MATHEMATICAL MODEL ON GLUCOSE, INSULIN AND β-CELLS MASS DYNAMICS IN TYPE 2 DIABETES

A PROJECT PRESENTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER OF SCIENCE (M.Sc.) DEGREE IN MATHEMATICS.

BY

ALWELL UZOMA

PG/M.Sc./14/68264

DEPARTMENT OF MATHEMATICS,

UNIVERSITY OF NIGERIA, NSUKKA

SUPERVISOR: PROFESSOR G. C. E. MBAH

AUGUST, 2016

CERTIFICATION

This work was carried out by **Alwell Uzoma, PG/M.Sc./14/68264** under the supervision of Professor G. C. E. Mbah both of the Department of Mathematics University of Nigeria, Nsukka. It is original work and has not been submitted in part or full for any other degree to this university or any other university.

Alwell, Uzoma **Date**
(Student)

Professor Mbah G. C. E **Date**
(Supervisor)

Professor Mbah G. C. E **Date**
(Head of Department)

External Examiner **Date**

DECLARATION

I, declare that this project is my original work, and that any work done by others or by myself previously has been acknowledged and referenced accordingly.

_____

Alwell, Uzoma
August, 2016

DEDICATION

This research work is dedicated to Almighty God for His divine wisdom, good health, protection, love and especially journey mercies while travelling Owerri-Nsukka road on weekly basis for two years.

ACKNOWLEDGEMENT

I am grateful to my supervisor, Professor G. C. E Mbah, for his comments, suggestions and assistance which made the completion of this work successful.Equally, I extend the gratitude to his Ph.D. students for logistic support leading to successful seminar presentation. Also, my gratitude goes to other lecturers in the Department of Mathematics, University of Nigeria Nsukka (UNN), mainly the professors I benefited from their wealth of knowledge; Professor M. O. Oyesanya, Professor F. I. Ochor, and especially Professor J. C. Amazigo who mostly inspired me.

I remain indebted to Mr. Obinna O. Kalu and Dr Obiora Cornelius Collins for their assistance. Also my academic models, whose words of wisdom and encouragement made me realize the need for academic development and excellence: Dr I. Egbo, Dr B. I. Nwoke, Mr. E. I. Ibebuike, Mr. L. N. Nnaji, Mrs. A. D. John Nwosu, Mrs. R. C. Ukagah, Mr. Nelson Nsiegbe, Mr. R. A. M. Ezeala and Mr. Okoro Ezekiel of First Class Education Services. My gratitude also goes to Mr. Sunday Onah and Mr. ChineduObasi, whose assistance in terms of material provision made the entire programme a success.

It was not a one man race hence, I appreciate Mr. OkoroUduUkpai, a partner in progress and the rest of other M.Sc. Mathematics students in 2014/2015 academic session for the commendable team work.

I remain grateful to the authors of all the works cited in this work. My profound gratitude goes to my mother-Mrs. Caroline Alwell, sisters, brothers, fiancée - Miss Eberendu Izuchi and a colleague at Alvan Ikoku Federal College of Education (A.I.F.C.E), Owerri. Mrs. Izzy-Onwukwe Nora O. for their love, care and encouragement while the programme lasted.

Finally, the management and staff of Department of Primary Education Demonstration School, A.I.F.C.E. Owerri, and all those who contributed to ensure the successful completion of the programme are deeply appreciated.

ABSTRACT

A mathematical model, describing glucose, insulin and β-cells mass dynamics of a type 2 diabetic patient was developed in the form of a system of ordinary differential equation, considering insulin resistance, the body inability to overcome the resistance and the fact that glucose production from food intake is not constant. Numerical solution of the model using RungeKutta code in MATLAB, graphically shows rise in blood glucose concentration and further decline over time in glucose concentration below fasting glucose level as a result of low storage of glucose by the liver from food intake; rise in insulin level and fall in β-cells mass. Results from the equilibrium and stability analysis are interesting and compare favourably with available medical literature. Simulation of insulin resistance parameters showed that glucose concentration in the body is proportional to insulin resistance rate.Also, insulin resistance in glucose conversion to glycogen has a significant impact on glucose concentration in the blood.

TABLE OF CONTENT

CHAPTER ONE
INTRODUCTION

Mankind in search for happiness has sought a disease free earth, trying to find long lasting solutions to the diseases threatening the existence of man through various means including mathematical modelling. The wide speculations that some diseases, including diabetes have no cure poses serious challenge to man. International Diabetes Federation (IDF) in 2013 reported that over 387 million people live with diabetes in the world. World Health Organization (WHO) puts it that diabetes led to approximately 3.4 million deaths worldwide in 2004 with 90 percent of the people suffering from diabetes suffer from type 2 diabetes. In 2010, American Diabetes Association (ADA) in their account listed diabetes as the seventh disease leading to death in United States of America. Hence, the call for the study of diabetes, types of diabetes, development, treatment and factors associated to it through the use of mathematical modelling.

1.1.1 Diabetes

Diabetes is a disorder of metabolism that results in excessive thirst and production of large volume of urine. It occurs in two forms; diabetes insipidus and diabetes mellitus. Although in most cases, diabetes is referred to as diabetes mellitus(Oxford Concise Medical Dictionary, 2003).

- **Diabetes Insipidus**

Diabetes Insipidus is a metabolic disorder caused by deficiency of vasopressin (antidiuretic), a pituitary hormone that regulates reabsorption of water by the kidney. It is characterized by the production of large volume of diluted urine and constant thirst, although it is a rare kind of disease (Oxford Concise Medical Dictionary, 2003).

- **Diabetes Mellitus**

Diabetes Mellitus, commonly referred to as diabetes is defined as chronic metabolic disorder of carbohydrates, proteins and fats occurring in the endocrine system (Jarald, Balakrishnan&

John; 2008), due to an absolute or relative deficiency of insulin secretion with/without varying degree of insulin resistance (Barar, 2000; Delvin 2006). This is a disease characterized by chronic high blood plasma glucose concentration (hyperglycaemia), as a result of sugar not being oxidized in the body to produce energy (Oxford Concise Medical Dictionary, 2003). The disease can cause the body to do any of the following; produce little insulin, cease to produce insulin at all or become progressively resistant to insulin action (Ranjan&Ramanujam, 2002).

Diabetes mellitus is classified into subclasses: Insulin-Dependent Diabetes Mellitus (IDDM) or Type 1 Diabetes (T1D), Non-Insulin Dependent Diabetes Mellitus (NIDDM) or Type 2 Diabetes (T2D), Gestational Diabetes Mellitus (GDM) etc. T1D is a case where there is production of little or no insulin because of destruction of the ɓ ï pancreatic cells or may be caused by factors such as genetic infections etc. (Oxford Concise Medical Dictionary, 2003).

In this work, the emphasis is on Type 2 Diabetes (T2D) disease in man. This type of disease is slow to develop occurring in older, obese individuals due to resistance to insulin action combined with a relative deficiency to overcome this resistance arising from the defectiveness in some features of insulin-response system (Nelson & Cox, 2005).

NIDDM/T2D is a heterogeneous disease, ranging from insulin resistance to insulin deficiency (Lokesh& Amit, 2006). It is caused by both genetic and non-genetic factors (Torben, 2002). It accounts for 90-95% of most adults who develop diabetes (Centres for Disease Control and Prevention, 2008). Development entails the process of growth or directed change. Hence, development of disease has to do with the process of growth of such a disease.

1.1.2 Insulin

Insulin is small peptide hormone that consist of 51amino acids and has a molecular mass of 5808 Daltons (Wikipedia, 2011g). In mammals, it is produced by the ɓ-cells of the islets of

Langerhans in the pancreas in the form of pre-proinsulin, a single-chain precursor composed of 110 amino acids. Other issues associated with insulin in diabetes include:

- **Synthesis and Release of insulin**

Insulin is coded on the short arm of chromosome II and synthesized in the ß-cells of the pancreatic islets of Langerhans as its precursor, proinsulin. Proinsulin is synthesized in the ribosomes of the rough endoplasmic reticulum (RER) from mRNA as pre-proinsulin. Pre-proinsulin is formed by sequential synthesis of a signal peptide, the ß chain, the connecting (C) peptide and then the A chain comprising a single chain of 100 amino acids. Removal of the signal peptide forms proinsulin, which acquires its characteristics 3 dimensional structure in the endoplasmic reticulum. Secretory vesicles transfer proinsulin from the RER to the Golgi apparatus, whose aqueous zinc and calcium rich environment favours formation of soluble zinc-containing proinsulinhexamers. As immature storage vesicles form from the Golgi, enzymes acting outside the Golgi convert proinsulin to insulin and C-peptide, Gisela (2005).

Insulin secretion from the islet cells into the portal veins is characteristically pulsatile, reflecting the summation of co-ordinate secretory bursts from millions of islet cells. In response to stimuli such as glucose, insulin secretion is characteristically biphasic, with an initial rapid phase of insulin secretion, followed by a less intense but more sustained release of the hormone, Gisela (2005).

- **Factors Influencing Insulin Biosynthesis and Release**

Insulin secretion may be influenced by alteration in synthesis at level of gene transcription, translation and post-translational modification in the Golgi as well as by factors influencing insulin release from secretory granules. Considering the insulinôs role in glucose utilization

and metabolism, glucose has multiple influences on insulin biosynthesis and secretion. Other factors also influence these process such as amino acids, fatty acids, acetyleholine, pituitary adenylate cyclase-activating polypeptide (PACAP), glucose-dependent insulinotropic polypeptide (GIP), glucagon ï like peptide ï 1 (GIP -1), in combination with other agonists, Gisela (2005).

On physiology of insulin secretion, glucose is the principal stimulus though other macronutrients, hormones, humoral factors and neural input may modify this response. Insulin, together with hormone glucagon, regulates blood glucose concentrations. Pancreatic ß cells secrete 0.025 ï 1.5 units of insulin per hour during fasting (or basal) state, sufficient to enable glucose insulin ï dependent entry into cells, which consequently, maintain normal fasting blood glucose levels, Gisela (2005)

- **Distribution of Insulin**

In the blood, insulin circulates in its free monomer form, where its volume of distribution almost equals the volume of extracellular fluid. During fasting periods, the pancreas secretes about 40□□ (1unit) of insulin per hour into the portal vein, in order to obtain an insulin concentration in the portal blood of 2 ï 4□□/□ □(50 to 100□ □□□□/□ □) and 0.5 □□/□ □(12 units/ml) or about 0.1 □□ in the peripheral circulation.

The ingestion of a meal leads to rapid rise in the concentration of insulin in the portal blood, followed by a parallel but a smaller rise in the peripheral circulation. At digestion, insulin release from the pancreas is not continuous rather it oscillates with a period of 3 ï 6 minutes, changing from generating a blood insulin concentration greater than 800pmol/l to less than 100pmol/l. Hellman, Gyife, Dansk andSalehi (2007).

- **Physiological Effects of Insulin**

The effects of insulin include the triggering notable array of biological responses. The most important target tissues for the regulation of glucose homeostasis by insulin are liver muscle

and adipocyte. Although insulin exerts potent regulatory effects on other cell types as it is basically the hormone responsible for controlling the uptake, use and storage of cellular, nutrients (Laurence, Lazo&Parker 2006). It also increases DNA replication and protein synthesis through the control of amino acid uptake with modification of the activity of several enzymes, Wikipedia (2011g). The anabolic action of insulin occurs mainly at high concentrations and it includes promotion of fatty acid synthesis. Enhancing amino acid uptake in order to synthesize proteins, promotion of protein translocation between cellular compartments, increases glycogen synthesis whereby insulin induces glucose storage in the lever and muscle cells in the form of glycogen. Insulin promotes the uptake of serum potassium thereby reducing potassium in the blood. Insulin also, increases the secretion of hydrochloric acid by the parietal cells in the stomach and induces arterial muscle relaxation by enhancing the flow of blood in micro arteries, Wikipedia (2011e).

- **Pancreas**

This is a gland organ of the digestive and endocrine system of vertebrates. The pancreas is an endocrine gland, which produces several important hormones such as insulin, glucagon and somatostatin. It equally secretes pancreatic juice containing digestive enzyme, Wikipedia (2011e). Islets of Langerhans is a portion of the pancreas which is made up a cluster of cells of about a million in number, which is about 1-2% of the mass of pancreas and compose of four main cell types namely: Alpha (□) cells that secretes glucagon, Beta (ϐ) cells that produces insulin and amylin, Delta (□) cells that produce somatostatin, Epsilon (□) cells that secretes Ghrelin, and pancreatic polypeptide (□□) cells that produces pancreatic polypeptide. (Oxford Concise Medical Dictionary, 2003).

1.1.3 Mechanism of Insulin Action on Glucose Level in Blood

The increase in the plasma glucose concentration induces insulin release, which in turn aids reduction and maintaining the level of glucose in the same plasma.

Insulin is important in hormone regulating cellular energy supply and macronutrient balance, directing anabolic processes of the fed state. It is essential for the intra-cellular transport of glucose into insulin-dependent tissues such as muscle and adipose tissue. Signalling abundance of exogenous energy, adipose tissue and fat breakdown is suppressed and its synthesis and stored in muscle cells. Glucose entry enables glycogen synthetize in muscle, Gisela (2005).

Sequel to glucose concentration in the blood plasma, the pancreas ϐ-cell releases insulin amylin. The insulin is released into the extra cellular fluid in the pancreas by exocytosis and it diffuses out into the blood stream, which are taken along to fluids surrounding the liver cells where insulin binds with appropriate protein on the plasma membrane and clear the proteins inhibiting glucose entry into the cells. Insulin binds with the receptors in the phosphorylated form or the unphosphorylated form, Quon and Campfield (1991).

