The book has discussed Stochastic Models to understand the processes of metabolism of glucose and insulin more specific to diabetic patients. This study mainly focuses on assessment of glucose/insulin levels through stochastic modeling approach for Type2-diabetes mellitus patients. It also consists of the mechanism of measuring the dynamics of glucose and insulin levels along with the factors like intake of diet, usage of external insulin and physical activity. Measuring the levels of both glucose/insulin through Markov point process is the core area of study. Further, the study has focused on the solving simultaneous differential equations and achieving the approximate values through numerical methods as the model has limitations in getting classical and abstract solutions. The study has many other focusing issues like consumption patterns of average number of glucose molecules and insulin granules in the blood stream. This study has a good scope of usage in health care industry by developing the suitable interface by converting all these mathematical models as user friendly devices by developing relevant computer software and data visualizations methodologies.

Dr. Kiran Kumar Paidipati, presently UGC-Post Doctoral Fellow in the Dept. of Statistics, Pondicherry University, India. He has published 6 research articles in national/International journals, He qualified an eligibility test APSET for Assistant Professor/LS. His research areas are Stochastic Modeling, Operations Research and Bio-statistics.

978-613-4-93088-8

Stochastic Models for Type 2 Diabetes

Kiran Kumar Paidipati
Tirupathi Rao Padi

Studies on Some Stochastic Models for Type-2 Diabetes Mellitus

Diabetes Modeling

LAP LAMBERT Academic Publishing

Paidipati, Padi

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Imprint

Cover image: www.ingimage.com

Publisher:
LAP LAMBERT Academic Publishing
is a trademark of
International Book Market Service Ltd., member of OmniScriptum Publishing Group
17 Meldrum Street, Beau Bassin 71504, Mauritius

Printed at: see last page
ISBN: 978-613-4-93088-8

Preface

In this study the authors have developed some stochastic models for Type-2 Diabetes Mellitus for measuring the parameters like Glucose and insulin levels. Diabetes is a metabolic disorder of the glucose-insulin regulatory system, in which the pancreas either release of insufficient insulin or insulin resistance. The intensity of diabetes is directly linked with function of endocrinology system, which regulates the levels of glucose and insulin in the blood plasma through glucose metabolism. Frequent and manual measuring procedures of glucose/insulin levels have practical limitations due to non-availability of suitable apparatus and lack of standard operating procedures (SOPs). Continuous monitoring of glucose/insulin levels at differentiable time points is not feasible manually. Hence, Mathematical biology, statistical modeling of metabolism processes have attracted the attention of many researchers in the current period. Several models based on the distributions of glucose and insulin have been developed with an objective of understanding the diabetes mechanism and its management. Estimation of glucose and insulin parameters through mathematical modeling is suitable option to address the problem.

This study is intended to understand the processes behind generation/utilization of glucose and secretion/ dispose of insulin along with regulating mechanism and metabolism processes of endocrine and digestive systems. Multi organ functioning of the body will influence the regulating system of metabolism by

keeping the glucose/insulin levels in normal range. Maintenance of glucose levels in threshold limits through insulin consumption is stochastic. It is assumed that arrivals and clearance processes of insulin as well as glucose are purely random in nature. Understanding the physiological mechanism of type-2 diabetes by stochastic modeling is the primary objective of this study. This study has considered the Markov Point Processes for measuring the levels of both glucose/insulin. The prime focus of the study is on maintaining the threshold range of glucose/insulin levels among T2DM patients through the 3-fold treatment mechanism of less carbohydrate diet intake, Induce of insulin through external sources and physical activity.

Book is organized in five chapters. The initial chapter includes introduction, basic information on glucose metabolism, and relevance of mathematical modeling in glucose/insulin regulatory system, literature review, motivation of the study. Chapter-2 deals with bivariate stochastic model of glucose/insulin regulatory system among T2DM patients with the notions of Poisson processes, differential equations, statistical measures on the developed model and sensitivity analysis by analytical methods, etc. Chapter-3 is on bivariate stochastic model with homogeneous birth-and-death processes of glucose/insulin regulatory system in healthy or normal individuals. Statistical measures are derived and sensitivity analysis carried with numerical methods on the developed model. Chapter-4 contains bivariate stochastic model with homogeneous birth-and-death processes of glucose/insulin regulatory system among T2DM

patients with the intervention of insulin. Statistical measures are derived and sensitivity analysis is carried out through numerical methods as in the case of previous chapter. Chapter-5 comprises bivariate stochastic model with homogeneous birth and death processes of diabetes management through the simultaneous intervention of physical activity and induced insulin from external sources. Statistical measures are obtained through numerical methods and the related sensitivity analysis is carried out with simulated numerical data sets.

The models of this study concentrated in controlling mechanism of glucose and insulin levels in normal and diabetic patients. The complexity of the model and its application in real time data with cumbersome data sets demands the speedy and accurate calculations, which in turn increase the demand of computer technologists to prepare suitable software. Development of user interface with suitable computer software will generate more effective decision support systems for the diabetes health care management.

