpha-\mu)\theta$

Proof: Consider the Jacobian J at (C^*, N^*) associated with f and g of the IVP (4.2), which is given by

$$J = \begin{pmatrix} -(\lambda+\theta) & \lambda \\ -(\alpha+\delta) & (\alpha-\mu) \end{pmatrix}$$

The characteristic equation of this matrix is given by

$$X^2 - trace(J)X + \det(J) = 0$$

The eigenvalues are negative or have negative real parts if

$trace(J) < 0$ and $\det(J) > 0$

And by Routh-Hurwitz stability criterion, the system the system will be locally asymptotically stable if the above conditions are satisfied.

Hence our system of differential equations (4.2) will be locally asymptotically stable if

$-\lambda - \theta - \alpha + \mu < 0$ and $-(\lambda + \theta)(\alpha - \mu) + \lambda(\alpha + \delta) > 0$

i.e. if $\alpha < 2\mu + \lambda + \delta + \gamma$ and $\lambda(\mu + \delta) > (\alpha - \mu)\theta$

4.4 The Non-linear System

We now assume that λ, the probability of a diabetic patient developing complications depends on C(t) and N(t) and it takes the form

$$\lambda = \lambda(t) = \beta \frac{C(t)}{N(t)}, \quad \text{.....} \quad (4.5)$$

Where β is a real positive constant.

The IVP (4.2) now becomes a non-linear system and may be written as

$$\dot{C}(t) \equiv f(C, N) = (\beta - \theta)C(t) - \beta \frac{C(t)^2}{N(t)}, t > 0, C(0) = C_0$$

$$\dot{N}(t) \equiv g(C, N) = (\alpha - \mu)N(t) - (\alpha + \delta)C(t), t > 0, N(0) = N_0 \quad \text{.....} \quad (4.6)$$

For simplicity sake, we write $C(t) = C$ and $N(t) = N$. Hence, we may write

$$\dot{C}(t) \equiv f(C, N) = (\beta - \theta)C - \beta \frac{C^2}{N}, t > 0, C(0) = C_0$$

$$\dot{N}(t) \equiv g(C, N) = (\alpha - \mu)N - (\alpha + \delta)C, t > 0, N(0) = N_0 \quad \text{.....} \quad (4.7)$$

Taking $\dot{C}(t) \equiv f(C, N) = 0$ and $\dot{N}(t) \equiv g(C, N) = 0$, we get a non-trivial critical point

$$(C^*, N^*) \equiv \left(\frac{\beta(\alpha-\mu)}{\beta(\alpha-\mu)-(\beta-\theta)(\alpha+\delta)}, \frac{\beta(\alpha+\delta)}{\beta(\alpha-\mu)-(\beta-\theta)(\alpha+\delta)}\right)$$

Note that $\dot{C}(t) \equiv f(C,N) = 0 \Rightarrow (\beta-\theta)C^* - \beta\frac{C^{*2}}{N^*} = 0$

$$\Rightarrow \frac{C^*}{N^*} = \frac{(\beta-\theta)}{\beta}$$

Now $C^* > 0, N^* > 0, \beta > 0$, therefore $\beta - \theta > 0$.

4.4.1 Stability analysis of non-trivial critical point (C^*, N^*)

Theorem 4.2: *The set*

$\sigma = \{(C,N): 0 \leq C + N \leq ce^{-\rho t}, where\ \epsilon = min\ (\alpha - \beta + 2\delta + \mu + \gamma, \mu - \alpha)\}$ *is a region of attraction for all the solutions initiating in the positive quadrant.*

Proof: We have,

$$\frac{dC}{dt} + \frac{dN}{dt} = (\beta-\theta)C - \beta\frac{C^2}{N} + (\alpha-\mu)N - (\alpha+\delta)C$$

$$\leq (\beta - \theta - \alpha - \delta)C + (\alpha-\mu)N, \text{ since } \beta\frac{C^2}{N} \geq 0$$

$$= -(\theta + \alpha + \delta - \beta)C - (\mu-\alpha)N$$

$$= -\{(\theta + \alpha + \delta - \beta)C + (\mu-\alpha)N\}$$

$$\leq -min\{(\theta + \alpha + \delta - \beta), (\mu-\alpha)\}(C+N)$$

$$= -\rho(C+N), \text{ where } \rho = min\{(\theta + \alpha + \delta - \beta), (\mu-\alpha)\}$$

Thus we have

$$\frac{dC}{dt} + \frac{dN}{dt} \leq -\rho(C+N)$$

$$\Rightarrow \frac{d(C+N)}{dt} \leq -\rho(C+N)$$

$$\Rightarrow \frac{d(C+N)}{(C+N)} \leq -\rho dt$$

$\Rightarrow C + N \leq ce^{-\rho t}$, where *c* is a constant of integration.

Hence, for all solutions initiating in the first (positive) quadrant, the set

$\Delta = \{(C,N): 0 \leq C + N \leq ce^{-\rho t}, where\ \rho = \min(\alpha - \beta + 2\delta + \mu + \gamma, \mu - \alpha)\}$ constitutes the region of attraction.

Theorem 4.3: *The interior-equilibrium point* (C^*, N^*) *is globally asymptotically stable if*

$$\left[\frac{\beta C^2}{\bar{N}N^*} - (\alpha + \delta)\right]^2 < 4(\alpha - \mu)\left[(\beta - \theta) - \frac{\beta(\bar{C}+C^*)}{N^*}\right], \text{ where } \bar{C}\epsilon\,\Delta, \bar{N}\epsilon\,\Delta$$

Proof: Consider the Lyapunov function

$$V = \frac{1}{2}c_1(C - C^*)^2 + \frac{1}{2}c_2(N - N^*)^2$$, where c_1 and c_2 are arbitrary constants

Or $\dot{V} = c_1(C - C^*)\dot{C} + c_2(N - N^*)\dot{N}$

$$= c_1(C - C^*)\left[(\beta - \theta)C - \beta\frac{C^2}{N}\right] + c_2(N - N^*)[(\alpha - \mu)N - (\alpha + \delta)C]$$

$$= c_1(C - C^*)\left[(\beta - \theta)C - \beta\frac{C^2}{N} - (\beta - \theta)C^* - \beta\frac{C^{*2}}{N^*} - \beta\frac{C^2}{N^*} + \beta\frac{C^2}{N^*}\right]$$

$$+ c_2(N - N^*)[(\alpha - \mu)N - (\alpha + \delta)C - (\alpha - \mu)N^* - (\alpha + \delta)C^*]$$

$$= c_1\left[(\beta - \theta) - \frac{\beta(C+C^*)}{N^*}\right](C - C^*)^2 + \left[c_1\frac{\beta C^2}{NN^*} - c_2(\alpha + \delta)\right](C - C^*)(N - N^*)$$

$$+c_2(\alpha - \mu)(N - N^*)^2$$

$$= -\frac{1}{2}X(C-C^*)^2 + Y(C-C^*)(N-N^*) - \frac{1}{2}Z(N-N^*)^2$$

Where $X = -2c_1\left[(\beta-\theta) - \frac{\beta(C+C^*)}{N^*}\right], Y = \left[c_1\frac{\beta C^2}{NN^*} - c_2(\alpha+\delta)\right], Z = -2c_2(\alpha-\mu)$

The condition for $\dot{V}$ to be negative definite is that $Y^2 < XZ$

i.e. if $\left[\frac{c_1\beta C^2}{NN^*} - c_2(\alpha+\delta)\right]^2 < 4c_1c_2(\alpha-\mu)\left[(\beta-\theta) - \frac{\beta(C+C^*)}{N^*}\right]$, where $C\epsilon\,\Delta, N\epsilon\,\Delta$

Since C and N are bounded in Δ, i.e.

$$0 < C < ce^{-\rho t}, \qquad 0 < N < ce^{-\rho t}, where\ \rho = \min(\alpha-\beta+2\delta+\mu+\gamma, \mu-\alpha)$$

Let $C = \frac{1}{2}(ce^{-\rho t}) = \bar{C}$ and $N = \frac{1}{2}(ce^{-\rho t}) = \bar{N}$