In a case of diabetic patient (T2D), there is an insulin resistance or deficiency, the pancreas fails to produce adequate or effective insulin to overcome the insulin resistance which makes it impossible for glucose entry into the cells for body use and storage. Hence, the glucose is not oxidized and this leads to excess glucose in the blood while the cells are starved of glucose.

1.1.4 Blood Glucose Concentration

Glucose is the main source of energy for body cells and blood lipids (in the form of fats and oils which are primary compact energy store). It is transported from intestines or liver to body cells through the bloods stream and presented to the cells for absorption via the hormone insulin. Blood sugar concentration or blood glucose level is the amount of glucose (sugar) present in the blood of a human or animal, Wikipedia (2011a).

The blood glucose concentration is measured based on international standards with respect to molar concentration. It is measured in units such as millimoles per litre(mm/l) or millimolar

(mM). In some countries such as the United States, blood glucose concentration is expressed as mass concentration of glucose in the blood with unit as mg/dl (milligrams per deciliter). Both units can be used interchangeably, since the molecular mass of glucose ($C_6H_{12}O_6$) is approximately 180g/ml. Thus the measurement of glucose is the difference between these two scales, which is the factor of 18. Therefore 1mmol/l of glucose is equal to 18 mg/dl, Wikipedia (2011a). Glucose concentrations vary prior to and after each meal consumption, so that with a substantial carbohydrate load the human blood glucose levels usually remain within the normal range, although shortly after eating, the blood glucose concentration could temporarily increase a bit in non-diabetics. Several factors influence an individualôs blood glucose concentration, such as homeostasis, that functions to restore blood glucose concentration back to normal. Normal blood glucose level/concentration varies among Medical professionals, with the values of blood use concentration at 4.4 - 6.1mmol/l (82-110mg/dl).

1.2 Objectives of the Study

The study aims at developing amathematical model on glucose production, insulin and ɓ-cells mass dynamics in development of type 2 diabetes. Specifically, the objectives are to:

- Develop mathematical model on glucose, insulin and ɓ-cells mass dynamics, describing development of T2D in a case of insulin resistance individuals.
- Obtain numerical solution of the model.
- Perform Equilibrium, Stability Analysis and Simulations on the model.

1.3 Scope of the Study

This study is restricted to T2D without loss of generality to other types of diabetes. Furthermore, all formulations are based on the results of the practical work of medical literature.

1.4 Limitations of the Study

It is known that there are two major types of diabetes mellitus caused by diferent factors. The study did not perform any physical experiment but relied solely on literature and limited itself to development of a mathematical model on glucose, insulin, ϐ-cells mass dynamics in an individual having insulin resistance and genetically predisposed to development of type 2 diabetes. Without considering other risk factors leading to development of type 2 diabetes, effects of Ŭ-cells in glucose production. Also, the case of type 1 diabetes and development of diabetes in other animals were not covered.

1.5 Significance of the Study

A mathematical formulation to assist in the quest for curative solutions to contemporary diseases cannot be over emphasized. This study presents T2D development pattern using mathematical biology contributing to the literature in the effort for better management and possible cure for T2D.

CHAPTER TWO

LITERATURE REVIEW

Attempts have been made to solve problems posed by diabetes disease, through the use of mathematical models. The literature on mathematical modelling in different aspects of diabetes including: diabetes progression, tools and computational study of diabetes models, plasma and insulin level in diabetes mellitus, homeostatic assessment, insulin sensitivity/resistance, plasma and blood glucose level regulation and human glucose-insulin regulatory system is very vast.

WHO (1999), through the expert committee released a report on Diabetes mellitus, which includes its classifications, types, symptoms, urination, diagnoses, amount of glucose in blood and many other ways, as well as treatment of diabetes.

Wild et al. (2004), estimated the incidence of diabetes and the number of diabetic people of all ages for years 2000 to 2030. The data collected for all age groups having diabetes mellitus worldwide was estimated to be 2.8% of the worldôs population in 2000 and 4.4% in 2030. The incidence of diabetes is higher in men than women, but as for the record there are more diabetic women as compared to men. These findings indicate that the ñdiabetes occurrenceò will continue even if levels of obesity remain constant.

In a review, Gisela (2005) provided an overview of insulin, its history, structure, synthesis, secretion, actions and interactions. Specifically, the work focused on insulin and manifestation of insulin resistance in specific organs and tissues; physiological, environmental and pharmacological influences on insulin action and insulin resistance. In conclusion, he stated that rapid globalization, urbanization and industrialization spawned epidemics of obesity, diabetes and their attendant co-morbidities. However, the approach to the work was non-mathematical.

Topp et al. (2000), developed amodel on Glucose (G), Insulin (I) and β-cells mass(β)given as follows:

$$\frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G \qquad (2.1)$$

$$\frac{dI}{dt} = \frac{\beta \sigma G^2}{(\alpha + G^2)} - kI \qquad (2.2)$$

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2)\beta \qquad (2.3)$$

Table 2.1.Topp et al. (2000) Model Parameters

Parameters.	Units	Biological Interpretation
R_0	$mg\ dl^{-1} d^{-1}$	Net rate at zero glucose production
E_{G0}	d^{-1}	Total glucose effectiveness at zero insulin
S_I	$ml\ \mu U^{-1} d^{-1}$	Total insulin sensitivity
β	mg	Pancreatic β-cells mass
σ	$\mu U\ mg^{-1} d^{-1}$	Maximal rate at which all β-cells are assumed to secret insulin
kI		Insulin clearance rate
k	d^{-1}	Clearance constant that represents the combined insulin uptake at the livers, kidneys and insulin receptors
d_0	d^{-1}	death rate of β-cells mass at zero glucose
r_1	$mg^{-1} dl\ d^{-1}$	Rate constant that determine the β-cells glucose tolerance range
r_2	$mg^{-2} dl^2 d^{-1}$	Rate constant that determine the β-cells glucose tolerance range

From (2.2), $\frac{G^2}{(\alpha + G^2)}$ is a Hill function with coefficient 2 that describe a sigmoid ranging from 0-1 which reaches half of its maximum at $G = \sqrt{\alpha}$.In (2.3), the model described the behaviour of β-cells mass with a second order degree polynomial.

The analysis done under two subsystems: fast (G, I) and slow (β, $\dot{\beta}$) gave three steady ï stable solutions; the physiological fixed point, the saddle point and the pathological fixed

points of the slow system. They stated that when blood glucose level is higher than $250\square\ \square\square\square^{\square\square}$, it leads to □-cells death rates to exceed replication rates and drives the system towards a pathological steady state.

The model did not introduce insulin resistance and genetic factors leading to type 2 diabetes, though it predicts three different pathways to diabetes (regulated hyperglycaemia, bifurcation and dynamical hyperglycaemia).

Hernandez et al. (2001), extended the Topp et al. (2000) models by incorporating the insulin receptor based on the fact that the insulin resistance which is the main cause of type 2 diabetes is associated with the down-regulation of the receptors on the muscle cells surface. They added insulin receptors to the Topp et al. model to have the fourth component of the nonlinear ODE system.

$$\frac{\square\square}{\square\square} = \square - \square\square + \square\square\square_{\square}\square\square \quad (2.4)$$

$$\frac{\square\square_{\square}}{\square\square} = \frac{\square\square\square^{\square}}{(\square\square\square)(\square\square\square^{\square})} - \square\square_{\square} - \square\square\square_{\square} \quad (2.5)$$

$$\frac{\square\square}{\square\square} = (-\square + \square\square - \square\square^{\square})\square \quad (2.6)$$

$$\frac{\square\square}{\square\square} = \square\square 1 - \square\square - \square\square\square - \square\square \quad (2.7),$$

$$\square \neq -1$$

Where R = the fraction of insulin receptors on the surface of the muscle cells

$\frac{\square}{\square\square\square}$ = rate at which a single ϐ-cell will secrete insulin and

$\square\square\square_{\square}$ = insulin clearance by muscle cells receptor.

The model provided a theoretical justification for the experimental result $\square = 0.84$, matching the fact that there are approximately 85% of insulin receptors on the surface of muscle cells. The model did not incorporate insulin resistance and development of T2D.

Boutayeb et al. (2014), modified the models of Topp, et al. and Hernandez, et al. and presented a model on β-cells mass, insulin and glucose dynamics to study the effects of genetic predisposition to diabetes, as represented (2.8), (2.9) and (2.91):

$$\frac{\square\square}{\square\square} = \square - \square\square\ \square\square\square - \frac{\square\square\square\square\square\ \square\square\square}{\square\square\ \square\ \square\square\square\ \square\square} \qquad (2.8)$$

$$\frac{\square\square}{\square\square} = \frac{\square\square\ (\square)\ \square\ (\square)^{\square}}{(\square\square\ \square\ \square\square\square^{\square})} - \square\square(\square) \qquad (2.9)$$

$$\frac{\square\square}{\square\square} = \square 1 - \square\square\square\ \square\square\square 1 - \frac{\square\ \square\square\square}{\square}\square + \square\square - \square + \square\square\ \square\square\square - \square\square\ \square\square\square^{\square}\ \square\square\square\square \qquad (2.91)$$

where □ = 1 indicates predisposition to diabetes.

The model showed three equilibrium points: a stable physiological equilibrium point (□ = 100, □ = 20, □ = 6000), a stable trivial pathological equilibrium point (□ = 600, □ = 0, □ = 0) and a saddle point (□ = 250, □ = 9.8, □ = 129.36) for □ = 1. In the case of □ = 0 (absence of predisposition to diabetes), the model has an unstable pathological equilibrium point (□ = 600, □ = 0, □ = 0) and a stable physiological equilibrium point (□ = 82.6, □ = 23, □ = 900). The model was further subjected to simulations to find the effects of obesity, physical exercise and other factors that affect insulin sensitivity.

De Gaetano et al. (2008), presented mathematical models of diabetes progression. A model of the pancreatic islet compensation was formulated, its physiological assumption were presented and some fundamental qualitative characteristics of its solutions established. Numerical values were assigned to model parameters. The performance over the lifetime span was simulated under certain conditions including worsening insulin resistance and primary replication defects. Equally, differences in the models as compared to previously proposed models of diabetes progression were highlighted. The model tries to give a descriptive evolution to the compensation of the glucose-insulin system in healthy and diabetic individuals.

Lin (2011), developed a glucose-insulin kinetics model with the development of type 2 diabetes in offspring of diabetic parents. Investigation using a population ï based Bayesian nonlinear hierarchical model of pharmacokinetics/pharmacodynamics (PK/PD) risk factors preceding the onset of T2D was done. Also, a methodology describing disease development of T2D was developed based on fasting blood glucose (FBG), fasting serum insulin (FSI), homeostatic model assessment of insulin resistance (HOMA-IR) and body mass index (BMI) of T2D.

Delay Differential Equation (DDE) models on diabetes were reviewed by Makroglou, Karaous, Li and Kuang (2011). They stated that DDE models can generate rich dynamics using minimum number of parameters, which makes the models to play important roles in a growing number in areas of diabetes study. They identified such areas to include insulin/glucose regulatory system, Intravenous Glucose Tolerance Test (IVGT), and insulin therapies. The models were presented with some computational results and theoretical results for models on ultradian oscillations of insulin and models for diagnostic tests.

The stability and disease free equilibrium of the diabetic population under combined effect of birth rate and treatment was studied through development of mathematical models by Adamu et al. (2016). The models were subdivided under population of diabetics without complications, diabetics with complications, diabetic with regulated glucose as a result of treatment and severely disabled sub-populations. The analysis of three developed differential equation models, established that ñBirth rate and the number of diabetics with complications determined the equilibrium solutions, and that the contribution of birth rate to the dynamics of the diabetics population depends on the dynamics of the diabetic gene and life style.ò

Chalishajaret al. (2014), utilized mathematical models based on advanced differential equation to analyse the effects of insulin infusions in human body geared towards

determining better modes of treatment for the metabolism of glucose. Three models called Insulin-Feedback models analysed the efficiency of insulin in regulating glucose dependency on the introduction of insulin in individuals. The first, second and third models analyses the mechanism of slow ultradia oscillation infusion of insulin into individuals with varying levels of infusion with respect to time and utilizing a time delay over short intervals which creates pulsatile in the infusion of glucose respectively.

Smith et al. (2009), modelled glucose homeostasis and its relationship with energy balance and body fat. The work explained the mechanisms behind the development of obesity. However, the models and the analysis were not presented.

Rohan (2010), worked on Ackerman model of Glucose Tolerance Test (GTT) in diabetes. The linearized system was analysed using stability test and a stable equilibrium was obtained. Further, the solution for the linear equation of glucose was obtained. Also, the natural period was obtained using natural frequency from forced damped oscillation. Two individuals were taken for the study, one diabetic and the other was not. MATLAB was used to obtain the least squares best fit. The reliability of the model was ascertained as the graphics showed that the individual noted to be diabetic has diabetes and the second subject was not.

Makroglou, Li and Kuang (2005), carried out an overview of mathematical models and software tools for the glucose insulin regulatory system and diabetes. This covered mathematical models in literature for use in the glucose-insulin regulatory system in diabetes and survey of available software. The models formed comprises ordinary differential, partial differential, delay differential and integro-differential equations. They also presented some computational results, without including type 2 diabetes.

Sandhya and Kumar (2011), proposed a mathematical model for the study of diabetes mellitus aimed at regulating the blood glucose level of a diabetic patient. The model takes into account all plasma glucose concentration, generalized insulin and plasma insulin

concentration. Effectiveness of the proposed work was evaluated using computer simulation. Numerical solution was used to present the complex situation of the diabetic patients.