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STUDIES ON

SOME STOCHASTIC MODELS FOR TYPE-2 DIABETES MELLITUS

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Tirupathi Rao Padi

Dedication of first author's family

This Book is dedicated to Loveliest being on earth, who sacrificed herself for me, my lovely wife,

Karumanchi Hemalatha

and to my gorgeous angel, beloved daughter

Linisha Paidipati

Preface

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Acronyms	
WHO	World Health Organization
IDF	International Diabetes Federation
SOPs	Standard Operating Procedures
IRI	Immuno-reactive Insulin concentration
IVGTT	Intravenous Glucose Tolerance Test
OGTT	Oral Glucose Tolerance Test
IDDM	Insulin Dependent Diabetes Mellitus
MM	Minimal Model
2CMM	Two-Compartment Minimal Model
HMM	Hot Minimal Model
RM	Reference Model
MGTT	Meal Glucose Tolerance Test
OMM	Oral Minimal Model
HOMA	Homeostatic Model Assessment
NIDDM	Non-Insulin Dependent Diabetes Mellitus
EHC	Euglycemic Hyperinsulinemic Clamp
T2DM	Type-2 Diabetes Mellitus
mg/dl	Milligrams/deciliter
μU/ml	Micro Units/milliliter

Chapter-1

Mathematical Modeling on Glucose Metabolism

Introduction

Diabetes is a metabolic disorder of the glucose-insulin regulatory system, in which the pancreas may either release insufficient insulin or it may insulin resistant. The intensity of diabetes is directly linked with the functioning of endocrinology system which regulates the levels of glucose and insulin in the blood plasma through glucose metabolism and digestive systems. According to the WHO, diabetes will be the 7^{th} cause of death by 2030. International Diabetes Federation (IDF 2015) estimated nearly about 415 million adults with disturbed mechanism of glucose and insulin metabolic systems. Among diabetes patients, 318 million have high risk of developing disease in the future. The indicators on severity of the disease have attracted many researchers to study the mechanism of glucose-insulin system through modeling. The basic idea behind the study is to transform a process into a set of mathematical equations to estimate the parameters which are influenced in rising glucose levels in blood plasma. Main objective of this study is focused on developing the models of glucose and insulin levels in a stochastic environment with healthy diet, proper medications and physical activity.

Glucose metabolism is the main source of getting energy to living cells. Normal and healthy human body has proper metabolism where the level of glucose shall be in the tight range of 70 to 110 mg/dl in the blood plasma. The endocrine system is playing a vital role in conversion of glucose into energy, which is normally referred as glucose metabolism. The mechanism of synchronized endocrine and digestive systems is to maintain the plasma glucose levels in the above mentioned normal range. If the glucose levels of plasma in fasting is more than 110 mg/dl then the problem is called hyperglycemia where as if the glucose levels of plasma in fasting is less than 70 mg/dl then the problem is referred as hypoglycemia. The person who is in either state is considered to be diabetic. Insulin is playing an important role in glucose absorption to tissues in muscles. This is an enzyme that facilitates the glucose molecule to enter in to interiors of a living cell in any tissue. It is cleared that the role of insulin is to orderly maintenance of glucose levels in the blood plasma. Some organs are having the cells of nature that they require insulin to get the glucose

through infusion technique. However, the living cells in some organs of the body may make use of glucose without involvement of insulin.

Glucose transporters are of two types, namely insulin independent and insulin dependent. Except brain and genital organs, the cells in all the other organs of the body require insulin to make use of glucose for getting energy to the cell. Among the healthy individuals, the minimum needed quantity of insulin will be produced by pancreas for glucose metabolism. However, insulin secretion depends on mass of beta cells in pancreas. The inferior functioning of pancreas or low quantum of insulin secretion are influenced by the factors like increased age, genetic history of diabetes, Sullen and sedentary life styles of an individual et.. Low levels of insulin in blood plasma may leads to not only causes to accumulation of glucose levels in the plasma but also further leads to many health complications.

Accumulation or consumption of glucose in blood stream is due to either adding or burning of calories. Food intake will increase the glucose whereas it is decreased through its consumption by physical activity of the body. Conversion of glucose into energy depends on the availability and consumption of insulin. Usually the source of insulin in the body will be either due to either after it is being secreted by pancreas or by means of inducing to blood through external sources. The endocrine system in coordination with digestive system and the process of glucose metabolism will regulate the levels of insulin. They are based on the requirement of blood glucose for various accounts of energy release. Failure of the above system's function results in imbalance of glucose and insulin, which is observed among the diabetic patients, particularly in Type-2 diabetes.

It is assumed that arrivals and clearance processes of glucose/insulin are random. Multi organ functioning of the body will influence the regulating system in keeping the glucose/insulin levels in normal range. Maintenance of glucose levels in threshold limits through insulin consumption is stochastic. Frequent and manual measuring procedures of glucose/insulin levels have practical limitations due to non-availability of suitable apparatus and lack of standard operating procedures (SOPs). Unlike the measurement of heartbeat, blood pressure, etc., continuous monitoring of glucose/insulin levels at differentiable time points is not feasible. Hence, estimation technique through mathematical modeling is suitable option to address the problem. These requirements have attracted the attention of researchers in the areas of mathematical biology, stochastic modeling and computational diabetes. Much

emphasis was given on distribution models for glucose/insulin through classical approaches of Mathematical and stochastic models.

This study intends to understand the processes behind generation/utilization of glucose and secretion/disposal of insulin through blood. This study mainly focuses on glucose/insulin levels of Type-2 diabetes mellitus with proper diet, external insulin and physical activity. Understanding the physiological mechanism of type-2 diabetes by stochastic modeling is the core objective of this study. Markov point processes are adopted for measuring the levels of both glucose/insulin.

Reported Research Studies on Diabetes

There is much emphasis on mathematical modeling of type-2 diabetes mellitus for measuring the glucose and insulin levels. The reported research literature is classified in to four categories as mathematical models on progression, diagnosis, control and complications. This study has given focus on the mathematical models of diagnosis and control of type-2 diabetes.

Mathematical Models on Diabetes Diagnosis

Bolie(1961) has pioneered the works of mathematical modeling on physiological coefficients of glucose and insulin tolerance curves by servomechanism theory. He proposed the methods for studying the coefficients of steady state characteristics of specific organs like liver, pancreas and peripheral tissues; transient state characteristics of normal animal tissues. The necessary differential equations were simulated by an electronic analogue computer to compare the relationship between theoretical and experimental results.