Hence the system (4.5) will be globally asymptotically stable if

$$Y^2 < XZ$$

i.e. if $\left[\frac{\beta C^2}{\bar{N}N^*} - (\alpha+\delta)\right]^2 < 4(\alpha-\mu)\left[(\beta-\theta) - \frac{\beta(\bar{C}+C^*)}{N^*}\right]$

4.5 Numerical simulation

We consider arbitrary values for the parameters as follows:

$$\alpha = 0.001, \mu = 0.000001, \lambda = 0.03, \delta = 0.0007, \gamma = 0.001,$$

$$\theta = \mu + \delta + \gamma = 0.0017, \beta = 0.0032,$$

The condition for local stability is satisfied as

$$\alpha = 0.001 < 2\mu + \lambda + \delta + \gamma = 0.0317$$

And $$\lambda(\mu + \delta) = 2.1030e - 005 > \theta(\alpha - \mu) = 1.6993e - 006$$

For validating the global stability condition, we consider the case as $t \to 0$, that is for $C + N \leq c$, i.e. $C \leq c$ and $N \leq c$. We again consider the particular case when $c = 5000$. Let $N = 4800$ and $C = 0.00005$. We see that the condition for global stability is also satisfied as

$$\left[\frac{c_1 \beta C^2}{4800 N^*} - c_2(\alpha + \delta)\right]^2 = 4.8552e - 007$$

$$< 4c_1 c_2(\alpha - \mu)\left[(\beta - \theta) - \frac{\beta(0.00005 + C^*)}{N^*}\right] 7.6222e - 007$$

Where $c_1 = 2$ and $c_2 = -0.25$.

Consider equation (4.1)

$$\frac{dD(t)}{dt} = \dot{D}(t) = \alpha D(t) - (\lambda + \mu)D(t) + \gamma C(t)$$

$$\frac{dC(t)}{dt} = \dot{C}(t) = \lambda D(t) - \theta C(t)$$

We generate graph for (4.1) taking initial values D(0)=2, C(0)=2 and taking the same values of the parameters but varying α.

When $\alpha = 0.001$, we see that D(t), the number of diabetics without complications drops down to 1.2 (approximately) and C(t), the number of diabetics with complications rises to 2.8 (approximately). We get the same result when $\alpha = 0.00001$. But when we take $\alpha = 1.0$,

we see that both D(t) and C(t) grow exponentially and D(t) grows at a faster rate than C(t). When we increase α further, to $\alpha = 10$, we see that both D(t) and C(t) grow at a faster rate. This result indicates that when the population of diabetics without complications grows at a constant positive rate, the population of diabetics with complications also grows significantly. This finding is consistent with the real world situation which shows that our model is valid and is in conformity with real world situation.