Shiang and Kandeel (2010), introduced a computational model of insulin secretion and glucose metabolism for assisting the diagnosis of diabetes mellitus. Methods for estimation of parameters for a system of Ordinary Differential Equations (ODEs) that represent the time course of plasma glucose and insulin concentration during glucose tolerance test (GTT) in physiological studies were proposed. The work aimed to explore how to interpret those laboratory glucose and insulin data and to enhance the Ackerman mathematical model. Application of R-base iterative computer programs on the Ackerman published data solution showed that model estimation parameters computed frequency and period values are good indicators of diabetes. In conclusion, it was stated that there is an introduction of computational algorithm to biomedical problems, particularly to endocrinology and metabolism fields which involved the two differential equations of Ackerman with four parameters describing the glucose-insulin regulatory system.

Boutayeb and Chetouani (2006), carried out a critical review of mathematical models in different aspects of diabetes including glucose and insulin dynamics, management and complications prevention, cost and cost effectiveness of strategies and epidemiology of diabetes in general, using various tools. The models cut across models that are deterministic and/or stochastic; continuous and/or discrete; using ordinary differential equations, partial differential equations, optimal control theory, integral equations, matrix analysis and computer algorithms.

Radziuk (2014), worked on the homeostatic model assessment and insulin sensitivity/resistance. Modelling and interpretation of glucose metabolism was carried out. A system of models including insulin kinetic model, glucose insulin feedback loops, glucose

production, glucose utilization and plasma insulin. Insulin resistance was estimated using HOMA-IR and its inverse S_1 from basal measurement of plasma insulin and glucose.

Geraghty (2008), explained the importance of Delay differential equations (DDE) with many different applications, particularly in the biological and medical worlds. It gives the further idea for insulin therapy by using the solution of the differential equations.

Adewale et.al. (2007) defined a mathematical model used for the study of diabetes mellitus and hence concluded on the impact of different levels of physical activities on the steadiness of the disease. They observed that when we exercise, the hazard of becoming diabetics reduces.

Yasini et.al. (2009) developed a model showing the regulations of the blood glucose level of diabetic patient (T1D) under an intensive insulin treatment. To maintain the normal glycaemic average of 80mg/dl and the normal condition for free plasma insulin concentration in severe initial state, reinforcement learning theory was used with the help of closed-loop control scheme expert knowledge. By using Q-learning algorithm, an offline insulin delivery rate was obtained without requiring a model of the environment dynamics. To evaluate the effectiveness of the proposed model and to check its superiority in controlling hyperglycaemia over other existing algorithms, Computer simulations were used.

Mbah (1998), worked on mathematical models describing the variations in the plasma glucose and insulin levels over time in an insulin-dependent diabetic person (IDD patient). The work showed that the models can correctly describe the variations when solved simultaneously. Analytic approach was adopted to solve non-linear differential equations. The work stated that the major determinants of the plasma insulin/glucose level are the pancreatic and liver cells. The work equally stated that due to wrong diagnosis, over dose of insulin into a patient can result to hypoglycaemia which complicates the state of health of the patient. However, the case of non-insulin dependent diabetes mellitus (T2D) was not treated.

Ackerman et al. (1965), formulated a model to help diagnose the condition of a diabetic patent. Additionally, they developed a graphical user interface to facilitate the patient's data entering and the visualization of the results.

The works of several scholars in mathematical modelling in different aspects of diabetes, has been reviewed. However, mathematical model of diabetes development of Type 2 Diabetic patient in literature remain scarce.

CHAPTER THREE

TYPE 2 DIABETES(T2D) DISEASE

3.1 Type 2 Diabetes (T2D) or Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Diabetes mellitus type 2 is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. (Wikipedia, 2011a). This type of diabetes is slow to develop, occurring mainly in older, obese individuals as a result of resistance to insulin action combined with a relative deficiency insulin secretion. Although insulin is still produced by the ϐ-cells, it is insufficient to overcome this resistance arising from the defectiveness in some features of insulin-response system (Nelson & Cox, 2005).

NIDDM/T2D is classified as a heterogeneous disease, ranging from insulin resistance to insulin deficiency (Lokesh& Amit, 2006), also as a multifactorial, with both genetic and monogenetic components/caused factors (Torben, 2002). It accounts for 90 - 95% of most adults who develop diabetes (Centres for Disease Control and Prevention, 2008) and it is associated also with family history of diabetes, history of gestational diabetes, physical inactivity impaired glucose metabolism and race/ethnicity.

3.2 The Aetiology of Type 2 Diabetes

This is the study of the causes or causative factors of type 2 diabetes.

3.2.1 Causes of T2D

The development of T2D is caused by a combination of lifestyle and genetic factors.

- **Lifestyle**

Lifestyle factors responsible for development of T2D include; obesity, lack of physical activities, poor diet, lack of sleep, stress, and urbanization which can be controlled. Other factors are increasing age, female gender, etc. A proper diet and exercise are the foundations

of diabetic cure. Low carbohydrate diet has been found to improve blood sugar control.(Wikipedia, 2011a)

- **Genetics**

Most cases of diabetes involved many genes as a small contributor to the cause of T2D. As of 2011, more than 36 genes had been found to be contributing to the risk of T2D**.** All of these genes account for only 10% of heritable component of the disease. Most of the genes linked to diabetes are involved in beta cells function. (Wikipedia, 2011a)

3.2.2 Risk Factors for the Development of Type 2 Diabetes

Recent medical findings show that the chances of developingtype 2 diabetes increases more with individuals with the following health problems;

- Family history of diabetes- If a parent or siblings of yours is diabetic, then the risk of developing diabetes type 2 increases.
- Age- At age forty-five and above, the chance of getting type 2 diabetes increases. Likewise the pancreas ages with time which in turn affects the production of insulin, leading to diabetes.
- Race or Ethnic background- The risk of developing type 2 diabetes is higher with Hispanics, Blacks, Native Americans and Asian.
- Metabolic syndrome- This is also known as insulin resistance syndrome.
- Obesity- This is the major risk factor for type two diabetes with a global incidence of about two million. Being overweight is said to be when the body mass index (BMI) is greater than 25, thus a person with BMI greater than 25 is likely to develop diabetes type 2. More weight connotes increased insulin resistance, because fat cells are not as receptive to insulin like muscle cells.
- Inactivity- This most at times leads to obesity, which is the number one factor for developing type 2 diabetes.

- Hypertension- High blood pressure above 140/90 nm/Hg, increases the risk of developing type 2 diabetes.
- Abnormal cholesterol levels- The development of type 2 diabetes is increased when one has a high density lipoprotein (HDL) level under 35mg/dl (mg/dl) and/or a triglyceride level greater than 250mg/dl.
- History of Gestational diabetes- Becoming diabetic during pregnancy or delivering a baby weighing 9 pounds or 4kg could increase the risk of developing type 2 diabetes.
- History of polycystic ovary disease.
- Vascular disease such as stroke(Wikipedia, 2011a).

3.3 Prevention

Early development of type 2 diabetes can be delayed or prevented through proper nutrition and regular exercise, especially for individuals with impaired glucose tolerance. Limiting intake of sugar drinks is encouraged. Low levels of vitamin D is associated with increased risk of developing diabetes.(Wikipedia, 2011a)

3.4 Management

Diabetes mellitus is a chronic disorder which has no cure except in specific situations. Hence management concentrate on keeping the blood sugar levels close to normal as possible without causing hypoglycaemia. Management of type 2 diabetes is achievable through patient education, adjustable lifestyle; proper diet and regular exercise, and lowering other cardiovascular risk factors such as hypertension, high cholesterol and micro albuminuria. (Oxford Concise Medical Dictionary, 2003).

3.5 Medication

Several classes of anti-diabetic medications are available. Metformin is generally recommended. Other classes of medications include; sulfonylureas, thiazolidinedione,

dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors, and glucagon-like peptide-1 analogy. Angiotensin-converting enzyme inhibitors (ACEIs) prevent kidney disease and improve outcome in diabetes. Also, injection of insulin depending on severity and nature. (Oxford Concise Medical Dictionary, 2003).

Also, weight loss surgery in those who are obese is an effective measure to treat diabetes for patients who cannot put their weight and blood sugar under control. (Wikipedia, 2011f).

3.6 Epidemiology of diabetes (T2D)

Diabetes was earlier regarded among the non-communicable diseases that has minor significance to world health. However, in early 2000 there has been an alarming increase in the number of people diagnosed with diabetes worldwide,Hans et al. (2000). Currently, it is admitted that diabetes is sweeping the globe as a silent epidemic largely contributing to the growing burden of non-communicable disease mainly caused by increasing cases of obesity and lack of exercise. (Ibrahim, Momoh& Tahir; 2016).

World Health Organization (2003), in a recent report has it that in 2003, an estimated 194 million people were diabetic, representing over 3% of the world population. It has been predicted that by the year 2025, the population of diabetic individuals will reach 333 million people (16.3%). The report further gave that for the first time, 314 million (8.2%) people are in the pre-diabetic stage which has the tendency of giving at least one third of the population to develop diabetes after ten years. (Boutayeb et al, 2014).

In addition to this alarming predictions, according to world table published by WHO in 2000, 3.4% Nigerians within 20 years and above are diabetic. (Adamu et al, 2005).

Adrienne (2014), put it that the International Diabetes Federation (IDF) reported that as of 2013, there are over 387 million people living with diabetes. WHO, estimates that 90 percent

of people around the world who suffer from diabetes, suffer from type 2 diabetes. In 2004, high blood sugar as a result of diabetes led to an estimated 3.4 million death worldwide. He stated that in developing nations, more than half of all diabetes cases go undiagnosed. By 2030, it anticipated that worldwide death attributable to diabetes will double (WHO). It is further put that globally as of 2010, there was an estimated 285 million people with type 2 diabetes making up about 90% of diabetes cases. This is about 2% of worldôs adult population.

American Diabetes Association (2015) listed diabetes as the seventh leading cause of death in the United States. In 2010, having 69,071 death certificates listing diabetes as an underlying or contributing cause of death.

Lin (2011), put the cumulative risk of developing T2D for individuals with one and two diabetic parents to 29.2% and 41.9% respectively and 14.0% for individuals with no diabetic parent, he stated that T2D can be prevented or its onset can be delayed by lifestyle modification and/or pharmacological interventions.

3.7 Signs and Symptoms of T2D

All kinds of diabetes mellitus are characterized by excessive amount of glucose circulating in the blood plasma, a condition known as hyperglycaemia (high blood sugar). Hyperglycaemia emanates from the failure of insulin-dependent tissues/cells to absorb glucose, also due to accelerated hepatic glycogenesis from amino acids derived from muscle proteins (Devlin, 2006). The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue. Many individuals experience no symptoms in early years.

The common symptoms of T2D include increased thirst, frequent urination leading to dehydration and unexplained weight loss. The symptoms may also include increase hunger, and sores that fails to heal (Wikipedia, 2011a).

3.8 Diagnosis of T2D (Blood Glucose Laboratory Tests/Screening)

A series of screening and diagnostic test are employed in determining high levels of glucose in plasma or serum in a particular circumstance. They are divided into:

i. **Non-challenge blood glucose tests**.

This is the measurement of glucose levels in blood samples without challenging (giving to drink) the subject with glucose solutions. Example of this test are,

- **Fasting Blood Glucose Test (FBS)**

The blood glucose concentration is determined after an 8 hour fast. This is the most popular method employed in indicating the overall glucose homeostasis, because food intake is avoided which can interfer in the actual glucose value.The test is characterized by abnormalities such as multiple control mechanism of glucose regulation (Wikipedia, 2011b).

- **Random glucose test**

Here, blood glucose is measured several times after a standardized amount of oral glucose intake. The random glucose test is adjudged as the gold standard of clinical tests of the insulin/glucose control system.It is marred by the difficulty in administration, time requirement and repeated blood tests.

ii. **Challenge Blood Glucose Tests**

This test entails drinking of glucose solution and the value of blood glucose is measured. Examples of such test are,

- **2–hour postprandial glucose test (2–hPPBS)**

Blood glucose concentration is measured 2ï hours after a meal or glucose load.

- **Screening glucose challenges test or O' Sullivan test**

  It is a simplified version of the oral glucose tolerance test (OGTT) and also known as Oô Sullivan test. It is carried out in pregnant women whose pregnancy are 24 ï 28 weeks old. The screening glucose challenges test is performed by drinking a 50 gram glucose solution and blood glucose measured after 1 hour (Metzger *et al*, 2006).

- **Oral glucose tolerance test (OGTT)**

This test entails an overnight fast of 8 to 14 hours, after the consumption of an unrestricted diet (containing at least 150g carbohydrate per day) for three days. The OGTT is performed in the morning after the fast and involves consuming a particular amount of glucose solution, after which the blood glucose concentration is measured at set time intervals after then (Medline plus, 2006).

Another method for OGTT involves the consumption of 75g glucose load and the blood glucose levels measured before and after 1 and 2 hours. The following are the values that the American diabetes association regarded as abnormal, during consumption of 100g of glucose in OGTT.

Fasting blood glucose level Ó95/dl (5.33 mmol/l).

1 hour blood glucose level Ó180g/dl (10mmol/l).

2 hour blood glucose level Ó155mg/dl (8.6mmol/l).

4 hour blood glucose level Ó140mg/dl (7.8 mmol/l).

- **Urinary Glucose Testing**: This involves the use of a dipsticks in the test subject urine. It is commonly used, although performs poorly.

Other kinds of screening/liquid glucose test include:

- Glycosylated haemoglobin (HbA_{1C}).
- Self ï monitoring of glucose level through patient testing.
- Intravenous glucose tolerance test (IVGTT).