Ackerman et al. (1964) developed a mathematical model for normal and abnormal conditions of diabetes by curve fitting to the cases by glucose tolerance test. The model deals with parameters of different types of curves in terms of physiological variables such as glucose removal and insulin release. The mean glucose concentration curves in the blood were carried out by least square method using an IBM 1620 computer. Ceresa et al. (1968) developed a two-compartment model on glucose and insulin regulatory system with a negative feedback used to study the mechanism of glucose/insulin for normal and diabetes patients by a computer based algorithm. Norwich (1969) has given an appeal of hepatic glucose production in single and two-compartmental models with the assumptions of plasma IRI and

glucose curves by estimating the rate of constants of theoretical functions in IVGTT's. Segre et al. (1973) developed a two-compartment model applied to normal, diabetes and obese patients to measure glucose load to insulin response for diabetic condition and glucose response to insulin in obese subjects. Toffolo et al. (1980) proposed a series of minimal models for precise estimation of insulin delivery and clearance dynamics during IVGTT.

Bergman et al.(1979, 1981, 1985, 1989)developed set of mathematical models on glucose disappearance to assess insulin sensitivity by considering time course of insulin as input; production and uptake of glucose as the output of physiological system. Minimal model for pancreas β-cell responsiveness and insulin sensitivity was developed to measure glucose kinetics during IVGTT. Further, they developed minimal models of glucose utilization and insulin kinetics with inclusion of parameters like ability of glucose production and independent changes in insulin to accelerate glucose uptake and suppress endogenous output (glucose effectiveness). They have provided complete review on assessment of insulin sensitivity through OGTT, open and close loop systems, insulin secretion test, glucose clamp studies and minimal models.

Cobelli et al. (1984, 1985, 1986, 1998, 1999, 2009) proposed physiological three-compartment model of glucose kinetics which provides new insights of insulin control in glucose distribution and disposition. They compared compartmental models with non-compartmental models and suggested that compartmental models are well suited to overcome the structural errors of complex mechanism of diabetes. They developed optimal input design for scalar case, minimal model approach and closed loop situations of glucose disappearance with equi-energy or equi-dose inputs. The minimal model of glucose consumption for estimating the influence of insulin on glucose uptake is also developed. They examined the optimal input design on glucose input involving associated drug stimulus and a tracer labeled glucose inputs. They have also developed a modified minimal model for basal and dynamic insulin IVGTT's; and verified them with previous developed minimal models of glucose effectiveness with IDDM subjects. Monte Carlo simulation studies were used for studying glucose kinetics with various insulin response patterns on two-compartment models. They suggested that representation of glucose kinetics in single-compartment leads to overestimation of glucose and over-simplification of insulin secretion patterns. They have further developed a two-compartmental model to assess the

accuracy of glucose effectiveness and insulin sensitivity with glucose kinetics using Bayesian approach. They also reviewed the control strategies for development of artificial pancreas by understanding the existing models proposed in-vivo on glucose-insulin system; further they reviewed the role of biomedical engineering models in control of diabetes and provided strategies to the develop artificial pancreas. Toffolo and Cobelli (2002) developed a two-compartment minimal model (2CMM) for the effect of glucose disposal in insulin-independent individuals with stable labeled IVGTT.

Ta-Chen Ni et al. (1997) developed a two-compartment model for glucose effectiveness and insulin sensitivity by including insulin action on hepatic glucose production and uptake. Vicini et al. (1997, 1999) developed a two-compartment minimal model (2CMM) for assessing the glucose, insulin kinetics and plasma clearance rate. They proposed the unlabeled and labeled (cold and hot) minimal models for estimating the glucose effectiveness and insulin sensitivity of glucose-insulin regulating system. Further they developed physiological reference model (RM) with Monte Carlo Simulation based on considering the problem of glucose kinetics in a single compartment. They have given detailed explanation of relations of MM, HMM and RM with glucose effectiveness, clearance and insulin sensitivity and suggested RM was well suited compared with MM and HMM.

Matsuda and DeFreonzo(1999)developed and compared different models on insulin sensitivity indices from OGTT with euglycemic insulin clamp technique. Caumo et al. (2000) developed an approach of estimating insulin sensitivity during OGTT/ MGTT in normal individuals. Gaetano and Arino (2000) developed a dynamic model for glucose effectiveness and insulin sensitivity to study the glucose-insulin homeostasis process. Gaetano et al.(2008)developed a model for diabetes progression on compensation of insulin islet of the glucose-insulin regulatory system in healthy and diabetic individuals. Mari et al. (2001, 2002a, 2002b)proposed a model for glucose-insulin system on OGTT based insulin sensitivity index to forecast glucose disappearance in a glucose clamp. They further developed a mathematical model for assessing the β-cell function and its impact on insulin sensitivity by meal tolerance, oral glucose tolerance test (OGTT) and euglycemic insulin clamp technique; also developed a dynamic glucose control model with β-cell function on insulin secretion by meal test.

Dalla Man et al. (2002, 2004, 2005, 2007) presented an integral equation model for glucose kinetics of OGTT or a meal to estimate insulin sensitivity; and developed an oral minimal model (OMM) for estimating rates of glucose absorption and insulin sensitivity by tracer-to-trace technique. They developed a simulated quasi-model strategy for glucose-insulin system in diabetes after a meal applied to normal as well as type-2 diabetes patients. Zheng and Zhao(2005)proposed a modified minimal model describing insulin infusion rates in healthy and type-2 diabetes patients with four sets of published data. They have simulated optimized parameters for measuring the glucose and insulin levels using single-compartment from experimental data. Pillonetto et al. (2006) formulated insulin sensitivity index which incorporates the dynamics of insulin and its properties. This index shows control of insulin on glucose kinetics and observed better results when compared to minimal model and euglycemic hyperinsulinaemic clamp techniques.