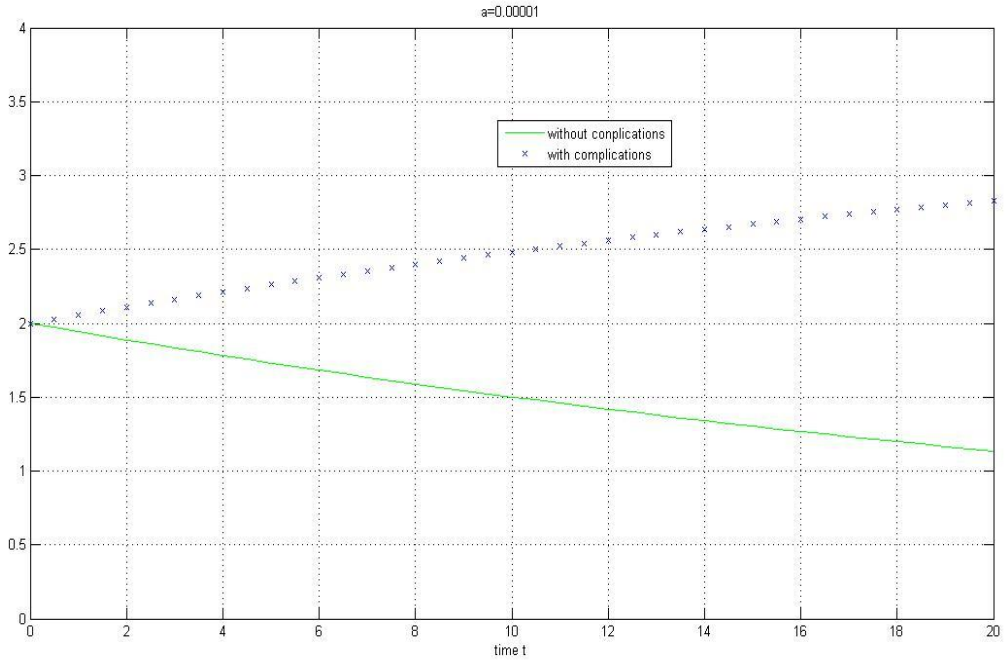

Figure 4.1 – Diabetes with and without complications when $\alpha = 0.00001$

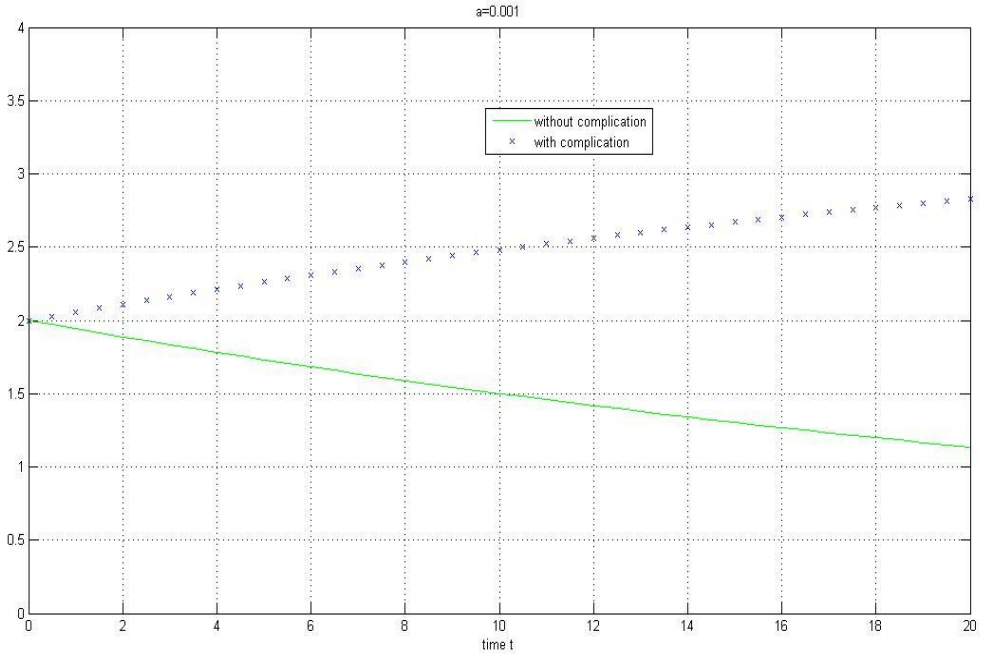

Figure 4.2 – Diabetes with and without complications when $\alpha = 0.001$

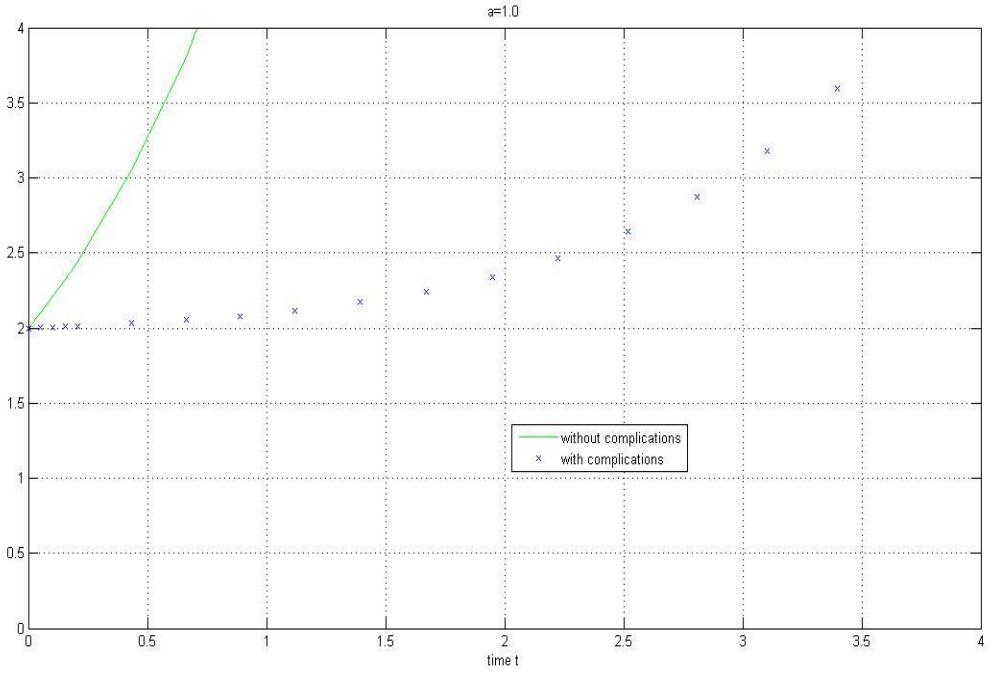

Figure 4.3 – Diabetes with and without complications when $\alpha = 1.0$

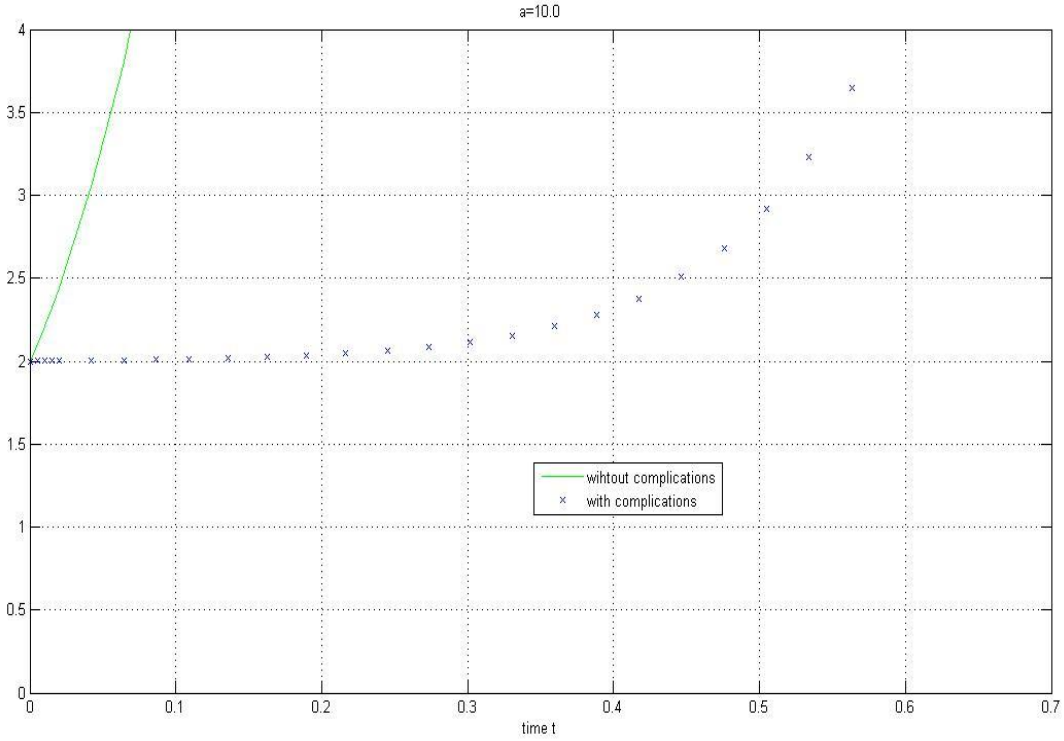

Figure 4.4 – Diabetes with and without complications when $\alpha = 10.0$

4.6 Conclusion

In this chapter, a mathematical model on the population of diabetics is developed where we categorize the population it into two: diabetics without complications and diabetics with complications. Local and global stability conditions are established using Routh-Hurwitz Criterion and Lyapunov function. These conditions are verified through numerical simulations. Graphs are generated for the mathematical model which indicates that when the rate at which diabetes occurs increases, the number of diabetics with complications increases significantly and if this increase is at a positive integral rate, the population of diabetics with complications

increases exponentially. 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.

CHAPTER 5

MODELING THE EFFECT OF AWARENESS PROGRAMS BY MEDIA ON THE CONTROL OF DIABETES

5.1 Introduction

Diabetes Mellitus is a chronic disease that can lead to complications over time. These complications can include coronary heart disease that can lead to a heart attack, cerebrovascular disease which can lead to stroke, retinopathy which can lead to blindness, neuropathy which can lead to, among other things, ulceration of the foot requiring amputation. Many of these complications produce no symptoms in the early stages, and can be prevented or minimized with a combination of medical care and blood sugar monitoring (D.K. McCulloch *et al*., www.uptodate.com). According to Diabetes Australia, diabetes is the world's fastest growing chronic disease and caused 5.1 million deaths worldwide in 2013 (www.diabetesaustralia.com.au). In India alone, diabetes kills approximately 1 million people every year (www.idf.org). The World Health Organization (WHO) predicted that diabetes will be the leading cause of death in 2030.

Education through media about diabetes and its control can make a huge difference in the current status as can be seen from existing works (Clarke *et al*., 2004; Eastman *et al*., 1997; Mohan *et al*., 2013). 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 as social

networks, blogs and patient self help sites allow them to contribute to content, share experiences and make contact with other people in a similar situation. 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 (Cooper and Kar, 2014). One way for people to gather practical information about managing their condition is from peers using social networks. There is an emergence of the use of social media in many areas of life and in the health arena platforms, such as "Patientslikeme", have created opportunities for conversations to be had between people who have similar health conditions. Social networks can also provide the environment and the tools for knowledge sharing and peer support. Farmer *et al.* (2009) reviewed activity surrounding common medical conditions, including diabetes, on Facebook and found a large number of user groups that created interactions that would not have been possible without the Facebook platform. There were 39,606 members of groups that related to type 1 diabetes and, since the review was undertaken five years ago and social networks have continued to grow in popularity, it would be safe to conclude that these membership numbers would now be even higher. In addition to the internet, the government is also taking steps to prevent and control diabetes by implementing awareness programs across different regions.

Even though many studies on mathematical modeling of diabetes (Ackerman *et al*., 1965; Della *et al*., 1970; Chandler and Varandhani, 1975; Cobelli *et al*., 1982; Cobelli and Mari, 1983; Quon and Campfield, 1991; Lehman and Deustch, 1995; Diabetes Control and Complications Trials Research Group, 1995, 1996, 1997; Jiwa, 1997; Norman and Litwack, 1997; Ratner, 1998; Cobelli *et al*., 1998; UKPDS, 1998; Brown *et al*., 2000; Nucci and

Cobelli, 2000; Diabetes Prevention Program Research Group, 2002; Stevens *et al.*, 2002; Herman, 2003; Bennett and Gourley, 2004; Mukhopadhyay *et al*., 2004; Palumbo *et al.*, 2004; Overgaard *et al*., 2006; Wang *et al*., 2009; Rovner, 2009; Chen *et al*., 2010; Adamu *et al.*, 2012; Huang *et al.*, 2012; McKnigth *et al.*, 2013; Samanta *et al*., 2013; Boutayeb *et al.*, 2014) can be found in literature, not many deals with the implications of awareness programs by media on the control of this disease.

5.2 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 and Y denote the aware population. Let C denote the population of diabetes who have developed complications. And let N denote the total diabetic population ie. 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

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

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

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

$$\frac{dM}{dt} = k\alpha C - \mu M \qquad \text{.....(5.1)}$$

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

k is the proportionality constant which governs the implementation of awareness programs

μ is the depletion rate of awareness programs due to ineffectiveness, economic constraints etc.