Table 3.1. 2006 World Health Organization Diabetes Criteria (World Health Organization, 2006)

Condition	**5 hours glucose mmol/l (mg/dl)**	**Fasting glucose mmol/l (mg/dl)**	
Normal	< 7.8 (<140)	< 6.1 (< 110)	
Impaired fasting glycemia	< 7.8 (<140)	Ó 6.1 (Ó 110) and	< 7.0 (< 126)
Impaired glucose tolerance	Ó7.8 (Ó140)	< 7.0 (< 126)	
Diabetes mellitus	Ó11.1(Ó200)	Ó7.0 (Ó126)	

The monitoring of blood glucose is a means of testing the concentration of glucose in the blood (glycemia) and It is essential in the care of diabetes mellitus. It is performed with a glucose metre or glucometre, a commercially available electronic device used for determining the approximate concentration of glucose in the blood. Blood glucose monitoring is performed by piercing the skin (especially the finger) with a lancet in order to draw blood by capillary action, onto active disposable ótest stripô inserted into a digital metre. Within few seconds the level of blood glucose is digitally displayed on the monitor of the metre, in mg/dl or mmol/l. Blood glucose monitor or glucose metre is the principal element of home blood glucose monitoring (HBGM) by diabetics or hypoglycemia patients (Wikipedia, 2011e).

Monitoring of blood glucose reveals individual patterns of blood glucose changes and assists in meal planning, activities and medication (Medline Plus,2006). Likewise it permits quick responses to high blood sugar (hyperglycemia) or low blood sugar (hypoglycemia). Upon such event, there may be the need for diet adjustments, exercise and insulin, based on health care provider instructions (Medline plus, 2006). People with fasting blood glucose levels of 100 - 125 mg/dl (5.6-6.9mmol/l) are regarded to have impaired fasting glucose. Others with plasma glucose of 140 - 200mg/dl (7.8-11.1mmol/l) two hours after the consumption of 75g oral glucose load, are said to have impaired glucose tolerance. These range of blood glucose

levels are grouped under Pre - diabetes, which is a condition where an individualôs blood glucose levels is higher than normal but not sufficient for the diagnosis of diabetes type 2.

Glucose monitors are mainly designed to give whole blood readings although recently some are made to give plasma glucose readings, which are 10-15% higher than that of whole blood glucose. The plasma blood glucose readings are equivalent to laboratory test blood glucose measurement (Wikipedia, 2011f).

Hyperglycemia as earlier said is the most common feature of diabetes mellitus and the persistency or prolonged exposure of the body tissues to elevated levels of glucose, is a factor responsible for the development of most complications in diabetes mellitus (Laurence *et al*, 2006) such as oxidative stress. Other factors that could generate or induce oxidative stress during diabetes are, prostanoid synthesis, polyol pathway and protein glycation (Kumawat *et al.*, 2009). This involves the accumulation of non-enzymatic glycosylated products, together with osmotically active sugar alcohols for example sorbitol, in the tissues as a result of the toxic effect of hyperglycemia (Laurence *et al*., 2006).

To distinguish T2D from T1D, antibody testing is used to comfirm T1D while C-peptide levels which is low in T1D, but normal or high in T2D may be used to comfirm T2D.

3.9 Insulin Resistance and Development of T2D

According to Lin (2011), insulin resistance refers to the reduced insulin effect on suppressing hepatic glucose production, on stimulating glucose removal and glycogen synthesis in skeletal muscles tissue, and on inhibiting the lipolysis of adipose tissue. The signs include hyperglycaemia and hyperinsulinemia. Longitudinal studies indicates that insulin resistance predicts development of T2D, though earlier than prediabetes stage. Insulin resistance has been traced to heredity and research indicated that excess body weight (Obesity) and lack of exercise significantly increase risk.

From the natural history, it is now well estalished that the development of T2D results from an interaction of a subjectôs genetic makeup and their environment, and that with the increasing prevalence of obesity, the prevalence of diabetes is reaching epidemic proportions. The development of obesity seems to be an important factor portending the development of insulin resistance, which in the presence of a genetically determined propensity to beta-cells dysfunction results in alterations in glucose tolerance. Unfortunately, while it had previously been considered that T2D was essentially a disease of middle aged and older subjects and that it took years to develop, this concept is currently undergoing re-evaluation. This is due to the emergence of T2D as a new and very serious health problem in children. It is of interest that the limited studies currently carried out in these children suggest the co-existence of obesity, insulin resistance and beta-cells dysfunction as occurs in older T2D patients. Historically, clinicians have found that controlling hyperglycaemia in T2D can be difficult,frequently requiring increasing doses of oral antidiabetic agents and the addition of insulin. This progressive nature of T2D has been further highlighted by two recent, large clinical studies performed on opposite sides of the Atlantic. In the United Kingdom Prospective Diabetes Study (UKPDS), despite treatments to establish euglycaemia in the intensive policy group, glycaemic control deteriorated such that additional pharmacological therapy was required. Thus, after 9 years, only 25% of the subjects in the intensive treatment arm were achieving a HbA1c of less than 7% with monotherapy alone. (Kahn, 2003).

CHAPTER FOUR
MODEL PRESENTATION AND ANALYSIS

4.1 Model Presentation

Considering the fact that the major condition leading to the development of type 2 diabetes is insulin resistance, the models of Mbah (1998), Topp et al. (2000) modified by Hernandez (2001) and subsequently Boutayeb et al. (2014) were extended to reflect the case of insulin resistance on the cells receptors of an individual having insulin resistance predisposed to development of T2D. Also, given the fact that glucose production from food intake is not constant as assumed by Topp et al. and Boutayeb et al., glucose production is given by $\square_{\square}\square\square^{\square\square(\square\square\square_{\square})}$. The resistance in the rate at which glucose is converted into glycogen in the cells (w) and resistance rate of insulin on the cells receptors (r) were introduced. Hence, the proposed model on Glucose, Insulin and ɓ-cells mass dynamics is given by the set of ordinary differential equations (4.1), (4.2) and (4.3) respectively.

Model on Glucose Production, Insulin and ɓ- cells Mass in T2D

$$G\square = \square_{\square}Qe^{\square\square(\square\square\square_{\square})} - \square_{\square}(1 - w)G - \square_{\square}\square 1 - r\square IG, \quad (4.1)$$

$$I\square = \frac{\square_{\square}\square\square^{\square}}{(\square_{\square}\square\square^{\square})} - b_{\square}I, \quad (4.2)$$

$$\beta\square = \square - c_{\square} + c_{\square}G - c_{\square}G^{\square}\square\beta. \quad (4.3)$$

Where G, I and β are functions of time (t). The definition and values of the parameters are summarized in table 4.1.

On the glucose dynamics represented by equation (4.1), $\square$ is the quantity of glucose concentration in the blood, $\square_{\square}$ is the rate at which glucose is produced after food intake, $\square\square^{\square\square(\square\square\square_{\square})}$ is the expression describing the rate at which glucose is released from food consumed. $\square$isthe equivalent of glucose in the quantity of food intake and $\square$ is decay parameter during glucose release to the blood. $\square_{\square}$is the constant representing the quantity of

glucose used in the body cells, β denotes the rate of resistance in glucose use in the cells. $\gamma$is the rate of insulin resistance at the cell receptors in body converting of glucose to glycogen, γ_γ is the constant denoting the quantity of glucose used by the insulin, $\gamma$is the quantity of insulin in the body. $\gamma, \gamma \neq 0, 0 < \gamma < 1$ $\gamma\gamma\gamma$ $0 < \gamma < 1$ in the case of insulin resistance. The first term of (4.1) describes glucose production, the final term describes glucose cells conversion of glucose into glycogen and the second term represents the glucose uptake by body use due to insulin sensitivity.

For insulin dynamics, the equation of Topp et al. was adopted assuming the net insulin secretion has the pattern of sigmoidal function reaching half of its maximum at $\gamma = \gamma_{\frac{\gamma}{\gamma}}$ and function given as $\frac{\gamma^{\gamma}}{\gamma_{\gamma}\gamma\gamma^{\gamma}}$, γ is the mass of pancreatic γ - cells, while $\gamma_{\gamma}\gamma$is insulin clearance and γ_{γ} is insulin clearance rate. Hence, the insulin dynamics is given by equation (4.2).

On the γ-cells mass dynamics which depends on genetic predisposition to diabetes, the equation of γ-cells mass of Topp et al. (2000) was adopted to give equation (4.3), which is the same with Boutayeb et al. equation for $\gamma = 1$.

Dynamics of γ- cells mass is a product of polynomial on G and γ- cells mass, the second degree polynomial in γindicates that γ-cells mass decreases outside the second degree polynomial zeroes, and increases when the zeroes of the polynomial are two real roots.

4.2 Definition of Model Parameters

The model parameters and the associated values for an average healthy personaccording to American Diabetes Association (ADA), are summarized in table 4.1.

Table 4.1. Parameters for an average healthy person, Boutayeb et al. (2014)

Parameters.	Value	Units	Biological Interpretation
α_0		$\frac{\square}{\square \cdot \square}$	Glucose production rate by liver at basal G level
α_1	1.44	$\square^{-1}$	Glucose clearance rate independent of insulin
α_2	0.72	$\frac{\square}{\square \cdot \square}$	Insulin induced glucose uptake rate
α_3	43.2	$\frac{\square}{\square \cdot \square \cdot \square}$	ϐ-cells maximum insulin secretory rate
α_4	20000	$\frac{\square^2}{\square}$	Gives inflection point of sigmoidal function
α_5	432	$\square^{-1}$	Whole body insulin clearance rate
α_6	0.06	$\square^{-1}$	ϐ-cells natural death rate
α_7	$0.84\square^{-1}$	$\frac{\square}{\square \cdot \square}$	Determines ϐ-cells glucose tolerance rate
α_8	$0.24\square^{-1}$	$\frac{\square}{\square \cdot \square}$	Determines ϐ-cells glucose tolerance rate

Parameter assumptions used for the analysis of the model

r	0.3, 0.75, 0.9, 0.95	Insulin resistance rate on cells receptors for conversion of glucose to glycogen in the liver
w	0.2, 0.5, 0.84,0.9	Rate of resistance for glucose use in the cells
α_0	17.28	Coefficient of glucose production rate
Q	50;100	Glucose equivalence of food intake
K	0.5	Decay rate during glucose production
α_1	84	Fasting glucose level
α_2	5	Minimal insulin production at time of food intake
α_3	100	$\square$ − cells mass at the time of food intake

4.3 Model Solution

The numerical solution of the model was obtained using the parameters in table 2. The RungeKutta code in MATLAB was used to obtain the solution of the model which is graphically represented in figures 1-3 for glucose, insulin concentration and ϐ - cells mass in T2D.

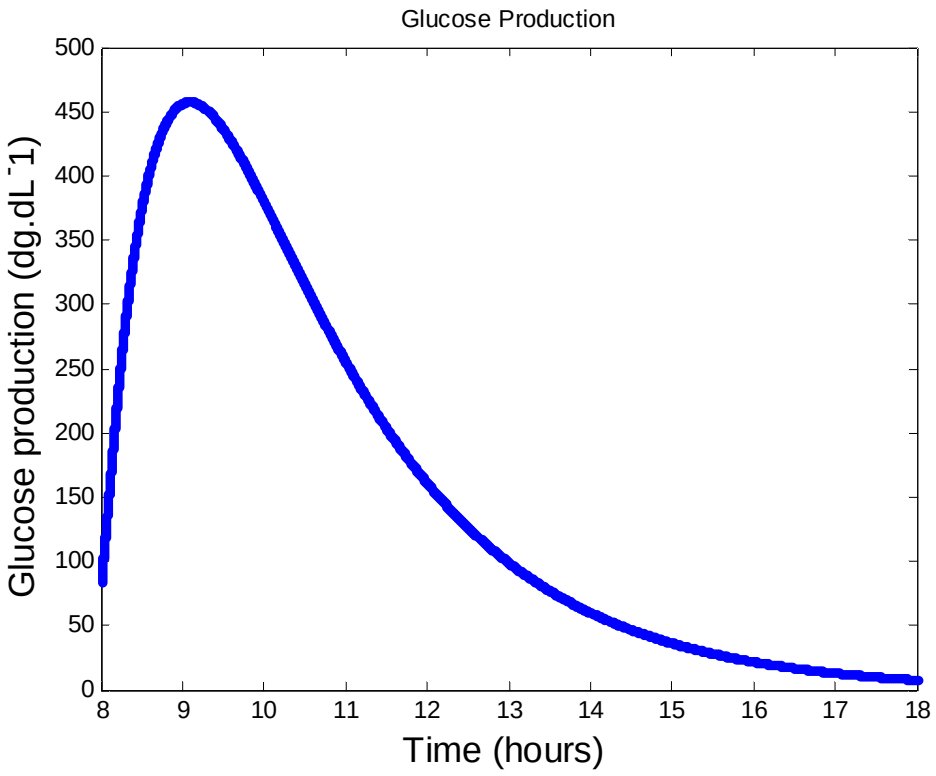

Figure 1. Graphical representation of glucose production, using MATLAB RungeKutta code.

The solution of the model as shown in figure 1 indicates that glucose production from food intake rises leading to high glucose concentration and falls over time from the time of the meal. This shows that glucose production from food is not constant rather a function of time that decays as the food digests. Consideringthe least fasting glucose level of a normal individual which is approximately84□. □□□, the figure indicates fall of glucose concentration below normal basal level after use of the produced glucose, which is attributed to low storage of glucose by the liver in the case ofhigh rate of insulin resistance in glucose conversion. This

shows that for the patient to avoid hypoglycaemia to maintain basal glucose level, another meal must be taken within the next five hours after the last meal.