Wallace et al. (2004) reviewed homeostatic model assessment (HOMA) methods for quantifying β-cell function and insulin resistance from basal glucose and insulin. Boutayeb and Chetouani (2006) reviewed mathematical models on different aspects of diabetes by ordinary and partial differential equations, integral equations, matrix analysis, optimal control theory and computer algorithms. Makroglou et al. (2006) presented an overview on mathematical models for glucose and insulin quantities of glucose-insulin regulatory system of diabetes patients in the form of different types of differential equations. Mitsis and Marmarelis(2007) developed models of dynamic behavior of insulin infusion on glucose concentration in human subjects. They compared minimal models (parametric) with Volterra models (non-parametric) by the results of computational and simulation studies on the quantitative descriptions of glucose and insulin. Montalvo et al. (2008) derived modified Bergman's model which includes the effects of glucose and insulin and meal disturbances in diabetes patients. Silber et al. (2009, 2010) developed an integrated model on glucose-insulin regulatory system with OGTT to assess the mechanism of anti-diabetic drugs and level of their effects on healthy and type-2 diabetes patients.

Chen et al. (2010) proposed a mathematical model to describe the glucose and insulin disparities with delay differential equations applied on normal and diabetic subjects. Jauslin et al. (2011) developed a simulated model consists of 24-hour glucose and insulin measurements following multiple meal tests in type-2 diabetes. Wu et al. (2011, 2013) proposed a two-compartmental model of glucose-insulin

regulatory system with two explicit delays in different organs and the oscillatory actions of the mechanism of glucose and insulin. They further developed a two-compartmental model for measuring the dynamics of glucose production and insulin administration in sub cutis for physiological mechanism of type-2 diabetes patients.

Mathematical Models on Diabetes Control:

Berger and Rodbard (1989) developed a simulated computer algorithm for glucose and insulin dynamics after intravenous dose of insulin. Fisher (1991) developed a mathematical model for dynamics of glucose and insulin interaction to control plasma glucose levels in diabetic individuals. Basing on mathematical optimization technique, a semi closed-loop algorithm was proposed for continuous insulin delivery to diabetic patients for assessing glucose levels. Shannon et al. (1994) formulated a compartmental model of pancreas, liver and plasma by utilizing the equi-molar production of insulin and C-peptide from the pancreas. They considered 235 patients of NIDDM based on fasting glucose concentration with different levels such as mild, moderate and severe respectively. In addition, the model successfully applied on 56 normal individuals with good fits using nonlinear and log-linear regression approaches. Drozdov and Khanina (1995) developed a mathematical model of ultradian oscillations to study the insulin secretion with time delays. Rao et al. (1997) reviewed mathematical models on beta-cell kinetics and gastro intestinal absorption for glucose in glucose-insulin feedback system. Freeland and Bonnecare(1999) developed an approach that predicts real-time input estimation for intravenous glucose concentration in blood plasma. Topp et al. (2000) developed a mathematical model on β-cell mass, insulin, and glucose dynamics, which consists of feedback systems (positive and negative) of β-cell mass and predicts the pathways for prolonged hyperglycemia. Hernandez et al. (2001) developed a model for glucose, insulin, β-cell mass and insulin receptor dynamics for glucose and insulin regulatory system of diabetes patients. They incorporated the dynamics of insulin receptors into an existing mathematical model by Topp et al. (2000) for precise estimation of parameters in the system.

Tolic et al. (2000) have formulated a model for insulin-glucose feedback regulation in human beings to assess the effects of an oscillatory supply of insulin compared to a constant supply. They suggested that the oscillatory supply was more efficient than the constant supply of insulin in lowering the blood glucose levels.

Nobel and Heeden (2000) developed an inventory model for finding lost demand and average inventory level using the Fourier transformations. Rao and Penrose (2000) developed a model for particle of biological individuals by Poisson point processes. Hovorka et al. (2002) proposed a model that describes the kinetics of glucose tracers and insulin in two and one compartmental structures to predict distribution, disposal of glucose and endogenous production with effects of insulin.

Li et al. (2001, 2006) developed a dynamical model on the interactions of glucose/insulin following the IVGTT with time delays. They have also developed a control model for explicit time delays and ultradian insulin secretor oscillations in glucose insulin regulatory mechanism. Nucci and Cobelli et al. (2000) reviewed models of insulin kinetics for glycemic control in the predictable therapy of insulin-dependent diabetes. Kansal(2004) reviewed mathematical and computational models for understanding the pathophysiological issues of type-2 diabetes mellitus and explored detailed strengths and limitations of the models developed during the past 25 years. Picchini et al.(2006)developed a Euglycemic Hyperinsulinemic Clamp (EHC) studies to determine insulin sensitivity with stochastic differential equations. They suggested that system noise should be considered in representing physiological assumptions of existing deterministic models.

Wang et al. (2007) developed delay differential equation model for simulated insulin administration in glucose-insulin regulatory system. Adewale et al. (2007) developed a mathematical model to monitor blood glucose levels which takes account glucose uptake and insulin injected as function of carbohydrate and protein intake at molecular weights in non-diabetes and suspected diabetes subjetcs. Islam et al. (2007) developed an algorithm that predicts insulin dosage for the glucose uptake after meal intake. Liu(2008) proposed mathematical control system of glucose-insulin regulatory mechanism which takes into account the dynamics of glucose, glycogen and its receptors to determine insulin sensitivity on glucose clearance and efficiency of insulin binding to its receptors. Kardar and Fallah (2008) developed a pharmacokinetic model for predicting insulin level, glucose level, glucose uptake and renal excretion. The simulated strategy of treatment was based on doses of regular insulin through an intravenous route 30 min prior to the each meal. Pedersen et al. (2008) presented a simulated model of insulin secretion patterns from the β-cells based on glucose concentration.