Let the total diabetic population be N i.e. N=X+Y+C.

Then, we get

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

The model becomes

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

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

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

$$\frac{dM}{dt} = k\alpha C - \mu M \qquad \text{……(5.2)}$$

The above model has two equilibrium points namely

i) The trivial critical point $\bar{E}(0,0,\frac{A}{\delta},0)$ and

ii) The non-trivial critical point $E^* = (C^*, Y^*, N^*, M^*)$

This equilibrium exists only if $\frac{\beta A}{\delta} > \gamma + \alpha + \delta$

The existence of equilibrium point $\bar{E}(0,0,\frac{A}{\delta},0)$ is trivial.

We obtain the critical values of C^*, Y^*, N^*, M^* as

$$Y^* = \frac{A - \alpha\, C^* - \delta\, C^*}{(1-\rho)\delta} - \frac{\alpha + \delta}{(1-\rho)\beta}$$

$$N^* = \frac{A - \alpha C^*}{\delta}$$

$$M^* = \frac{k\alpha C^*}{\mu}$$

Where C^* satisfies the equation

$$A_1 C^{*^2} + A_2 C^* + A_3 = 0$$

Where $A_1 = \frac{k\lambda}{\mu}\left\{\frac{\alpha+\delta}{(1-\rho)\delta} - \frac{\alpha}{\delta} - 1\right\} + \frac{\beta\rho(\alpha+\delta)}{(1-\rho)\delta}$

$$A_2 = \frac{k\lambda}{\mu}\left\{\frac{A}{\delta} - \frac{A}{(1-\rho)\delta} + \frac{\gamma+\alpha+\delta}{\beta(1-\rho)}\right\} + p\gamma - \beta\rho\left\{\frac{A}{(1-\rho)\delta} - \frac{\gamma+\alpha+\delta}{\beta(1-\rho)}\right\} + \frac{\delta(\alpha+\delta)}{(1-\rho)\delta}$$

$$A_3 = \delta\left\{\frac{\gamma+\alpha+\delta}{\beta(1-\rho)} - \frac{A}{(1-\rho)\delta}\right\}$$

We get $C^* = \frac{-A_2 \pm \sqrt{A_2^2 - 4A_1A_3}}{2A_1}$

For $C^* > 0$, we take $C^* = \frac{-A_2 + \sqrt{A_2^2 - 4A_1A_3}}{2A_1}$

5.3 Stability Analysis

Consider the Jacobian matrix of (5.1) given by

$$J = \begin{pmatrix} \beta(N-(1-\rho)Y-2C)-(\gamma+\alpha+\delta) & -\beta(1-\rho)C & \beta C & 0 \\ -\lambda M + p\gamma - \beta\rho Y & -\lambda M - \beta\rho C - \delta & \lambda M & \lambda(N-Y-C) \\ -\alpha & 0 & -\delta & 0 \\ k\alpha & 0 & 0 & -\mu \end{pmatrix}$$

At $\bar{E}(0,0,\frac{A}{\delta},0)$

$$J_{\bar{E}} = \begin{pmatrix} \frac{\beta A}{\delta} - (\gamma + \alpha + \delta) & 0 & 0 & 0 \\ p\gamma & -\delta & 0 & \frac{\lambda A}{\delta} \\ -\alpha & 0 & -\delta & 0 \\ k\alpha & 0 & 0 & -\mu \end{pmatrix}$$

We now use the transformation $C = T + \bar{C},\ Y = U + \bar{Y}, N = V + \bar{N}, M = Z + \bar{M}$ and then linearize the system

$$\begin{pmatrix} \dot{T} \\ \dot{U} \\ \dot{V} \\ \dot{Z} \end{pmatrix} = J_{\bar{E}} \begin{pmatrix} T \\ U \\ V \\ Z \end{pmatrix} = \begin{pmatrix} \frac{\beta A}{\delta} - (\gamma + \alpha + \delta) & 0 & 0 & 0 \\ p\gamma & -\delta & 0 & \frac{\lambda A}{\delta} \\ -\alpha & 0 & -\delta & 0 \\ k\alpha & 0 & 0 & -\mu \end{pmatrix} \begin{pmatrix} T \\ U \\ V \\ Z \end{pmatrix}$$

We get the linearized system

$$\dot{T} = \left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right) T$$

$$\dot{U} = p\gamma T - \delta U + \frac{\lambda A}{\delta} Z$$

$$\dot{V} = -\alpha T - \delta V$$

$$\dot{Z} = k\alpha T - \mu Z$$

Theorem 5.1: *The trivial critical point* $\bar{E}(0,0,\frac{A}{\delta},0)$ *is locally asymptotically stable if*

$$(a_2 p\gamma)^2 < -\frac{2}{3}a_1 a_2 \delta\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$$

$$(-a_3\alpha)^2 < -\frac{4}{3}a_1 a_3 \delta\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$$

$$(a_4 k\alpha)^2 < -\frac{2}{3}a_1 a_4 \mu\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$$

$$\left(a_4\frac{\lambda A}{\delta}\right)^2 < a_2 a_4 \delta\mu$$

where a_1, a_2, a_3 and a_4 are arbitrary constants

Proof: Consider the Lyapunov function

$$V_1 = \frac{1}{2}a_1 T^2 + \frac{1}{2}a_2 U^2 + \frac{1}{2}a_3 V^2 + \frac{1}{2}a_4 Z^2$$

where a_1, a_2, a_3 and a_4 are arbitrary constants.

Therefore, $\dot{V}_1 = a_1 T\dot{T} + a_2 U\dot{U} + a_3 V\dot{V} + a_4 Z\dot{Z}$

$$= a_1\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)T^2 + a_2\left(p\gamma T - \delta U + \frac{\lambda A}{\delta}Z\right)U + a_3(-\alpha T - \delta V) + a_4(k\alpha T - \mu Z)$$

$$= -\frac{1}{2}A_{11}T^2 + A_{12}TU - \frac{1}{2}A_{22}U^2 - \frac{1}{2}A_{11}T^2 + A_{13}TV - \frac{1}{2}A_{33}V^2 - \frac{1}{2}A_{11}T^2 + A_{14}TZ$$

$$-\frac{1}{2}A_{44}Z^2 - \frac{1}{2}A_{22}U^2 + A_{24}UZ - \frac{1}{2}A_{44}Z^2$$

Where $A_{11} = -\frac{2}{3}a_1\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$, $A_{12} = a_2 p\gamma$, $A_{13} = -a_3\alpha$, $A_{14} = a_4 k\alpha$

$A_{22} = a_2\delta$, $A_{33} = 2a_3\delta$, $A_{44} = a_4\mu$, $A_{24} = a_4\frac{\lambda A}{\delta}$

The conditions for $\dot{V}_1$ to be negative definite is that

$$A_{12}{}^2 < A_{11}A_{22}$$

$$A_{13}{}^2 < A_{11}A_{33}$$

$$A_{14}{}^2 < A_{11}A_{44}$$

$$A_{24}{}^2 < A_{22}A_{44}$$

i.e.

$$(a_2 p\gamma)^2 < -\frac{2}{3}a_1 a_2\delta\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$$

$$(-a_3\alpha)^2 < -\frac{4}{3}a_1 a_3\delta\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$$

$$(a_4 k\alpha)^2 < -\frac{2}{3}a_1 a_4\mu\left(\frac{\beta A}{\delta} - \gamma - \alpha - \delta\right)$$

$$\left(a_4\frac{\lambda A}{\delta}\right)^2 < a_2 a_4\delta\mu$$

Which gives the conditions for the trivial critical point $\bar{E}(0,0,\frac{A}{\delta},0)$ to be locally asymptotically stable.