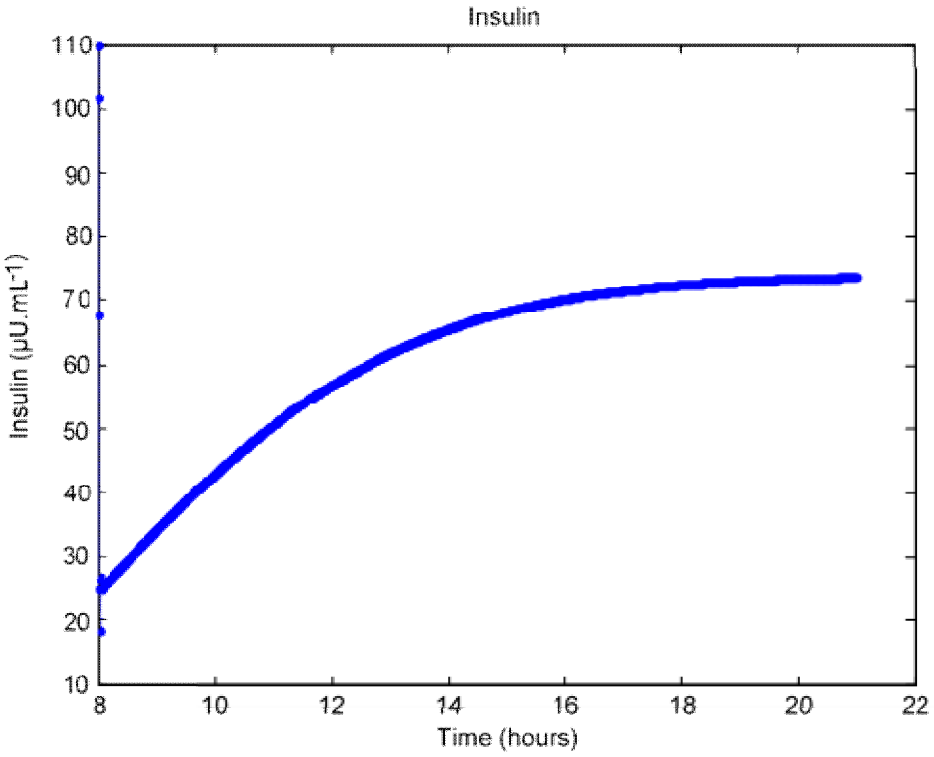

Figure 2.Graphical representation of insulin dynamics using MATLAB RungeKutta code.

Figure 2 shows that insulin risesfrom approximately 25 □□.□ □ □□ to 70 □□.□ □ □□in response to the producedglucose in the bloodwithin the time of food digestion, to take care ofrising blood plasma glucose level. Comparing this graph with figure 1, we can see that there was initial delay in the response of the ϐ-cells mass in the release of insulin which led to high level of glucose in the plasma. But as the insulin level rises, the glucose level starts to decrease which takes hours because of insulin resistance. This continues to rise until when the glucose level starts to fall below basal level then the insulin level starts to decline.This behaviour appears normal since there is high resistance in glucose conversion for storage, so there are not enough glycogen stored in the liver that can be reconverted toglucose to maintain glucose basal level.

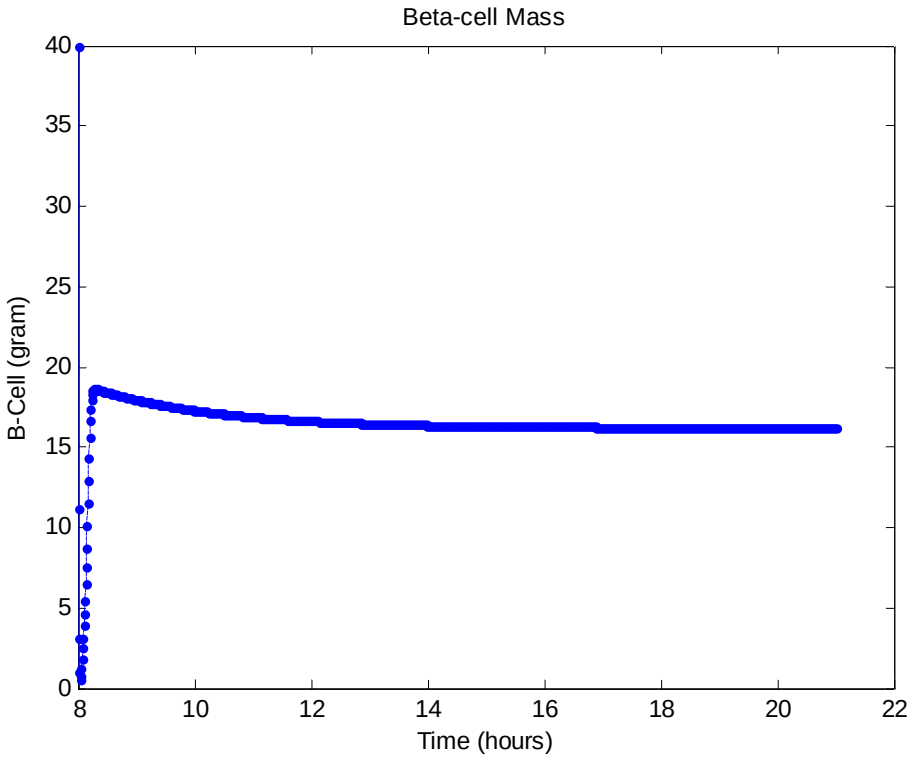

Figure 3.Graphical representation of β-cells dynamics, using MATLAB RungeKutta code.

Figure 3, shows that in response to glucose production and consequently rise in insulin level, the ɓ-cells mass declines from approximately19g to 17g. This implies that ɓ-cells mass depletes by 2gas they handle variations in glucose levels during production ofinsulin.

Comparing insulin release (fig. 2) with ɓ-cells mass level (fig. 3), the result obtainedshows that as the ɓ-cells mass changes, there is a corresponding reflation in the level of insulin released into the plasma and as such corresponding effects in the plasma glucose level even in the presence of the cell insulin resistance. Note that there is some level of initial usage and so, insulin level falls since there is no further rise in ɓ-cells mass production.

4.4 Equilibrium Analysis of the Model.

Equilibrium analysis of the model on glucose, insulin and ɓ ï cellsmass dynamics, indicates three pathways to development of type 2 diabetes with varying possible degrees of insulin resistance over time. The three pathways to development of T2D from equilibrium analysis

are denoted by β_1, β_2 and β_3. As shown on table 4.2, using parameters on table 4.1, at the varying degrees of insulin resistance over time.

Table 4.2. Equilibrium points at the varying degrees of insulin resistance over time

Time(t)	Pathways	$\beta_1, \beta_2, \beta_3$
t	$\beta_1, \beta_2, \beta_3$	$(\frac{\beta_1 \beta_2 e^{\beta_2(\beta_2 - \beta_3)}}{\beta_3(1-\beta_3)}, 0, 0)$
For Q = 100	***r = 0.75,***	***w = 0.5***
10:00am	$\beta_1, \beta_2, \beta_3$	(324.8, 0, 0)
10:00am	$\beta_1, \beta_2, \beta_3$	(24.33, 141.11, 490.6)
10:00am	$\beta_1, \beta_2, \beta_3$	(1.52, 231.2, 1990.11)
For Q = 50,	***r = 0.75,***	***w = 0.5***
12:00pm	$\beta_1, \beta_2, \beta_3$	(162.4, 0, 0)
12:00pm	$\beta_1, \beta_2, \beta_3$	(24.34, 22.69, 788.64)
12:00pm	$\beta_1, \beta_2, \beta_3$	(1.52, 422.1, 3632.52)

4.5 Stability Analysis of the Model

Using Jacobian method, the stability analysis of the model equilibrium points at the varying degrees of insulin resistance after two hours (10am) and four hours (12pm) after meal is summarized on table 3. Putting insulin resistance in glucose oxidization in cells and insulin resistance to glucose conversion w and r = 0.5 and 0.75 respectively, while meal time is considered to be 8:00am.

Table 4.3. Summary of stability analysis, using parameter values in table 2.

Time(t)	Pathways	□□□, □, □□	Stability
t	□□□, □, β□	$(\frac{□□□□(□□□□)}{□□(1-□)}, 0,0)$	Asymptotically Stable
For Q = 100	***r = 0.75,***	***w = 0.5***	
10:00am	□□□, □, β□	(324.8, 0, 0)	Asymptotically Stable
10:00am	□□□, □, β□	(24.33, 141.11, 490.6)	Unstable
10:00am	□□□, □, β□	(1.52, 231.2, 1990.11)	Asymptotically Stable
For Q = 50,	***r = 0.75,***	***w = 0.5***	
12:00pm	□□□, □, β□	(162.4, 0, 0)	Asymptotically Stable
12:00pm	□□□, □, β□	(24.34, 22.69, 788.64)	Unstable
12:00pm	□□□, □, β□	(1.52, 422.1, 3632.52)	Asymptotically Stable

Table 4.3 indicates that for the varying degrees of insulin resistance over time, □□ and □□are asymptotically stable while the □□isunstable.

4.6 Model Simulation with Varying Degrees of Insulin Resistance.

The model was simulated in MATLAB, using parameters in table 4.1in order to see how the varying degrees of insulin resistance w and r in (4.1) affect the model over time.

- **Simulation for impact of variations in insulin resistance at the cells receptors(r) for storage of glucose as glycogen, when resistance in body use w = 0.5 and 0.84**

Taking fasting glucose level, initial insulin and □ï cells mass to be84g.d□□,5□□. □ □□ □□□100g respectively at the time of meal.Figures 4, 5 and 6 indicatea rise in glucose concentration from food intake, initial rise and subsequent decline in insulin concentration as well as decline in the□ï cellsmass after meal. For the rate of insulin resistance in glucose conversion into glycogen; w = 0.5 and 0.84, variations over time in insulin resistance rate at the receptors for glucose storagehaslittle impact in glucose and

insulin concentration with no significant impact on ï cells massthroughout the digestion period taken time of meal to be 8:00am.

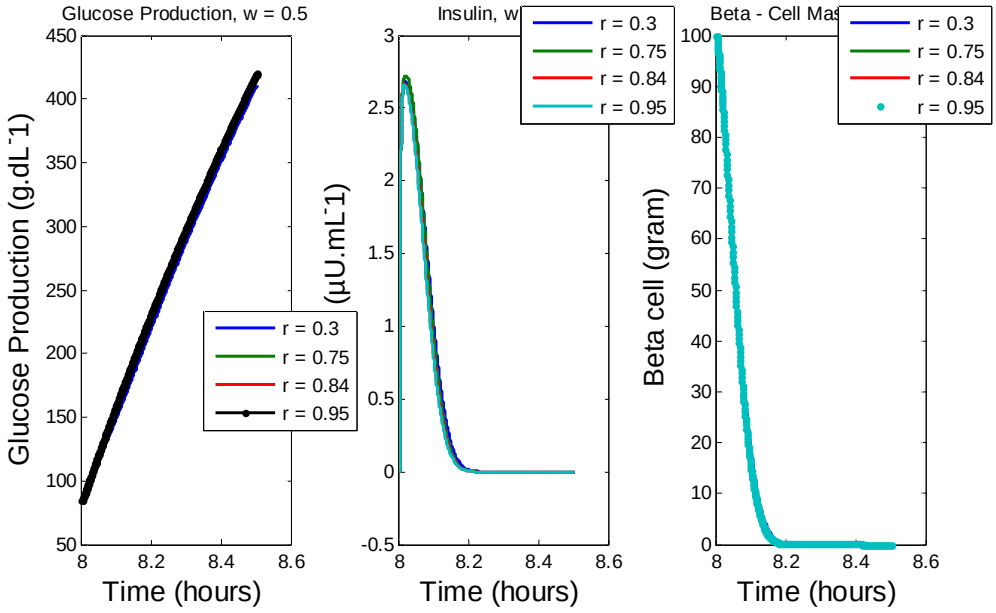

Figure 4. Results of simulation using parameter values in table 2 over r, for w = 0.5

In figure 4, When insulin resistance in body use of glucose (w) is 0.5, thevariations in insulin resistance in glucose conversion to glycogen (r) does not have significant impact on glucose, insulin concentration and ß ï cell mass of the patient over time, rather the resistances in insulin actions makes the patients plasma glucose level to rise and remain high over hours of food intake. Considering the initial rise and consequently fall in insulin level in less than 20 minutes from time of food intake while plasma glucose level remains high andß ï cells mass depletes.This is a case of development of T2D.