Li and Johnson (2009) reviewed the models on insulin analogues to simulate the insulin dynamics with insulin and closed-loop systems. Chew et al. (2009) developed Michaelis–Menten kinetic model combined with glucose regulation and insulin signaling pathways for understanding the metabolic disorders of type-2 diabetes. Stahl et al. (2009) presented a system identification and predictive control model for estimating the quantitative measures of glucose, insulin and glucose-insulin interaction. Chuedoung et al. (2009) developed a mathematical model for role of β-cells and time delays in glucose-insulin control mechanism. Krishnamurthy et al. (2009), simulated multiple priority generations in a queuing model to estimate highest priority of customer waiting time through Markovian arrival processes. Kagade and Bajaj (2009), developed a multi-objective problem to assign the number of jobs to number of machines by minimizing the cost and time. Amulya et al.(2010), assessed the concepts and attitudes of patients and their immediate family members about diabetes complications, diet, physical exercise, drug therapy and insulin usage. Udhayakumar et al. (2010) developed a simulated based algorithm for solving chance constrained fractional programming problem for any continuous distribution. Vahidi et al. (2011) developed a Particle filtering algorithm for estimating glucose/insulin levels for detecting dysfunction of organs such as pancreas, liver and adipose tissues for type-2 diabetes patients. Tirupathi Rao et al. (2011, 2012) developed a stochastic model for glucose levels in Type-2 DM patients and also derived the of optimal glucose control policies in the blood stream. A stochastic model on glucose and insulin regulatory system for management of Type-2 diabetes patients was developed by assuming the rates of arrival and consumption of glucose/insulin follows Poisson processes. Further a programming problem for optimal management of glucose/insulin in the blood stream was formulated.

Zakeri (2012) proposed a new feedback controller of artificial pancreas for regulating glucose levels in diabetic patients. Huang et al. (2012) proposed mathematical model that monitor the glucose levels by giving insulin injection for type-2 diabetes mellitus. Adamu et al. (2012) presented a model of glucose-insulin regulatory system with dieting and physical activity simultaneously for management of glucose homeostasis. Kumar et al. (2012) reviewed the impact of endogenous insulin production, insulin sensitivity and exogenous insulin administration on bone metabolism in patients with T2DM. Jose and Manoharan (2013) investigated structural properties of steady state characteristics of various discrete time queuing

models. Ajmera et al. (2013) provided global review on developed mathematical models on the mechanisms of glucose metabolism, diabetic state and its related difficulties for the past five decades and highlighted the research areas to focus for future. Ahmed et al. (2014), developed an approach to solve the bi-objective bottle-neck cost transportation problem. Kannan and Chandrasekharan (2015) developed a stochastic model for estimating expected time distributions for seroconversion of HIV transmission under alertness.

Studies on Physical Activity versus Diabetes:

Helmrich et al. (1991) recommended that physical activity will increase the energy expenditure for burning the calories and reduce the higher risk of NIDDM through an empirical study. Moy et al. (1993) have conducted another empirical study and suggested that the physical activity has beneficial effect of longevity in insulin-dependent Diabetes Mellitus. Laaksonen (2005) conducted a study with the subjects of male and females and observed that the increasing physical activity will reduce the high-risk of type-2 diabetes patients. Sigal et al. (2006)suggested that 150 minutes/week of moderate to vigorous physical exercise and diet with energy restriction will improve glycemic control and body weight in patients with diabetes. They recommended aerobic exercise amount and intensity to improve glycemic control, cardiovascular disease. And also suggested resistance exercise of 3 times/week for will maximize health benefits and reduce the risk of injuries. Araiza et al. (2006) recommended the walk 10000 steps per day have significant changes in the insulin sensitivity, glycemic control and cardiovascular risk in type-2 diabetes mellitus patients. Bjorgaas et al. (2008) investigated walking on pedometer will enhance the beneficial effects of physical activity in patients with type-2 diabetes mellitus.

Motivation and Focus of the Study

There is significant literature evidence pertaining to deterministic models such as minimal and compartmental models for understanding glucose/insulin regulatory system based on physiological assumptions related with diabetes. The variations in glucose/ insulin levels are influenced by many uncertain factors and they are vulnerable with respect to time. Keeping the complexity of manual measurements of glucose/insulin levels, there is a need of assessing the quantum of glucose/insulin in

plasma at a point of time through differential equations. Stochastic modeling is one such proper choice for Type-2 Diabetic patients to make effective assessment of glucose/insulin quantity levels. Development of differential equations for glucose/insulin is more in traditional approach with minimal models. Compartmentalization, multiple factors of converting food ingredients in to glucose, roles of pancreas and liver in regulating mechanism of glucose/ insulin, etc. have limitations on usage of traditional differential equations to get the fluctuations in infinitesimal interval of time Δt. In order to avoid these limitations, the approach of differential equations for assessing the dynamics of glucose/ insulin levels during time $(0, t)$ based on observations with the processes during $(t, t+\Delta t)$ is a suitable option. It requires the method of differential difference equations in order to get the ordinary differential equations. All the arrival/departure processes of glucose/insulin among diabetic patients are assumed to follow the Poisson distribution. Very few research works has been reported in the literature on the development of stochastic differential equations for glucose/ insulin dynamics with Poisson processes.

This study has focused on formulating differential equations through differential difference equations for glucose/insulin regulatory system. The notion of arrival and departure processes of glucose/insulin working with endocrinology system considered Poisson postulates. The principles of birth and death processes have considered for understanding the simultaneous arrival/consumption among glucose molecules and insulin granules. It is the most realistic approach of finding the levels of glucose/insulin in the plasma during a unit time by observing the process in infinitesimal time interval Δt, when compared the traditional approaches in development of differential equations. Measuring the statistical characteristics after solving the differential equations with analytical and numerical methods are the core objectives of the study. The necessity of developing suitable models and predicting the decision parameters in a stochastic environment has motivated the researcher to carry out this work.