At $E^* = (C^*, Y^*, N^*, M^*)$

J_{E^*}

$$= \begin{pmatrix} \beta(N^* - (1-\rho)Y^* - 2C^*) & -(\gamma + \alpha + \delta) & -\beta(1-\rho)C^* & 0 \\ -\lambda M^* + p\gamma - \beta\rho Y^* & -\lambda M^* - \beta\rho C^* - \delta & \lambda M^* & \lambda(N^* - Y^* - C^*) \\ -\alpha & 0 & -\delta & 0 \\ k\alpha & 0 & 0 & -\mu \end{pmatrix}$$

We now use the transformation $C = P + C^*,\ Y = Q + Y^*, N = R + N^*, M = S + M^*$ and then linearize the system

$$\begin{pmatrix} \dot{P} \\ \dot{Q} \\ \dot{R} \\ \dot{S} \end{pmatrix} = J_{E^*} \begin{pmatrix} P \\ Q \\ R \\ S \end{pmatrix}$$

$$= \begin{pmatrix} \beta(N^* - (1-\rho)Y^* - 2C^*) & -(\gamma + \alpha + \delta) & -\beta(1-\rho)C^* & 0 \\ -\lambda M^* + p\gamma - \beta\rho Y^* & -\lambda M^* - \beta\rho C^* - \delta & \lambda M^* & \lambda(N^* - Y^* - C^*) \\ -\alpha & 0 & -\delta & 0 \\ k\alpha & 0 & 0 & -\mu \end{pmatrix} \begin{pmatrix} P \\ Q \\ R \\ S \end{pmatrix}$$

We get the linearized system

$$\dot{P} = \{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}P - \beta(1-\rho)C^*Q + \beta C^*R$$

$$\dot{Q} = (-\lambda M^* + p\gamma - \beta\rho Y^*)P - \lambda M^* - \beta\rho C^* - \delta\ Q + \lambda M^* R + \lambda(N^* - Y^* - C^*)S$$

$$\dot{R} = -\propto P - \delta R$$

$$\dot{S} = k\alpha P - \mu S$$

Theorem 5.2: The *non-trivial critical point* $E^* = (C^*, Y^*, N^*, M^*)$ *is locally asymptotically stable if*

$$\{-b_1\beta(1-\rho)C^* + b_2(-\lambda M^* + p\gamma - \beta\rho Y^*)\}^2$$

$$< -\frac{4}{9}b_1b_2\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}(\lambda M^* + \beta\rho C^* + \delta)$$

$$(b_1\beta C^* - b_3\alpha)^2 < -\tfrac{2}{3}b_1b_3\delta\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}$$

$$(b_4k\alpha)^2 < -\tfrac{2}{3}b_1b_4\mu\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}$$

$$(b_2\lambda M^*)^2 < \tfrac{2}{3}b_2b_3\delta(\lambda M^* + \beta\rho C^* + \delta)$$

$$\{b_2\lambda(N^* - Y^* - C^*)\}^2 < \frac{2}{3}b_2b_4\mu(\lambda M^* + \beta\rho C^* + \delta)$$

where b_1, b_2, b_3 and b_4 are arbitrary constants.

***Proof*:** Consider the positive definite function

$$V_2 = \tfrac{1}{2}b_1P^2 + \tfrac{1}{2}b_2Q^2 + \tfrac{1}{2}b_3R^2 + \tfrac{1}{2}b_4S^2$$

where b_1, b_2, b_3 and b_4 are arbitrary constants.

$$\dot{V}_2 = b_1P\dot{P} + b_2Q\dot{Q} + b_3R\dot{R} + b_4S\dot{S}$$

$$= b_1[\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}P^2 - \beta(1-\rho)C^*PQ + \beta C^*PR] +$$

$$b_2[(-\lambda M^* + p\gamma - \beta\rho Y^*)PQ - (\lambda M^* + \beta\rho C^* + \delta)Q^2 + \lambda M^*QR + \lambda(N^* - Y^* -$$

$$C^*)]QS + b_3(-\alpha PR - \delta R^2) + b_4(k\alpha PS - \mu S^2)$$

$$= -\frac{1}{2}B_{11}P^2 + B_{12}PQ - \frac{1}{2}B_{22}Q^2 - \frac{1}{2}B_{11}P^2 + B_{13}PR - \frac{1}{2}B_{33}R^2 - \frac{1}{2}B_{11}P^2 + B_{14}PS -$$

$$\frac{1}{2}B_{44}S^2 - \frac{1}{2}B_{22}Q^2 + B_{23}QR - \frac{1}{2}B_{33}R^2 - \frac{1}{2}B_{22}Q^2 + B_{24}QS - \frac{1}{2}B_{44}S^2$$

The condition for $\dot{V}_2$ to be negative definite is that

$$B_{12}{}^2 < B_{11}B_{22}$$

$$B_{13}{}^2 < B_{11}B_{33}$$

$$B_{14}{}^2 < B_{11}B_{44}$$

$$B_{23}{}^2 < B_{22}B_{33}$$

$$B_{24}{}^2 < B_{22}B_{44}$$

i.e.

$$\{-b_1\beta(1-\rho)C^* + b_2(-\lambda M^* + p\gamma - \beta\rho Y^*)\}^2$$

$$< -\frac{4}{9}b_1b_2\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}(\lambda M^* + \beta\rho C^* + \delta)$$

$$(b_1\beta C^* - b_3\alpha)^2 < -\frac{2}{3}b_1b_3\delta\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}$$

$$(b_4k\alpha)^2 < -\frac{2}{3}b_1b_4\mu\{\beta(N^* - (1-\rho)Y^* - 2C^*) - (\gamma + \alpha + \delta)\}$$

$$(b_2\lambda M^*)^2 < \frac{2}{3}b_2b_3\delta(\lambda M^* + \beta\rho C^* + \delta)$$

$$\{b_2\lambda(N^* - Y^* - C^*)\}^2 < \frac{2}{3}b_2b_4\mu(\lambda M^* + \beta\rho C^* + \delta)$$

which gives the conditions for the non-trivial equilibrium point $E^* = (C^*, Y^*, N^*, M^*)$ to be locally asymptotically stable.

Lemma 5.1: *The set* $\Phi = \left\{(C, Y, N, M): 0 \leq C, Y \leq N \leq \frac{A}{\delta}, 0 \leq M \leq \frac{k\alpha A}{\mu\delta}\right\}$ *is a region of attraction for all the solutions initiating in the positive octant.*

Proof: From equation (5.2), we have

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

For critical point, let $A - \delta N - \alpha C = 0 \Rightarrow \delta N + \alpha C = A \Rightarrow \delta N \leq A \Rightarrow N \leq \frac{A}{\delta}$

Since N=X+Y+C, we have $0 \leq C, Y \leq N \leq \frac{A}{\delta}$

Also from equation (5.2), we have

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

For critical point, let $k\alpha C - \mu M = 0 \Rightarrow M = \frac{k\alpha C}{\mu} \Rightarrow M \leq \frac{k\alpha A}{\mu\delta}$

Hence $0 \leq M \leq \frac{k\alpha A}{\mu\delta}$

Theorem 5.3: *The non-trivial critical point* $E^*(C^*, Y^*, N^*, M^*)$ *is globally asymptotically stable if*

$$\{-c_1\beta(1-\rho)C + c_2(-\lambda M^* + p\gamma - \beta\rho Y)\}^2$$

$$< -\frac{4}{9}c_1c_2[\beta\{N^* - (1-\rho)Y^* - (C + C^*)\} - (\gamma + \alpha + \delta)](\lambda M + \beta\rho C^* + \delta)$$

$$(c_1\beta C - c_3\alpha)^2 < -\frac{2}{3}c_1c_3\delta[\beta\{N^* - (1-\rho)Y^* - (C + C^*)\} - (\gamma + \alpha + \delta)]$$

$$(c_4k\alpha)^2 < -\tfrac{2}{3}c_1c_2\mu[\beta\{N^* - (1-\rho)Y^* - (C + C^*)\} - (\gamma + \alpha + \delta)]$$

$$(c_2\lambda M)^2 < \tfrac{2}{3}c_2c_3\delta(\lambda M + \beta\rho C^* + \delta)$$

$$\{c_2\lambda(N^* - Y^* - C^*)\}^2 < \frac{2}{3}c_2c_4\mu(\lambda M + \beta\rho C^* + \delta)$$

where c_1, c_2, c_3 and c_4 are arbitrary constants.