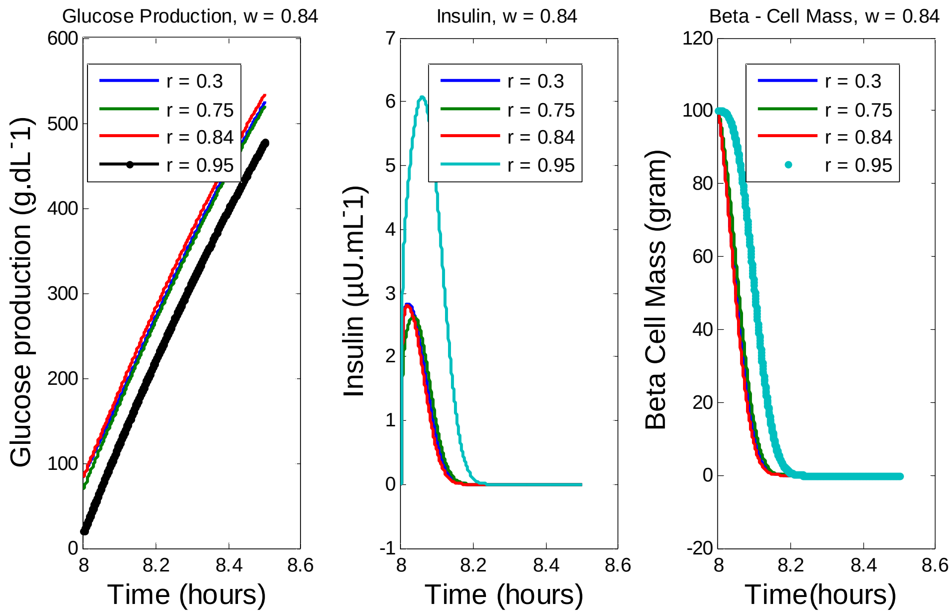

Figure 5. Results of simulation using parameter values in table 2 over r, *for w = 0.84*

Putting ▯▯(▯▯▯▯▯▯▯ ▯▯▯▯▯▯ ▯▯▯▯▯) = 84, as a result of insulin resistance in cell use of glucose (w = 0.84) andinsulin resistance in glucose conversion to glycogen(r) is 0.9 leading to little use and low storage of glucose, variations in insulin resistance in glucose conversion has significant impact on glucose, insulin production and the б ї cells mass over time. It indicates that when insulin resistance in glucose conversion to glycogen(r) is 0.9, there is a corresponding high rise in insulin level to handle the rise in glucose level, but there is a failure since there is high resistance both in storage and cell use of glucose, which keeps glucose concentration high and rise in insulin concentration which falls over time.

Similar to figure 4, as glucose concentration rises, insulin plasma level rises and falls over time without a corresponding fall in blood plasma glucose level after hours of food intake and б ї cells mass depletes.This implies that when the patientĝs insulin resistance in the body use of glucose is 0.5 and above, having high resistance to convert glucose to glycogen,this high rate of insulin resistance results to hyperglycaemia (high blood glucose concentrations) sequel to the inability of the patient to return the glucose level to normal in the presence of insulin resistance thereby the individual tends to develop T2D.

- **Simulation for impact of variations in insulin resistance in thecell use of glucose (w), when resistance in conversion to glycogen(r) = 0.3 and 0.75**

Taking the fasting glucose level, insulin and ïi cells mass to be84g.d, 5. , 100g respectively at the time of meal.

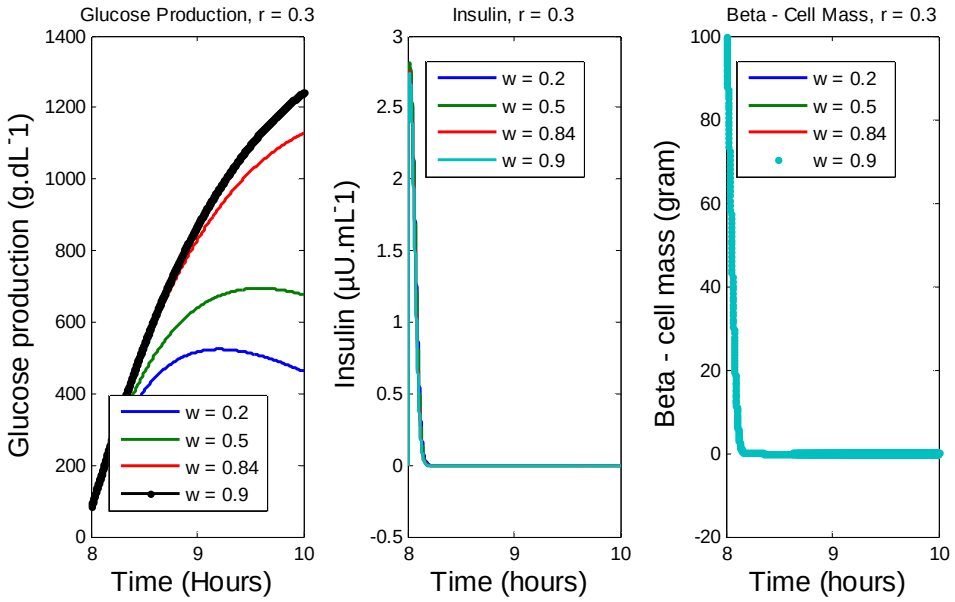

Figure 6. Results of simulation using parameter values in table 2 over w, for r = 0.3

The figure reveals that for insulin resistancein the cells receptors (r)= 0.3,glucose level reaches1300g.d when w = 0.9, above 1100g.dfor w = 0.84, approximately 700g.d for w = 0.5 with no significant impact on insulin and ïi cells mass. Glucose concentration rises and falls within 3 hours as glucose is been produced from food intake, there is also rise and fall in insulinproductionwithin few minutes from time of food intake to handle the variations in glucose production. However, following low conversion of glucose to glycogen, the individual suffers high glucose level for hours before returning to normalcy and further fall below normal glucose level which is attributed to low storage the major cause of weight loss and lack of energy in T2D in line with medical literature.(Oxford Concise Medical Dictionary, 2003).

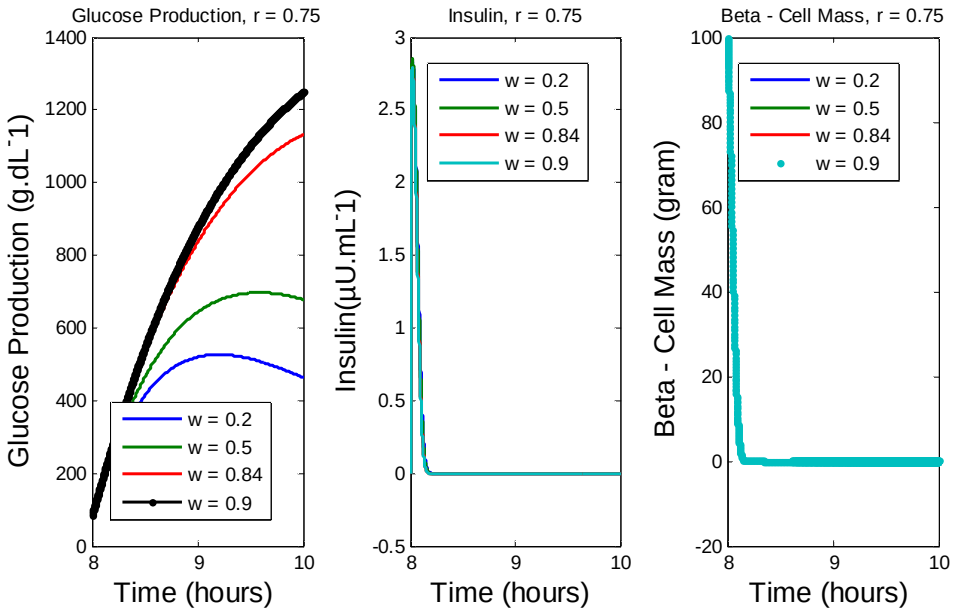

Figure 7. Results of simulation using parameter values in table 2 over w, for r = 0.75

For insulin resistance on the cells receptors (r) = 0.75, figure 7 shows that there is increase in glucose concentration within the first two hours from the time of meal which subsequently decreases after hours,glucose concentration is proportional to insulin resistance rate. Figures 6 and 7, having r = 0.3 and 0.75 shows that variations in insulin resistance in glucose conversion to glycogen has significant impact on glucose concentration in the blood, which has little or no impact on insulin concentration and ?ï cells mass over time.

In summary of the simulations, comparing figures 4, 5 and figures 6, 7; it suffices to saythat insulin resistance in cell use of glucose has more effects on the plasma glucose level of patient than insulin resistance in conversion of glucose for storage as glycogen. This is because figures 4 and 5 shows that high resistance to cell use of glucose in the presence of insulin resistance in glucose conversion makes the plasma glucose level to remain high, hence inability of the body to return glucose level to normal after few hours of food intake, which leads to T2D and equally low storage of glucose. While figures 6 and 7 indicates that with low resistance to the cell useof glucose and high resistance to glucose conversion to glycogen, the plasma glucose level falls after hours of meal intake.

CHAPTER FIVE

DISCUSSION AND RECOMMENDATIONS

5.1 Discussion of the Results

Mathematical model on glucose, insulin, and ϐ-cells mass dynamics considering insulin resistance as a major factor leading to development of type 2 diabetes, was presented in the form of a system of ordinary differential equations. The numerical solution using RungeKutta code in MATLAB was obtained graphically for the model behaviour. This shows rise in blood glucose level and further decline over time of glucose production below fasting glucose level from food intakewhich can be as a result of low conversion for storage in the liver. There isrise in insulin level because of insulin resistance and consequently, a slight fall in ϐ-cells mass to overcome insulin resistance. The equilibrium points and stability analysis over time under the varying rate of insulin resistance indicated three pathways to development of T2D of which two are asymptotically stable while one is unstable at different degrees of glucose production from food intake. Further the model simulation of the parameters reveals that insulin resistance, has a significant impact on glucose concentration in the body, where high rate of insulin resistance results in high blood glucose level leading to development of T2D and low storage of glucose.

The model developed which was an extension of Mbah (1998) model is similar to those of Topp et al. (2000), Hernandez et al. (2001) and Boutayeb et al. (2014). For glucose, insulin, and ϐ-cells mass dynamics. However, it differs significantly by its peculiarity in the case of type 2 diabetes, for taking care of insulin resistance at the cells receptors and reduction in the rate of sugar oxidation in the cells as a result of insulin resistance in T2D. Also, the realistic nature on glucose production from food intake which is never constant, rather decreases with time over the period of digestion, contrary to the assumption that glucose production is constant by some of the works reviewed.

The result of equilibrium analysis undervarying degrees of insulin resistance in type 2 diabetes gave three pathways to the development of T2D over time, in line with the three pathway equilibrium points of the results of the general diabetes models obtained by Topp et al. (2000)and genetically predisposition consideration in Boutayeb et al. (2014) model.However, the work deviated with Boutayeb et al. (2014) in area of risk factor to the development of diabetes, where Boutayeb et al. (2014) considered genetic predisposition.

Also, the simulation of the model over the varying degrees of insulin resistance, upholds Topp et al. (2000)submission that when plasma glucose concentration is above 250mg.□□□, it results in death rate of ϐ ï cells exceeding replication rates, which accounts for the depletions of ϐ ï cells mass.

The result also upholds the proposition of Samantha (2009) and Ibrahim et al. (2016) that lack of exercise in case of insulin resistance significantly increase risk of T2D.

5.2 Conclusion

We noticed a persistent increase in glucose concentration within the first two hours from the time of meal, which subsequently decreases after hours. This shows that glucose concentration is proportional to insulin resistance rates.

Furthermore, variations in insulin resistance in glucose conversion to glycogen has significant impact on glucose concentration in the blood.

5.3 Recommendations

In order to check the prevalence of T2D as a result of insulin resistance, physical exercise and diet control are good control measures for individuals having insulin resistance. This will help to cushion the effects of high glucose concentration in the body.

5.4 Suggestion for Further Studies

The following has been suggested for further studies;

- The extension of the model on glucose production, insulin and ϐ-cells mass dynamics in a case of insulin resistance to include Ŭ-cells mass dynamics.
- A mathematical model on body glucose concentration from glucose production, insulin and ϐ-cells mass dynamics in a case of individuals having insulin resistance and genetically predisposed to development of diabetes is to be carried out.

REFERENCE

Ackerman E., Gatewood L. C., Rosevear J. W., &Molnar G.D (1965). Model studiesof blood glucose regulation. *Bull Math Biophys* 1965, 27:21-24.

Adamu, I., Momoh, A. A &Tahir, A. (2016). Stability analysis of the mathematical model for the dynamics of diabetic population under the combined effects of birth rate and treatment. *International Journal of Science and Technology5(1)*: 26-35

Adewale, S. O., Ayeni, R. O. & Aj O. A. (2007) ñA new Generalized Mathematical model for the study of Diabetes Mellitusò *Research Journal of Applied Sciences 2(5)*: 629-632.

Aderine, S. L.(2014). Type 2 diabetes statistics and facts. Available on www.healthline.com.

American Diabetes Association (2015). Statistics About Diabetics: American Diabetes Association. Retrieved from www.diabetes.org/diabetes.../statistics

Barar, F.S.K. (2000). *Essential of Pharmacotherapeutics*. 3rd Ed. New Delhi: Chand and Company Ltd.

Boutayeb, A. & Chetouani, A. (2006). A critical review of mathematical models and data used in diabetology. *Biomedical Engineering Online 5(43),* doi:10.1186/1475-925-5-43.

Boutayeb, W., Lamlili, M. E. N., Boutayeb, A. & Derouich, M. (2014). Mathematical Modelling and Simulation of ϐ-Cell Mass, Insulin and Glucose Dynamics: Effect of Genetic Predisposition to Diabetics. *J. Biomedical Science and Engineering,* 7, 330-342. http://dx.doi.org/10.4236/jbise.2014.76035.

Centres for Disease Control and Prevention (2008). www.diabetes.niddk.nih.gov/dm/pubs/statistics

Chalishajar, D., Andrew, C. & Stanford, C. (2014). Mathematical analysis of insulin-glucose feedback system of diabetes. *International Journal of Engineering and Applied Sciences. 5(2) July.* Retrieved from www.eaas-journal.org.

Devlin, M.T. (2006). Text Book of Biochemistry with Clinical Correlations. 6th Ed. Wiley-Liss, New York. pp 861 - 882.

De Gaetano, A. D., Hardy, T., Beck, B., Abu-Raddad, E., Palumbo, P., Bue-Valleskey, J. & Porksen, N. (2008). Mathematical models of diabetes progression. *Am J Physiol Endocrinol Metab.* 295:E1462-E1479, doi:10.1152/ajpendo.90444.2008

Geraghty, E. (2008) *Delay differential equations in modeling insulin therapies for diabetes*(Masters Thesis, University of Portsmouth).