Organization of Book

The book is organized in five chapters. The initial chapter includes introduction, basic information on glucose metabolism, relevance of mathematical modeling in glucose/insulin regulatory system, literature review, identified research gaps and motivation of the study. Chapter-2 deals with bivariate stochastic model of

glucose/insulin regulatory system among T2DM with the notion of Poisson processes, differential equations, statistical measures on the developed model and sensitivity analysis by analytical method. Bivariate Poisson processes have been considered for deriving differential difference equations with the said assumptions. The approach of probability generating function is used for getting the system of simultaneous linear differential equations. Statistical measures like expected number of glucose molecules and average number of insulin granules in blood plasma at a point of time 't' are derived from the system of developed linear differential equations. While deriving the first order moments, it is assumed that the second order moments are constant. Numerical illustrations are provided and the required sensitivity analysis is carried out.Chapter-3 is on bivariate stochastic model with homogeneous birth-and-death processes of glucose/insulin regulatory system in healthy or normal individuals. Statistical measures are derived, numerical illustrations and sensitivity analysis carried with numerical methods on the developed model. Chapter-4 contains bivariate stochastic model with homogeneous birth-and-death processes of glucose/insulin regulatory system among T2DM patients with the intervention of insulin. Statistical measures are derived and sensitivity analysis is carried out through numerical methods. Chapter-5 comprises bivariate stochastic model with homogeneous birth and death processes of diabetes management through second simultaneous intervention of physical activity in addition to induced insulin. Statistical measures are obtained through numerical methods and the related sensitivity analysis is carried out with simulated numerical data sets. Summary and scope for the future work was added in the end.

Chapter-2

Stochastic Model on Glucose & Insulin Levels in Diabetic Patients

Introduction

Regular monitoring of glucose and insulin levels in continuous and regular small intervals of times is the order of the day for proper assessment of diabetes severity. Obtaining the measurements of glucose and insulin levels in plasma through clinical methods has a significant drawback as frequent blood sample collection creates unwanted traumas. Exposing diabetic patients to vulnerable testing procedures or generic experimentations will have many other issues. Making uninterrupted blood sample collection and getting the parameters out of it is not suggestible in the case of T2DM patients due to many practical constraints. In order to achieve this objective, experimenter may choose the alternative modeling approaches such as of forecasting the wanted parameters by developing a suitable models. Mathematical modeling of glucose/insulin levels in T2DM patients is considered to be right choice for the said purpose. Addressing the biological issues of diabetes modeling through mathematical biology is one of the suitable options. Hence, formulation of mathematical models for studying the glucose-insulin regulatory system attracted the attention of researchers.

Much emphasis was given in the literature in usage of mathematical models for getting the parameters of glucose and insulin levels in blood plasma. Most of the literature is focused on the mathematical modeling of diabetes with minimal models, compartment models and simple differential equations approaches. However, there is little evidence in making use of differential difference equations approach to formulate the differential equations for glucose and insulin dynamics. In order to get the generalized phenomena of glucose and insulin levels in a period of time (0,t) by studying their dynamics in a small and infinitesimal period of time Δt is the new approach. This approach is an open challenge and no research work has been reported on the said domain.

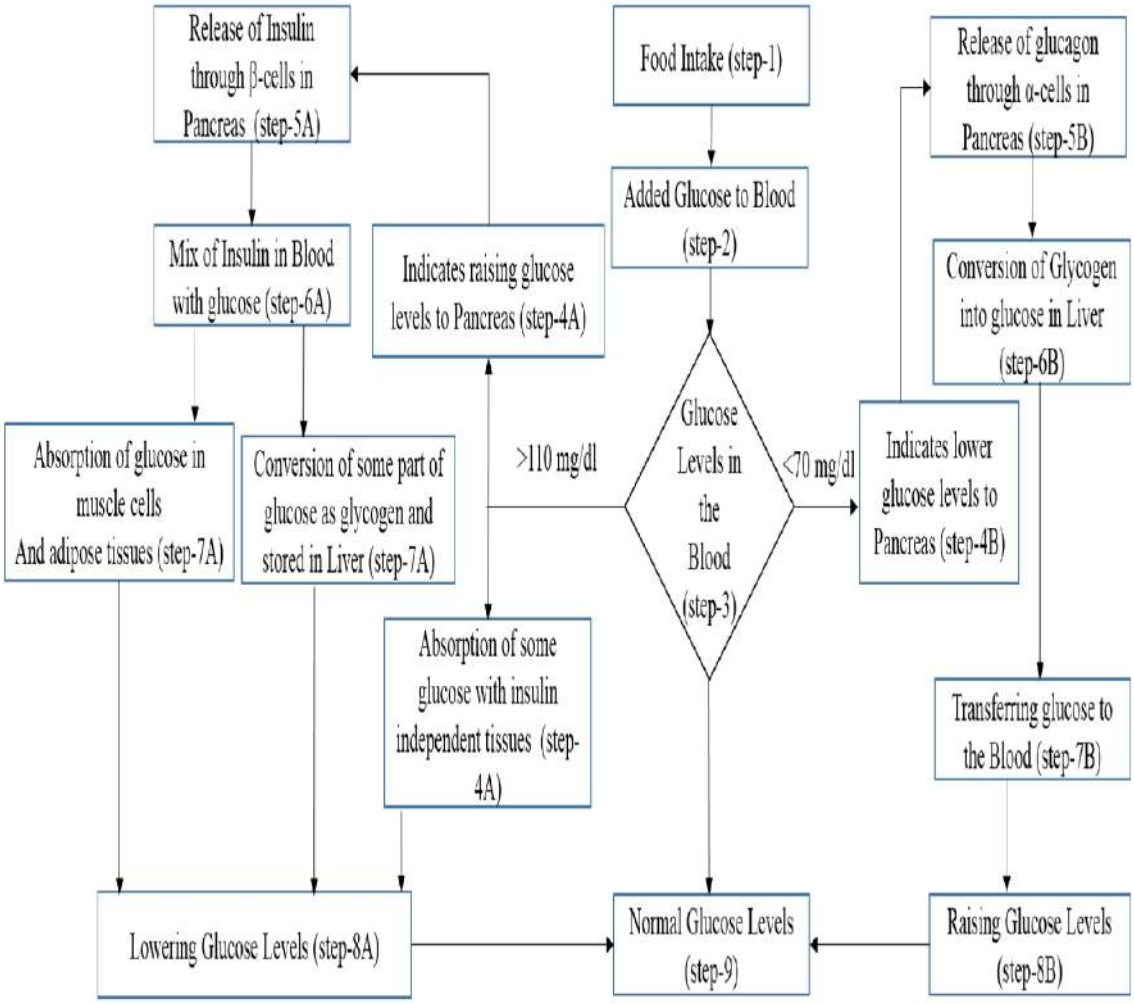
The arrival rates of glucose molecules and insulin granules are assumed as discrete random variables follows Poisson arrival patterns. Further it is assumed that the rate of disappearances of glucose molecules and insulin granules also follows Poisson patterns. The joint activities of arrival and consumption of both glucose and