Proof: Consider the Lyapunov function

$$V_3 = \frac{1}{2}c_1(C - C^*)^2 + \frac{1}{2}c_2(Y - Y^*)^2 + \frac{1}{2}c_3(N - N^*)^2 + \frac{1}{2}c_4(M - M^*)^2$$

where c_1, c_2, c_3 and c_4 are arbitrary constants.

$$\dot{V}_3 = c_1(C - C^*)\dot{C} + c_2(Y - Y^*)\dot{Y} + c_3(N - N^*)\dot{N} + c_4(M - M^*)\dot{M}$$

$$= c_1(C - C^*)\{\beta(N - (1-\rho)Y - C)C - (\gamma + \alpha + \delta)C\}$$

$$+ c_2(Y - Y^*)\{\lambda(N - Y - C)M + p\gamma C - \delta Y - \rho\beta YC\}$$

$$+ c_3(N - N^*)\{A - \delta N - \alpha C\} + c_4(M - M^*)\{k\alpha C - \mu M\}$$

$$= c_1(C - C^*)\{\beta(N - (1-\rho)Y - C)C - (\gamma + \alpha + \delta)C - \beta(N^* - (1-\rho)Y^* - C^*)C^* + (\gamma + \alpha + \delta)C^* + \beta N^*C - \beta N^*C + \beta(1-\rho)Y^*C - \beta(1-\rho)Y^*C\} + c_2(Y - Y^*)\{\lambda(N - Y - C)M + p\gamma C - \delta Y - \rho\beta YC - \lambda(N^* - Y^* - C^*)M^* - p\gamma C^* + \delta Y^* + \rho\beta Y^*C^* + \lambda N^*M - \lambda N^*M + \lambda Y^*M - \lambda Y^*M + \lambda M^*C - \lambda M^*C + \beta\rho C^*Y - \beta\rho C^*Y\} + c_3(N - N^*)\{A - \delta N - \alpha C - A + \delta N^* + \alpha C^*\} + c_4(M - M^*)\{k\alpha C - \mu M - k\alpha C^* + \mu M^*\}$$

$$= c_1\{\beta N^* - \beta(1-\rho)Y^* - \beta(C + C^*) - (\gamma + \alpha + \delta)\}(C - C^*)^2 + \{-c_1\beta C(1-\rho) + c_2(-\lambda M^* + p\gamma - \beta\rho Y)\}(C - C^*)(Y - Y^*) - c_2(\lambda M + \delta + \beta\rho C^*)(Y - Y^*)^2 - c_3\delta(N - N^*)^2 - c_4\mu(M - M^*)^2 + c_4k\alpha(C - C^*)(M - M^*) + (c_1\beta - c_3\alpha)(C - C^*)(N - N^*) + c_2\lambda M(Y - Y^*)(N - N^*) + c_2\lambda(N^* - Y^* - C^*)(Y - Y^*)(M - M^*)$$

$$= -\frac{1}{2}C_{11}(C - C^*)^2 + C_{12}(C - C^*)(Y - Y^*) - \frac{1}{2}C_{22}(Y - Y^*)^2 - \frac{1}{2}C_{11}(C - C^*)^2 + C_{13}(C - C^*)(N - N^*) - \frac{1}{2}C_{33}(N - N^*)^2 - \frac{1}{2}C_{11}(C - C^*)^2 + C_{14}(C - C^*)(M - M^*) - \frac{1}{2}C_{44}(M - M^*)^2 - \frac{1}{2}C_{22}(Y - Y^*)^2 + C_{23}(Y - Y^*)(N - N^*) - \frac{1}{2}C_{33}(N - N^*)^2 - \frac{1}{2}C_{22}(Y - Y^*)^2 + C_{24}(Y - Y^*)(M - M^*) - \frac{1}{2}C_{44}(M - M^*)^2$$

Where $C_{11} = -\frac{2}{3}c_1[\beta\{N^* - (1-\rho)Y^* - (C + C^*)\} - (\gamma + \alpha + \delta)]$

$C_{22} = \frac{2}{3}c_2(\lambda M + \beta\rho C^* + \delta)$, $C_{33} = c_3\delta$, $C_{44} = c_4\mu$,

$C_{12} = -c_1\beta(1-\rho)C + c_2(-\lambda M^* + p\gamma - \beta\rho Y)$,

$C_{13} = c_1\beta C - c_3\alpha$, $C_{14} = c_4k\alpha$, $C_{23} = c_2\lambda M$, $C_{24} = c_2\lambda(N^* - Y^* - C^*)$

The sufficient conditions for $\dot{V}_3$ to be negative definite is that

$$C_{12}{}^2 < C_{11}C_{22}$$

$$C_{13}{}^2 < C_{11}C_{33}$$

$$C_{14}{}^2 < C_{11}C_{44}$$

$$C_{23}{}^2 < C_{22}C_{33}$$

$$C_{24}{}^2 < C_{22}C_{44}$$

i.e.

$$\{-c_1\beta(1-\rho)C + c_2(-\lambda M^* + p\gamma - \beta\rho Y)\}^2$$

$$< -\frac{4}{9}c_1c_2[\beta\{N^* - (1-\rho)Y^* - (C+C^*)\} - (\gamma+\alpha+\delta)](\lambda M + \beta\rho C^* + \delta)$$

$$(c_1\beta C - c_3\alpha)^2 < -\frac{2}{3}c_1c_3\delta[\beta\{N^* - (1-\rho)Y^* - (C+C^*)\} - (\gamma+\alpha+\delta)]$$

$$(c_4k\alpha)^2 < -\tfrac{2}{3}c_1c_2\mu[\beta\{N^* - (1-\rho)Y^* - (C+C^*)\} - (\gamma+\alpha+\delta)]$$

$$(c_2\lambda M)^2 < \tfrac{2}{3}c_2c_3\delta(\lambda M + \beta\rho C^* + \delta)$$

$$\{c_2\lambda(N^* - Y^* - C^*)\}^2 < \frac{2}{3}c_2c_4\mu(\lambda M + \beta\rho C^* + \delta)$$

which are the required conditions for the non-trivial equilibrium point $E^*(C^*, Y^*, N^*, M^*)$ to be globally asymptotically stable.

5.4 Numerical Simulation

We take arbitrary values for the parameters and let $A = 400, \beta = 0.00001, \rho = 0.35, \delta = 0.01, \lambda = 0.0004, \alpha = 0.005, \mu = 0.5, k = 0.1, p = 0.23, \gamma = 0.33$

The trivial critical point becomes

$$\bar{C} = 0, \bar{Y} = 0, \bar{N} =, \bar{M} = 0$$

To validate the local asymptotical stability conditions, we take $a_1 = -10, a_2 = 1, a_3 = 5,\ a_4 = 10000.$