Gisela, W. (2005). Insulin and insulin resistance. *Clin Biochem 26*. Article posted on www.ncbi.nlm.nih.gov/.../PMS1204764/

Hans, S. I., Jonathan, S. & Paul Z.(2003). Guidelines for the detection of Diabetes Mellitus-Diagnostic criteria and rational for screening. *Clin Biochem 24(77-80).*

Hernandez, R. D., Lyles, D. J., Rubin, D. B., Voden, T. B. & Wirkus, S. A. (2001). A Model of ϐ-Cell Mass, Insulin, Glucose and Receptor Dynamics with Application to Diabetes. *An Academic Institute in the Mathematical, Computational and Modeling Sciences Center*. College of Liberal Arts and Sciences. Arizona State University.

Hellman, B., Gyife, E., Grapengiesser, E., Dansk, H. & Salehi, A. (2007). *"Insulin ossicilations clinically important rhythm: Antidiabetics should increase the pulsative component of the insulin release*. *Lakartidningen*. **104** (32-33): 2236-2239.

International Diabetes Federation (2003). IFD report 2003. http:// www.idf.org/home/index.cfm.

Jarald, E., Balakrishnan, S., J. & John, C.D. (2008). Diabetes and herbal medicines. *Iran Journal of Pharmacology and Therapeutics*. *7*: 97 - 106.

Kahn, S. E. (2003). The relative contribution of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia***46**: 3-19. Doi 10.1007/s00125-002-1009-0.

Kumawat, M., Pahwa, M.B., Gahlaut, V.S. & Singh, N. (2009). Status of antioxidant enzymes and lipid peroxidation in type 2 diabetes mellitus with microvascular complications. *The Open Endocrinology Journal.* **5**: 12 - 15.

Laurence, L.B., Lazo, J.S. & Parker, K.L. (2006). 'Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill. New York. pp:1124-1160.

Lin, C. (2011), Modeling glucose-insulin kinetics and development of type 2 diabetes in offspring of diabetic parents. (Doctoral dissertation, University of Iowa). Available on http://ir.uiowa.edu/etd/2741. Downloaded on 23rd March, 2016

Lokesh, D. & Amit, S.D. (2006). Diabetes mellitus its possible pharmacological evaluation techniques and naturothepay. *International Journal of GreenPharmacy*. *1* : 15 - 28.

Mbah, G. C. E. (1998). *A mathematical modeling for the variations in the plasma glucose and insulin levels over time in an insulin-dependent diabetic patient.*(Doctoral dissertation, University of Nigeria Nsukka).

Makroglou, A., Li, Jiaxu & Kuang, Y., (2005). Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: An overview. *56(2006)* 559-573. Doi:10.1016/j.apnum.2005.04.023.

Medline Plus Encyclopedia. (2006). Glucose Tolerance Test. www.nlm.nih.gov/medilineplus/ency/article/003466.htm

Metzger, B.E., Biastre, A. & Gardner, R.D. (2006). What I need to know about "Gestational Diabetesò. National Diabetes Informational Clearing Househttp://diabetes.niddk.ndi.gov/dm/pubs/gestional/.download:7/4/2011

Nelson, D.L. and Cox, M.M. (2005). *Lehninger Principle of Biochemistry*.(4th Ed). W.H. Freeman and Company, New York. pp: 909.

Oxford Concise Medical Dictionary (2003). Oxford University Press, Oxford. pp 330 - 331.

Quon, M. J. & Campfield L. A. (1991). A Mathematical Modeland Computer Simulation Study of Insulin Receptor Regulation. J. Theor. Biol. 150 pp 59-72.

Radziuk, J. (2014). Homeostastic model assessment and insulin sensitivity/resistance. Diabetes. 63: 1850-1854 doi:10.2337/db14-0116.

Ranjan, C. and Ramanujam, R. (2002). Diabetes and insulin resistance associated disorders: Disease and therapy. *Current Science*. **83**: 1533 - 1538.

Rohan, F. (2010), Modeling diabetes. Math 636. Retrieved from www.rohan.sdsu.edu/.../

Sandhya & Kumar, D. (2005). Mathematical model for glucose-insulin regulatory system of diabetes mellitus *2(1*) 39-46. Retrieved from http://www.irphouse.com.

Shiang, K. & Kandeel, F. (2010). A computational model of the human glucose-insulin regulatory system. *Journal of Biomedical Research, 24*(5): 347-364. Available on www.sciencedirect.com.

Smith, M. D., Maas, A., Garnsworthy, C., Owen, R., Coombes S., Pillay., S., Barrett, A. & Symonds, E. (2009). Mathematical modeling of glucose homeostasis and its relationship with energy balance and body fat. *17(4)* 632-639 doi:10:1038/oby.2008.604.

Topp, B., Promislow, K., De Vries, G., Miura, R., & Finegood, D. T. (2000). A Model of ß-Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes. *J. theor. Biol. (2000)***206,** 605-619 doi:10.1006/jtbi.2000.2150.

Torben, H. (2002). Genetics of type 2 diabetes. *Current Science*.**83**:1477-1482.

Wikipedia (2011a). *Diabetes*. http://en.wikipedia.org/wiki/diabetes.

Wikipedia(2011b).*DiabeticAngiopathy*. http://en.wikipedia.org/wiki/diabeticangiopathy.

Wikipedia (2011c). *Eucalyptus globulus*. http://en.wikipedia.org/wiki/eucalyptus globulus.

Wikipedia(2011d).*Hypercholesterolemia*. http://en.wikipedia.org/wiki/hypercholesterolemia.

Wikipedia (2011e). *Hyperglycemia*. http://en.wikipedia.org/wiki/hyperglycemia.

Wikipedia (2011f). *Hyperlipidemia*. http://en.wikipedia.org/wiki/hyperlipidemia.

Wikipedia (2011g). *Insulin*. http://en.wikipedia.org/wiki/insulin.

Wild, S., Roglic, G., Green, A., Sicree,R., King, H. (2004). Global Prevalence of Diabetes, Estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047ï 1053.

World health Organization (2003). The world health report 2003, Geneva. **Today's challenges**http://www.who.int/whr/2003/en.

World health Organization (WHO) Department of Noncommunicable Disease Surveillance Geneva (1999) ñDefinition, Diagnosis and Classification of Diabetes Mellitus and its Complicationsò WHO/NCD/NCS/99.2

Yasini, S., Naghibi-Sistani, B. M., Karimpour, A. (2009). Agent-based simulation for blood glucose control in diabetic patients. *International Journal of Applied Science, Engineering and Technology 5(1)*.

APPENDIX A
MATLAB SYNTAX FOR RUNGE KUTTA CODE USED TO SOLVE THE MODEL

```
% RungeKutta code to solve set of differential equations on glucose,
% insulin and B-cell dynamics
% dG/dt=a1*Q*exp(-k(t-t0)) -a2*(1-w)*G -a3*(1-r)*I*G %Glucose
% dI/dt=(((b1*beta*I)*G^2)/(b2 + G^2))- b3*I % Insulin
% constants
a1=17.28;
a2=1.44;
a3=0.72;
b1=43.2;
b2=20000;
b3=432;
r=0.3;0.5;0.84;
beta=30
w=0.2;
Q=100;
k=0.5;
c2=0.84*exp(-3);
c1=0.06;
c3=0.24*exp(-0.5);
t0=8.5
% define function handles
fG=@(t,I,G) a1*Q*exp(-k*(t-t0)) - a2*(1-w)*G-a3*(1-r)*I*G;
fI=@(t,I,G) (((b1*beta)*G^2)/(b2+G^2))-b3*I;
fbeta=@(t,I,G) (-c1 + c2*G -c3*G^2)*beta;
% initial conditions
t(1)=0;
G(1)=84;
I(1)=0;
beta(1)=40;
% step size
h=0.01;
tfinal=13;
N=ceil(tfinal/h);
% update Loop
fori=1:N
% update time
t(i+1)=t(i)+h;
% update G & I
    K1G=fG(t(i),G(i),I(i));
    K1I=fI(t(i),G(i),I(i));
    K1beta=fbeta(t(i),G(i),I(i));
    K2G=fG(t(i) + h/2,I(i) + h/2 * K1G,G(i)+h/2*K1I);
    K2I=fI(t(i) + h/2,I(i) + h/2 * K1I,G(i)+h/2*K1I);
    K2beta=fbeta(t(i) + h/2,beta(i) + h/2 * K1beta,G(i)+h/2*K1I);
    K3G=fG(t(i) + h/2,G(i) +h/2 * K2G,I(i)+h/2*K2I);
    K3I=fI(t(i)+ h/2, I(i) +h/2 * K2I,I(i)+h/2*K2I);
    K3beta=fbeta(t(i)+h/2, beta(i) + h/2 * K2beta,I(i)+h/2*K2I);
    K4G=fG(t(i)+h, G(i)+h * K3G,I(i)+h*K3I);
    K4I=fI(t(i)+h, I(i)+h * K3G,I(i)+h*K3I);
    K4beta=fI(t(i)+h, beta(i)+h * K3beta,I(i)+h*K3I);
G(i+1)=G(i)+h/6*(K1G + 2*K2G +2*K3G + K4G);
I(i+1)=I(i)+h/6*(K1I+ 2*K2I + 2*K3I + K4I);
beta(i+1)=beta(i)+h/6*(K1beta+ 2*K2beta + 2*K3beta + K4beta);
end
%plot solution
figure(1);
plot(t,G, '--.')
```

```
title('Glucose Production')
xlabel('Time (hours)')
ylabel('Glucose (g.dL^-1)')
figure(2);
plot(t,I, ':.')
title('Insulin')
xlabel('Time (hours)')
ylabel('Insulin (µU.mL^-1)')
figure(3);
plot(t,beta, '--.')
title('Beta-cell Mass')
xlabel('Time (hours)')
ylabel('B-Cell (gram)')
```

APPENDIX B
EQUILIBRIUM ANALYSIS

Equilibrium points

$\dot{G} = \alpha_0 Q e^{\alpha_1 (\alpha_2 t)} - \alpha_3 (1 - w) G - \alpha_4 (1 - r) I G = 0$ (a)

$\dot{I} = \frac{\alpha_5 \alpha_6 t}{(\alpha_7 \alpha_8 t)} - b_0 I = 0$ (b)

$\dot{\beta} = \beta(-c_0 + c_1 G - c_2 G^2) \beta = 0$ (c)

$\because c \Longrightarrow$ either $\beta = 0$ or $-c_0 + c_1 G - c_2 G^2 = 0$, case 1 and 2.

Case 1: $\beta = 0$

Putting $\beta = 0$ in (b) it follows that $I = 0$, $\Longrightarrow G = \frac{\alpha_5 \alpha_6 \alpha_7 \alpha_8 t}{\alpha_4 \alpha_7 \alpha_8 t}$.

$\therefore$ The equilibrium point is $(G, I, \beta) = \left(\frac{\alpha_0 Q^{\alpha_2 t}}{\alpha_3 (1 - w)}, 0, 0\right)$

Using Microsoft Mathematics 4.0 application, to solve for G when

Q = 50, w = 0.5, r = 0.75, t = 12, $\alpha_2 = 8$ and using parameters on table 4.1.

$(G, I, \beta) = (162.4, 0, 0)$

For Q=100, w = 0.5, r= 0.75, t = 10, $\alpha_2 = 8$,

$(G, I, \beta) = (324.8, 0, 0)$,

Case 2: $-c_0 + c_1 G - c_2 G^2 = 0$

$\Longrightarrow G = 24.33$ or 1.52 (d)

From (a), $G = \frac{\alpha_0 Q^{\alpha_2 t} \alpha_2 \alpha_3 \alpha_4 \alpha_7 \alpha_8 t}{\alpha_3 \alpha_4 \alpha_7 \alpha_8 t}$ (e)

From (b) $I = \frac{\alpha_5 \alpha_6 t}{\alpha_7 (\alpha_8 t)}$ (f)

Solving (d), (e) and (f) in Microsoft Mathematics 4.0, using parameter values in table 4.1.

For Q=100, w = 0.5, r= 0.75, t = 10, $\alpha_2 = 8$,the two equilibrium points are given as

(G, I, β) and (G, I, β)

$(G, I, \beta) = (24.33, 141.11, 490.6)$, $(G, I, \beta) = (1.52, 231.2, 1990.11)$.

For Q = 50, w = 0.5, r = 0.75, t = 12, $\alpha_2 = 8$.

[illegible] = (24.34, 22.69, 788.64), [illegible] = (1.52, 422.097, 3632.52).