insulin among diabetic patients is assumed to follow the bivariate Poisson process and hence the corresponding differential equations of glucose and insulin levels are derived.

Stochastic Model for Glucose & Insulin Regulatory System

The following flow chart will help to understand the processes and dynamics of glucose and insulin in glucose metabolism.

Flow Diagram of Glucose Metabolism



Usually the arrival of glucose to the blood stream will be done through food intake after breaking of ingredients such as carbohydrates, proteins and fats. There are three ways of glucose consumption, out of which one is insulin independent and two are insulin dependent. Insulin independent consumption of glucose will be observed in the tissues of some organs such as brain and genital organs. Once blood plasma has received the glucose from hepatic porous system and if it is more than the

normal range (70-110 mg/dl), then pancreas will get the signals of rising glucose levels. Pancreas will release insulin through beta cells in to blood. As insulin is a key hormone to enter the glucose in to cells, some part of the glucose will be absorbed in to muscle cells and adipose tissues. Further, some part of glucose in blood plasma will be converted as glycogen and stored in the liver. Continuous usage of glucose leads to fluctuations of its levels in plasma. When glucose levels will come down less than the desired normal range, pancreas will alert the endocrinology system and release glucagon through alpha cells. It will convert the stored glycogen in liver as glucose and released to blood stream. This mechanism of glucose metabolism is a continuous process and influenced by time, adding and consumption of glucose as well as insulin in to blood.

Regarding the inflow and out flow of insulin is concerned, Insulin will be generated from beta cells in pancreas. The level of insulin secretion depends on the size/mass of beta cells. If the mass of beta cells are sufficient to produce the required quantum of insulin, then the body will manage its activity with the available resources. However, the insulin consumption is of two ways, the major part is with insulin dependent glucose transportation to the cells of muscles/ adipose tissues and the minor part of it is for conversion of glucose in to glycogen through liver.

The total mechanism indicates that the accumulation and disposal of glucose molecules and insulin granules shall be viewed as discrete random processes. Their sizes are interdependent and regulated by some intervening processes similar to arrivals and departures of stochastic processes. The happening of arrivals, conversion and departure of glucose molecule; the arrival and departure of insulin granule are in simultaneous processes. This study is initiated based on bivariate linear Poisson processes for deriving differential difference equations.

Assumptions and Postulates of the Model:

The mechanism of food intake and its consumptions are influenced by random factors. The following schematic diagram will explain the arrival and disposal of both Glucose and Insulin.