We get

$$A_{11} = 0.3667, A_{22} = 0.001, A_{12} = 0.0076, A_{33} = 0.1000, A_{13} = -0.0250 A_{44} = 330,$$

$$A_{14} = 5, A_{24} = 1.6$$

The local asymptotic stability conditions are satisfied as

$$A_{12}^2 = 5.7608e-005 < A_{11}A_{22} = 3.6667e-004$$

$$A_{13}^2 = 6.2500e-004 < A_{11}A_{33} = 0.0367$$

$$A_{14}^2 = 25 < A_{11}A_{44} = 1210$$

$$A_{24}^2 = 2.560 < A_{22}A_{33} = 3.300$$

The non-trivial critical point becomes

$$C^* = 32.6095, Y^* = 8.3863e + 003, N^* = 3.9984e + 004, M^* = 0.0326$$

To validate the local asymptotical stability at $E^*(C^*, Y^*, N^*, M^*)$

We take $b_1 = 300, b_2 = 1.5, b_3 = 200, a_4 = 90000$

We get

$$B_{11} = 0.0652, B_{22} = 0.0101, B_{12} = 0.0062, B_{33} = 2, B_{13} = 0.0978, B_{44} = 45000,$$

$$B_{14} = 45, B_{23} = 1.9566e - 005, B_{24} = 18.9389$$

Then the conditions of local asymptotical stability is satisfied as

$$B_{12}^2 = 3.8613e - 005 < B_{11}B_{22} = 6.6048e - 004$$

$$B_{13}^2 = 0.0096 < B_{11}B_{33} = 0.1304$$

$$B_{14}^2 = 2025 < B_{11}B_{44} = 2.9349e + 003$$

$$B_{23}^2 = 3.8282e - 010 < B_{22}B_{33} = 0.0203$$

$$B_{24}^2 = 358.6812 < B_{22}B_{44} = 455.7230$$

For validating global asymptotic stability

We take $c_1 = 300, c_2 = 0.75, c_3 = 70, c_4 = 9000.$

Then

$$C_{11} = 0.1000, C_{22} = 0.0251, C_{12} = -0.0445, C_{33} = 0.7000, C_{13} = -0.2, C_{44} = 4500,$$

$$C_{14} = 4.5000, C_{23} = 0.03, C_{24} = 9.4694$$

The conditions of global asymptotic stability are satisfied as

$$C_{12}^2 = 0.0020 < C_{11}C_{22} = 0.0025$$

$$C_{13}^2 = 0.0400 < C_{11}C_{33} = 0.0700$$

$$C_{14}^2 = 20.25 \ < C_{11}C_{44} = 450$$

$$C_{23}^2 = 9e - 004 < C_{22}C_{33} = 0.0175$$

$$C_{24}^2 = 89.6703 < C_{22}C_{33} = 112.7568$$

Using the above data, we generate graphs to validate our model. Figure 5.1 shows that when the dissemination rate of awareness, λ = 0.0004, the number of diabetes with complications rises to 300000 and the aware population is negligible. When $\lambda = 0.04$ (Figure 5.2), the number of diabetes with complications still remains the same but the aware population has now risen to 150000. When λ takes an integral value, say $\lambda = 4.0$ (Figure 5.3), the number of diabetes with complications is almost zero and the aware population has risen to 20000000.

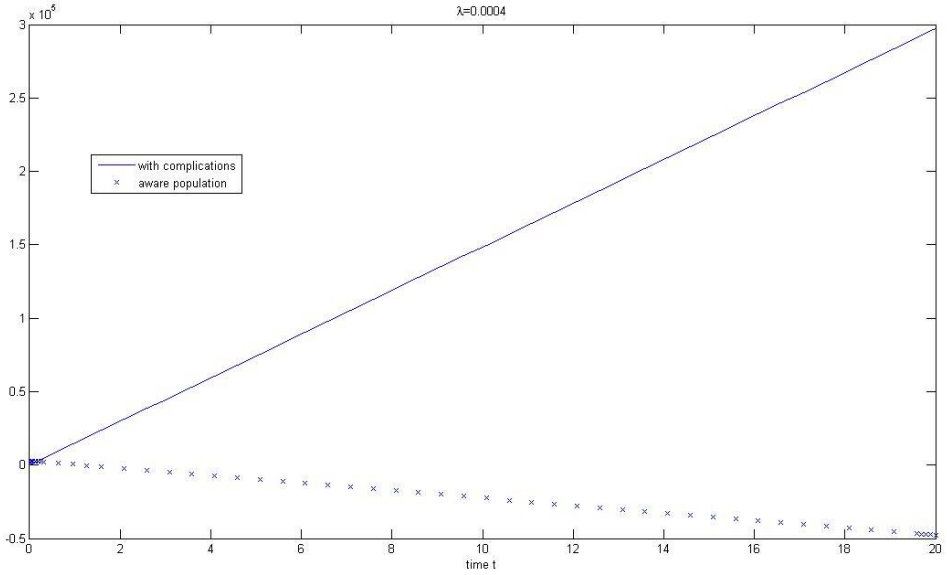

Figure 5.1 - Comparison of diabetes with complications with aware populations when dissemination rate of awareness is 0.0004

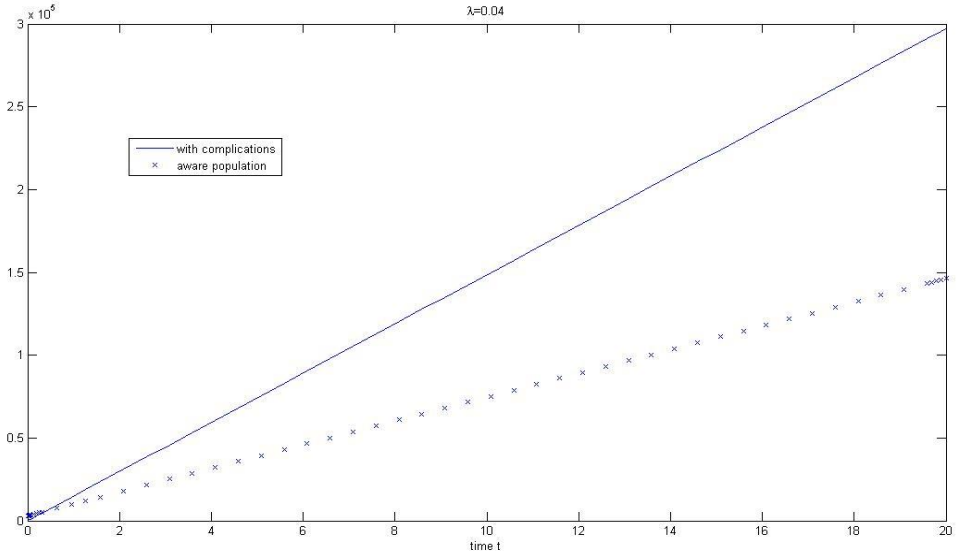

Figure 5.2 - Comparison of diabetes with complications to aware populations when dissemination rate of awareness is 0.04

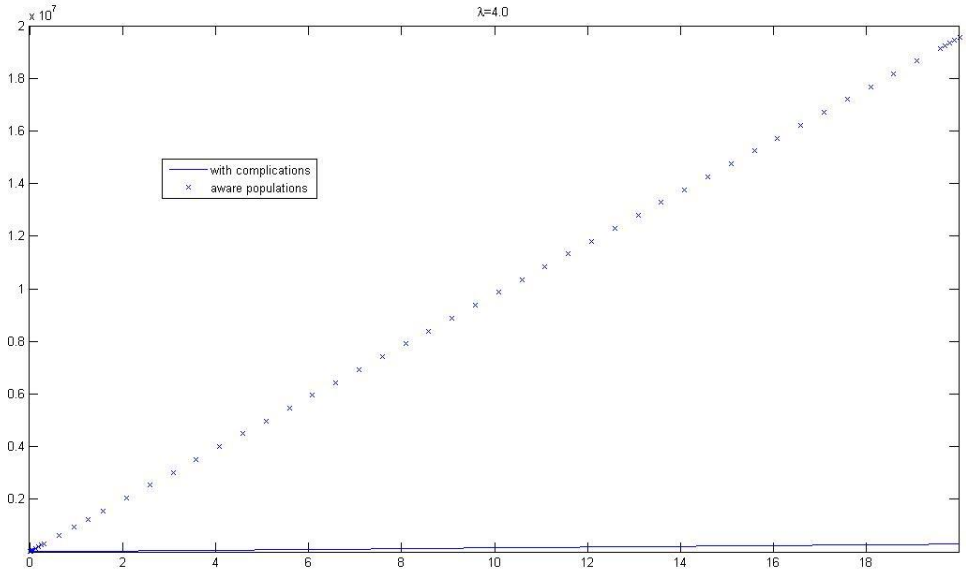

Figure 5.3 - Comparison of diabetes with complications to aware populations when dissemination rate of awareness is 4.0

5.5 Conclusion

Even though there is no specific cure of diabetes, it is a controllable disease if proper awareness is provided (National Diabetic Information Clearing House NDIC). Awareness programs through media inform the people on the prevention of diabetes by taking proper care in diet and physical exercise so as to reduce their chances of developing the disease. They also inform those with the disease on how to take measures so as to avoid complications by taking proper medications, meals and physical activities.