APPENDIX C

STABILITY ANALYSIS OF THE MODEL

The Jacobian matrix of the system is given by:

$$J=\begin{pmatrix} \frac{\partial}{\partial G}\frac{dG}{dt} & \frac{\partial}{\partial I}\frac{dG}{dt} & \frac{\partial}{\partial \beta}\frac{dG}{dt} \\ \frac{\partial}{\partial G}\frac{dI}{dt} & \frac{\partial}{\partial I}\frac{dI}{dt} & \frac{\partial}{\partial \beta}\frac{dI}{dt} \\ \frac{\partial}{\partial G}\frac{d\beta}{dt} & \frac{\partial}{\partial I}\frac{d\beta}{dt} & \frac{\partial}{\partial \beta}\frac{d\beta}{dt} \end{pmatrix}$$

$$= \begin{pmatrix} -a_2(1-w)-a_3(1-r)I & -a_3(1-r)G & 0 \\ \frac{2b_1b_2\beta G}{(b_2+G^2)^2} & -b_3 & \frac{b_1G^2}{b_2+G^2} \\ (c_2-2c_3G)\beta & 0 & -c_1+c_2G-c_3G^2 \end{pmatrix}$$

For case 1, the trivial equilibrium point: $(G, I, \beta) = \left(\frac{b_2(a_2(1-w)+a_3(1-r)I)}{a_3(1-r)(b_1-b_2)}, 0, 0\right)$

$$J=\begin{pmatrix} -a_2(1-w) & -a_3(1-r)G & 0 \\ 0 & -b_3 & \frac{b_1G^2}{b_2+G^2} \\ 0 & 0 & -c_1+c_2G-c_3G^2 \end{pmatrix}, \text{ since } I=0$$

∴ Characteristic equation of the Jacobian matrix:

$$|J-\lambda I| = 0 \Rightarrow \begin{vmatrix} -a_2(1-w)-\lambda & -a_3(1-r)G & 0 \\ 0 & -b_3-\lambda & \frac{b_1G^2}{b_2+G^2} \\ 0 & 0 & -c_1+c_2G-c_3G^2-\lambda \end{vmatrix}$$

$$= -(\lambda + b_3)(\lambda + a_2w - a_2)(\lambda - c_2G^2 + c_2G - c_1) = 0$$

$$\therefore \lambda_1 = -b_3, \qquad \lambda_2 = a_2(w-1), \qquad \lambda_3 = -c_2G^2 + c_2G - c_1$$

Since $0 < r < 1$. (The rate of resistance in the cells), $G > 0, \forall G$ (the quantity of glucose produced cannot be negative); b_3, a_2, c_1, c_2 and c_3 from table 4.1. $\lambda_3 = -(c_2G^2 + c_1) + c_2G$, $(c_2G^2 + c_1) > c_2G, \forall G$

$$\Rightarrow \lambda_1, \lambda_2, \lambda_3 < 0$$

Hence, the model solution is asymptotically stable for $\square_{\square}\square\square, \square, \square\square = \square\frac{\square_{\square}\square\,\square^{\square\square}\,\square\square\square\square\,\square_{\square}\square}{\square_{\square}(\square\square\,\square)}, 0\; 0\square,$

$0 < \square < 1$

Solving the characteristic equation, using Microsoft Mathematics 4.0 and parameter values in table 4.1:

$$\square\lambda + b_{\square}\square\square - \lambda + \square_{\square}w - \square_{\square}\square\square - \lambda - c_{\square}G^{\square} + c_{\square}G - c_{\square}\square = 0$$

For Q = 50, w = 0.5, r = 0.75, t = 12, $\square_{\square} = 8, \square_{\square}\square\square, \square, \square\square =$ (162.4, 0, 0)

$\Longrightarrow \lambda_{\square} = -432,\ \lambda_{\square} = -0.72,\ \lambda_{\square} = -35.92.$

For Q=100, w = 0.5, r= 0.75, t = 10, $\square_{\square} = 8,\ \square_{\square}\square\square, \square, \square\square =$ (324.8, 0, 0),

$\Longrightarrow \lambda_{\square} = -432,\ \lambda_{\square} = -0.72,\ \lambda_{\square} = -157.08$ Since $\lambda < 0 \forall$ Reλ. Hence, the equilibrium point is asymptotically stable.

Case 2:

/J-∂I/ =

$$\det\begin{pmatrix} \square - \square_{\square}\square\square 1 - \square\,\square - \square_{\square}\square 1 - \square\square\square - \square & \square - \square_{\square}\square\square 1 - \square\square\square & 0 \\ \frac{\square\square_{\square}\square_{\square}\square\,\square}{\square\square_{\square}\square\,\square^{\square}\square^{\square}} & -\square_{\square} - \square & \frac{\square_{\square}\square^{\square}}{\square_{\square}\square\,\square^{\square}} \\ \square\square_{\square} - 2\square_{\square}\square\,\square\square & 0 & -\square_{\square} + \square_{\square}\square - \square_{\square}\square^{\square} - \square \end{pmatrix} = 0$$

Solving the characteristic equation, using MicrosoftMathematics 4.0 and parameter values in table 4.1. For Q=100, w = 0.5, r= 0.75, t = 10, $\square_{\square} = 8$,

$\square_{\square}\square\square, \square, \square\square =$ (24.33, 141.11, 490.6). $\lambda_{\square} \cong 0.0088,\ \lambda_{\square} \cong -431.4739,\ \lambda_{\square} \cong -26.65445,$ $\lambda_{\square} > 0$, the equilibrium point is unstable.

$\square_{\square}\square\square, \square, \square\square =$ (1.52, 231.2, 1990.11). $\lambda_{\square} \cong -0.001675,\ \lambda_{\square} \cong -432.0092,\ \lambda_{\square} \cong -42.3268.$ Since $\lambda < 0 \forall$ Reλ. Hence, the equilibrium point is asymptotically stable.

For Q = 50, w = 0.5, r = 0.75, t = 12, $\square_{\square} = 8$. $\square_{\square}\square\square, \square, \square\square =$ (24.34, 22.69, 788.64), $\lambda_{\square} \cong 0.0647,\ \lambda_{\square} \cong -431.1954,\ \lambda_{\square} \cong -5.6736.$ $\square_{\square}\square\square, \square, \square\square =$ (1.52, 422.1, 3632.52); $\lambda_{\square} \cong$

$-0.0002, \lambda_{\square} \cong -431.9816, \lambda_{\square} \cong -76.7164 \Longrightarrow \square_{\square}\square\square, \square, \square\square = \square 24.34, 22.69, 788.64\square$

is unstable since $\lambda_{\square} > 0. \square_{\square}\square\square, \square, \square\square =$ (1.52, 422.1, 3632.52)is asymptotically stable, since$\lambda < 0 \forall$ Reλ.

APPENDIX D

MATLAB SYNTAX FOR MODEL SIMULATION

The model code for variations r, for w=0.5

```
functiondZ = Alwell3aa(t,Z)
dZ = zeros(12,1);

a1 = 17.28;
a2 = 1.44;
a3 = 0.72;
b1 = 43.2;
b2 = 20000;
b3 = 432;
c1 = 0.06;
c2 = 0.0418;
c3 = 0.0016;
Q = 50;
K = 0.5;
t0 = 8.5;
w = 0.95;
r = 0.84;
t = 8;

% let Z(1) = G, Z(2) = I, Z(3) = B;

w1 = 0.5;
w2 = 0.5;
w3 = 0.5;
w4 = 0.5;

r1 = 0.3;   % estimation
r2 = 0.75;
r3 = 0.84;
r4 = 0.95;

dZ(1) = a1*Q*exp(-K*(t-t0))- a2*(1-w1)*Z(1)-a3*(1-r1)*Z(2)*Z(1);
dZ(2) = (b1*Z(3)*Z(1)^2)/(b2+Z(1)^2)-b3*Z(2);
dZ(3) = (-c1+c2*Z(1)-c3*Z(1)^2)*Z(3);

dZ(4) = a1*Q*exp(-K*(t-t0))- a2*(1-w2)*Z(4)-a3*(1-r2)*Z(5)*Z(4);
dZ(5) = (b1*Z(6)*Z(4)^2)/(b2+Z(4)^2)-b3*Z(5);
dZ(6) = (-c1+c2*Z(4)-c3*Z(4)^2)*Z(6);

dZ(7) = a1*Q*exp(-K*(t-t0))- a2*(1-w3)*Z(7)-a3*(1-r3)*Z(8)*Z(7);
dZ(8) = (b1*Z(9)*Z(1)^2)/(b2+Z(7)^2)-b3*Z(8);
dZ(9) = (-c1+c2*Z(7)-c3*Z(7)^2)*Z(9);

dZ(10) = a1*Q*exp(-K*(t-t0))- a2*(1-w4)*Z(10)-a3*(1-r4)*Z(11)*Z(10);
dZ(11) = (b1*Z(12)*Z(1)^2)/(b2+Z(10)^2)-b3*Z(11);
dZ(12) = (-c1+c2*Z(10)-c3*Z(10)^2)*Z(12);
```

```
%Alwell3bb
options = odeset('RelTol',1e-4,'AbsTol',[1e-9 1e-9 1e-91e-91e-91e-91e-91e-
91e-91e-91e-9 1e-9]);

[T,Y] = ode45(@Alwell3aa, [8 8.5],[84 0 600 84 0 100 840 100 840
100],options);

%plot
figure(4)
subplot(1,3,1)
plot( T,Y(:,1),  T,Y(:,4),'--', T,Y(:,7),':', T,Y(:,10),'.-
.k','MarkerSize',5, 'LineWidth',1.5)
xlabel('Time (hours) ', 'FontSize', 14)
ylabel(' Glucose Production (g.dL^-1)', 'FontSize', 14)
title('Glucose Production, w = 0.5')
legend('r = 0.3', 'r = 0.75', 'r = 0.84', 'r = 0.95', 'Location','Best');

subplot(1,3,2)
plot( T,Y(:,2),  T,Y(:,5),'--', T,Y(:,8),':',  T,Y(:,11),'MarkerSize',5,
'LineWidth',1.5)
xlabel('Time (hours) ', 'FontSize', 14)
ylabel(' Insulin (µU.mL^-1)', 'FontSize', 14)
title('Insulin, w = 0.5')
legend('r = 0.3', 'r = 0.75', 'r = 0.84', 'r = 0.95', 'Location','Best');

subplot(1,3,3)
plot( T,Y(:,3),  T,Y(:,6),'--', T,Y(:,9),':',
T,Y(:,12),'.','MarkerSize',5, 'LineWidth',1.5)
xlabel('Time (hours) ', 'FontSize', 14)
ylabel(' Beta cell (gramme)', 'FontSize', 14)
title('Beta - Cell Mass, w = 0.5')
legend('r = 0.3', 'r = 0.75', 'r = 0.84', 'r = 0.95', 'Location','Best');
```

The model code for variations w, for r = 0.3

```
functiondZ = Alwell2aa(t,Z)
dZ = zeros(12,1);

a1 = 17.28;
a2 = 1.44;
a3 = 0.72;
b1 = 43.2;
b2 = 20000;
b3 = 432;
c1 = 0.06;
c2 = 0.0418;
c3 = 0.0016;
Q = 50;
K = 0.5;
t0 = 8.5;

% let Z(1) = G, Z(2) = I, Z(3) = B;

r1 = 0.3;
r2 = 0.3;
r3 = 0.3;
r4 = 0.3;

w1 = 0.2; % estimation
w2 = 0.5;
w3 = 0.84;
w4 = 0.9;

dZ(1) = a1*Q*exp(-K*(t-t0))- a2*(1-w1)*Z(1)-a3*(1-r1)*Z(2)*Z(1);
dZ(2) = (b1*Z(3)*Z(1)^2)/(b2+Z(1)^2)-b3*Z(2);
dZ(3) = (-c1+c2*Z(1)-c3*Z(1)^2)*Z(3);

dZ(4) = a1*Q*exp(-K*(t-t0))- a2*(1-w2)*Z(4)-a3*(1-r2)*Z(5)*Z(4);
dZ(5) = (b1*Z(6)*Z(4)^2)/(b2+Z(4)^2)-b3*Z(5);
dZ(6) = (-c1+c2*Z(4)-c3*Z(4)^2)*Z(6);

dZ(7) = a1*Q*exp(-K*(t-t0))- a2*(1-w3)*Z(7)-a3*(1-r3)*Z(8)*Z(7);
dZ(8) = (b1*Z(9)*Z(1)^2)/(b2+Z(7)^2)-b3*Z(8);
dZ(9) = (-c1+c2*Z(7)-c3*Z(7)^2)*Z(9);

dZ(10) = a1*Q*exp(-K*(t-t0))- a2*(1-w4)*Z(10)-a3*(1-r4)*Z(11)*Z(10);
dZ(11) = (b1*Z(12)*Z(1)^2)/(b2+Z(10)^2)-b3*Z(11);
dZ(12) = (-c1+c2*Z(10)-c3*Z(10)^2)*Z(12);
```

```
%Alwell2bb
options = odeset('RelTol',1e-4,'AbsTol',[1e-9 1e-9 1e-91e-91e-91e-91e-91e-
91e-91e-91e-9 1e-9]);

[T,Y] = ode45(@Alwell2aa, [84 0 600 84 0 100 84 0 100 84 0 100],options);

%plot
figure(6)
subplot(1,3,1)
plot( T,Y(:,1),  T,Y(:,4),'--', T,Y(:,7),':', T,Y(:,10),'.-
.k','MarkerSize',5, 'LineWidth',1.5)
xlabel('Time (hours) ', 'FontSize', 14)
ylabel(' Glucose production (g.dL^-1)', 'FontSize', 14)
title('Glucose Production, r = 0.3')
legend('w = 0.2', 'w = 0.5', 'w = 0.84', 'w = 0.9', 'Location','Best');

subplot(1,3,2)
plot( T,Y(:,2),  T,Y(:,5),'--', T,Y(:,8),':',  T,Y(:,11),'MarkerSize',5,
'LineWidth',1.5)
xlabel('Time (hours) ', 'FontSize', 14)
ylabel(' Insulin (µU.mL^-1)', 'FontSize', 14)
title('Insulin, r = 0.3')
legend('w = 0.2', 'w = 0.5', 'w = 0.84', 'w = 0.9', 'Location','Best');

subplot(1,3,3)
plot( T,Y(:,3),  T,Y(:,6),'--', T,Y(:,9),':',
T,Y(:,12),'.','MarkerSize',5, 'LineWidth',1.5)
xlabel('Time (hours) ', 'FontSize', 14)
ylabel(' Beta - cell mass', 'FontSize', 14)
title('Beta - Cell Mass, r = 0.3')
legend('w = 0.2', 'w = 0.5', 'w = 0.84', 'w = 0.9', 'Location','Best');
```