We have formulated a mathematical model which shows the effect of awareness programs on the control of complications in diabetic patients. We obtained two critical points; one trivial and the other non-trivial and have obtained the local asymptotic stability conditions

for the trivial critical points. We also obtained the local and global asymptotic stability of the non-trivial critical points. Numerical simulations are carried out by giving arbitrary values to the parameters which satisfies the conditions of existence of both the critical points and also the local and global stability conditions. Graphs are generated for the two variables namely C(t), the number of diabetics with complications and Y(t), the number of aware diabetics. The value of the parameter λ (dissemination rate of awareness) was varied. It was observed that when λ is very small, say, $\lambda = 0.0004$, the number of diabetes with complications is very high (300000 approx.) and the aware population is negligible. When λ is a bit larger, say, 0.04, the number of diabetics with complications remains the same but the number of aware diabetics has risen considerably high (150000 approx.). When λ takes an even larger integral value 4.0, the number of diabetes with complications is almost nil and the aware population has risen to 20000000 (approx.). This shows the positive effect of awareness on the control of complications in diabetes.

In most theoretical studies on awareness, the fundamental assumption is that awareness can change the pattern of disease spread and reduce the infection rate. It is also observed that if the awareness of the local prevalence of a disease is not covered by the media or by health authorities, it is more likely to be raised by the acts of informal information spread through untrained and unqualified persons (Samanta *et al.*, 2013). If proper information about the control of complications in diabetes is disseminated in the population, people adapt their behavior as a result of their awareness of the disease. Therefore, we feel that more emphasis should be given to the dissemination of awareness of diabetes so as to prevent its occurrence as well as to control the complications so easily brought about by it.

CHAPTER 6

SUMMARY AND CONCLUSION

The 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.

In Chapters 2 and 3, the dynamics on the interaction of insulin and glucose in the body is studied and mathematical models are developed to represent the system. In Chapter 2, 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 disappearance of glucose due to insulin action (insulin-dependent) as well as the disappearance of glucose due to tissue uptake such as the brain and nerve cells (insulin-independent) and rise in glucose level due to infusion through meal intake, oral glucose intake, continuous nutrition absorption and constant infusion are considered. The model is then analyzed for stability in the small as well as in the large sense. The model was first linearized and analyzed for local stability using Routh-Hurwitz criterion as well as Lyapunov's method. The system is locally asymptotically stable under certain conditions on the parameters. The non-linear case was then considered and analyzed using Lyapunov's method and was found that the system is globally asymptotically stable under certain conditions on the parameters and

for the insulin concentration limited to a certain region of attraction. The model is also validated through numerical simulations and graphs are also generated to indicate the role of insulin in the regulation process of glucose in the human body. Chapter 3 illustrates the effect of physical exercise on the dynamics of glucose and insulin. 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. Graphs are generated which indicate that an increase in the rate constant expressing the effect of physical exercise in increasing the muscular and liver sensibility to the action of insulin, results in lower level of glucose in the blood thereby indicating that physical exercise does help in maintaining lower glucose level. We conclude that both the mathematical models in Chapters 2 and 3 are physiologically consistent and may represent a useful tool for further research on diabetes.

In Chapter 4, 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. Local and global stability conditions are established using Routh-Hurwitz Criterion and Lyapunov function. Numerical simulations are carried out to validate the system as well the stability conditions. Graphs are generated for the mathematical model and when that rate at which diabetes occurs is high (10), both the number of diabetics with and without complications grows exponentially with the number of diabetes growing at an even larger rate. But when the rate at which diabetes occurs takes a small value (0.001), the growth rate of both the number of diabetics with and without complications is

reduced considerably. Our finding is consistent with the real world problem and conforms with real observations. 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 Chapter 5, we propose a mathematical model to show the effect of awareness programs on the control of complications in diabetic patients. Local stability as well as global stability conditions are obtained using Lyapunov functions. Numerical simulations are carried out and graphs are generated to show the positive effects of awareness programs through media in controlling complications due to diabetes. From the graphs, we observe that when the dissemination rate of awareness is low (0.0004), the number of diabetics with complications rises at an alarming rate and the aware population is also negligible. But when this dissemination rate is increased significantly (4.0), the number of diabetics with complications is negligible and the aware population is increased at a large rate. This shows the positive effect of awareness on the control of complications in diabetes. Our findings indicate that awareness through the media about this killer disease diabetes plays an important in the control and regulation process of this disease. It is our recommendation that more awareness programs should be taken up by the Government, Public Bodies, NGOs, and Medical Organizations etc. through media such as television programs and print media such as newspapers and magazines. Also, social networking has become a popular trend especially among the youths and information is now readily available at the palm of the hand thanks to the internet. This may

also be explored more effectively so as to reduce the incidence of diabetes by informing the non-diabetic population on how to reduce their chances of developing the disease by taking proper diet and physical exercise. The different media available today may also be employed so as to inform those with the disease on how to take measures so as to avoid complications by taking proper medications, meals and physical activities.

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APPENDIX A

LIST OF PUBLICATIONS:

1. Jamal Hussain and Denghmingliani Zadeng. A mathematical model of glucose-insulin interaction. *Science Vision*, Volume 14 Issue No 2, April-June, 2014.
2. Jamal Hussain and Denghmingliani Zadeng. Mathematical modeling on the effect of exercise on the interactions of glucose and insulin. Published in the *International Journal of Applied Engineering Research*, ISSN 0973-4562, Volume 9, Number 22 (2014) pp. 16211-16221.

APPENDIX B

LIST OF PAPERS PRESENTED IN CONFERENCE/SEMINAR/WORSHOP:

1. Denghmingliani Zadeng, R. Lalawmpuii, Jamal Hussain. Non-linear Models for Two Competing Species with Time-Delay. *International Conference on Modelling of Engineering & Technical Problems (ICEMPT 2009)* held at BMAS Engineering College, Keetham, Agra during January 14-16, 2009.
2. Denghmingliani Zadeng, Jamal Hussain. A generalized mathematical model on glucose-insulin interaction. *National Conference on Mathematical Sciences* held at Pachhunga University College during November 24-25, 2011.

3. Denghmingliani Zadeng, Jamal Hussain. A model on the interaction of glucose and insulin. *2nd International Symposium on Complex Dynamical System and Applications (CDSA II)* held at Presidency University, Kolkata during January 9-11, 2012.
4. Denghmingliani Zadeng. Year of Mathematics 2013. *A one day popularization of Science Seminar*, organized by Science Promotion Wing, State Council of Educational Research & Training, Mizoram in collaboration with NCERT, New Delhi held on 25th October, 2013 at Govt. Chaltlang High School, Mizoram.
5. Denghmingliani Zadeng, Jamal Hussain. Mathematical modeling through Matlab. *A two day workshop on Software Based Teaching and Learning of Mathematics for High School* held at ICT Laboratory, SCERT, Mizoram during August 12-13, 2014.
6. Denghmingliani Zadeng. Mathematics in Everyday Life. *A three-week course on "Research Methodology"* held at Mizoram University during September 9-21, 2014 organized by Academic Staff College, Mizoram University

APPENDIX C

LIST OF CONFERENCE AND WORKSHOP ATTENDED:

1. *"International Conference on Modelling of Engineering & Technical Problems (ICEMPT 2009)"* held at BMAS Engineering College, Keetham, Agra during January 14-16, 2009.
2. "*Two weeks Short Term Course on Mathematical Methods in Engineering and Science"* held at IIT Kanpur during January 19-31, 2009.
3. "*National Conference on Mathematical Sciences"* held at Pachhunga University College during November 24-25, 2011.
4. " *2nd International Symposium on Complex Dynamical System and Applications (CDSA II)"* held at Presidency University, Kolkata during January 9-11, 2012.
5. *"ISI-MZU School on Soft Computing and Applications"* held at Mizoram University during November 5-9, 2012.
6. "*A three-week course on Research Methodology"* held at Mizoram University during September 9-21, 2014 organized by Academic Staff College, Mizoram University