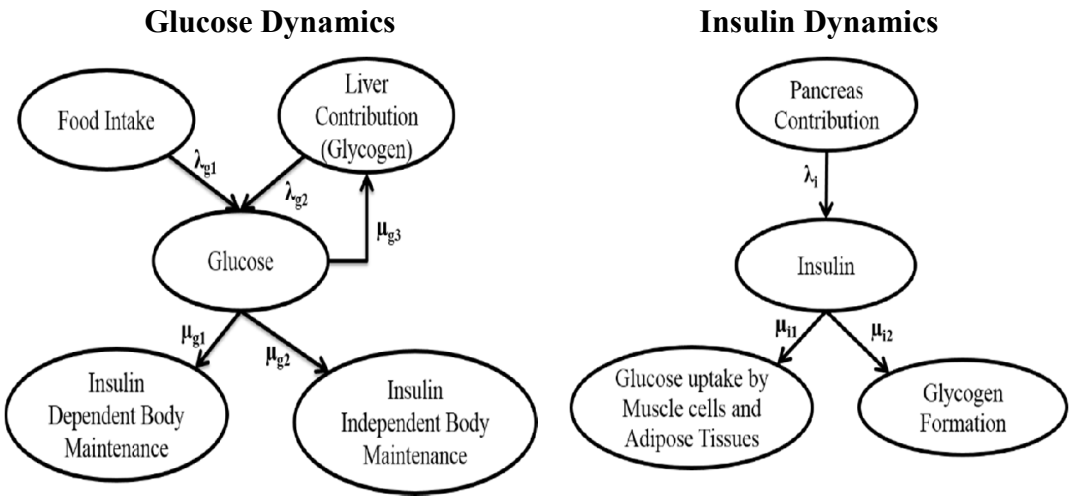


Figure -2. 1:Schematic Diagram for Glucose and Insulin arrivals/ disposals

- Let λ_{g1}, λ_{g2} be the rates of accumulation of glucose molecules to the blood stream through food intake and through liver contribution respectively per unit time.
- Let λ_i be the rate of arrival of insulin granules from the Pancreas per unit time.
- Let μ_{g1}, μ_{g2}, μ_{g3} be the rates of consumption of glucose molecules per unit time due to insulin dependent body maintenance, insulin independent body maintenance and conversion of glucose into glycogen format respectively.
- Let μ_{i1}, μ_{i2} be the rates of insulin consumption per unit time in the process of glucose absorption to the adipose tissues/muscle cells and in the process of glucose conversion as glycogen respectively.
- Let 'b' be the number/ mass of β-cells in pancreas.
- Let 'n' be the number of glucose molecules in the blood stream at a point of time.
- Let 'm' be the number of insulin granules in the blood stream at a point of time.
- Further assume that the accumulation and consumption of both glucose molecules and insulin granules follows Poisson processes.

The following are the proposed postulates with the above mentioned assumptions.

- Probability of existing of 'n' glucose molecules and 'm' insulin granules in the blood stream at a point of time 't' is $P_{n,m}(t)$.

- Probability of adding one glucose molecule to the blood stream due to food intake during Δt is $\lambda_{g1}\Delta t + O(\Delta t)$.
- Probability of adding one glucose molecule to the blood stream due to liver contribution during Δt is $\lambda_{g2}\Delta t + O(\Delta t)$.
- Probability of usage of one glucose molecule during Δt, given that there are 'n' glucose molecules and 'm' insulin granules during (0, t) in the blood stream with a reason of insulin dependent body maintenance is $nm\mu_{g1}\Delta t + O(\Delta t)$.
- Probability that usage of one glucose molecule during Δt provided there exists 'n' glucose molecules during (0, t) in the blood stream as a reason of insulin independent body maintenance is $n\mu_{g2}\Delta t + O(\Delta t)$.
- Probability that usage of one glucose molecule during Δt, for converting glucose into glycogen, provided there exists 'n' glucose molecules and 'm' insulin granules during (0, t) in the blood stream (where $n > n_u$) is $nm\mu_{g3}\Delta t + O(\Delta t)$.
- Probability of arrival of one insulin granule during Δt, given that the arrival of insulin granules is based on 'b' number of β-cells in the pancreas during (0, t) is $b\lambda_i\Delta t + O(\Delta t)$.
- Probability of disappearing one insulin granule during Δt provided there exist 'n' glucose molecules and 'm' insulin granules in the blood stream during (0, t) for the process of glucose absorption to the adipose tissues and muscle cells is $nm\mu_{i1}\Delta t + O(\Delta t)$.
- Probability of disappearing one insulin granule during Δt provided there exists 'm' insulin granules due to converting 'n' glucose molecules as glycogen during (0, t) is $nm\mu_{i2}\Delta t + O(\Delta t)$.
- The probability of occurrence of more than one happening and also occurrence of other than the above events during an infinitesimal interval of time Δt is $o(\Delta t)^2$.

Differential- Difference Equations of the Model

Let the processes of arrival and disposal of both glucose molecules and insulin granules follows Poisson distribution. Given $P_{n,m}(\mathrm{t})$ is the probability of existing of 'n' glucose molecules and 'm' insulin granules in the blood stream at a point of time 't'. The Differential Difference equation is

$$\begin{aligned}
P_{n,m}(t+\Delta t) = {} & P_{n,m}(\mathrm{t})\{[1-(\lambda_{g1}\Delta t+O(\Delta t))][1-(\lambda_{g2}\Delta t+O(\Delta t))] \\
& [1-nm\mu_{g1}\Delta t+O(\Delta t)][1-n\mu_{g2}\Delta t+O(\Delta t)][1-nm\,\mu_{g3}\Delta t+O(\Delta t)] \\
& [1-b\lambda_i\Delta t+O(\Delta t)][1-nm\mu_{i1}\Delta t+O(\Delta t)][1-nm\mu_{i2}\Delta t+O(\Delta t)]\} \\
& + P_{n-1,m}(t)\{[\lambda_{g1}\Delta t+O(\Delta t)]+[\lambda_{g2}\Delta t+O(\Delta t)]\} \\
& + P_{n+1,m}(t)\{[(n+1)m\mu_{g1}\Delta t+O(\Delta t)+[(n+1)\mu_{g2}\Delta t+O(\Delta t)]+[(n+1)m\mu_{g3}\Delta t+O(\Delta t)]\} \\
& + P_{n,m-1}(t)\{b\lambda_i\Delta t+O(\Delta t)\} \\
& + P_{n,m+1}(t)\{[n(m+1)\mu_{i1}\Delta t+O(\Delta t)]+[n(m+1)\mu_{i2}\Delta t+O(\Delta t)]\} \\
& + P_{n\pm i,m\pm i}(t)[O(\Delta t)^2]\ for\ i\geq 2
\end{aligned} \qquad \ldots(2.1)$$

The other difference equations for m = 0,1 and n = 0,1 are

$$\begin{aligned}
P_{0,0}(t+\Delta t) = {} & P_{0,0}(t)\{[1-(\lambda_{g1}\Delta t+O(\Delta t))][1-(\lambda_{g2}\Delta t+O(\Delta t))] \\
& [1-b\lambda_i\Delta t+O(\Delta t)]\}+P_{1,0}(t)\{[\mu_{g2}\Delta t+O(\Delta t)]\}\ for\ n,m\geq 1
\end{aligned} \qquad \ldots (2.2)$$

$$\begin{aligned}
P_{1,0}(t+\Delta t) = {} & P_{1,0}(t)\{[1-(\lambda_{g1}\Delta t+O(\Delta t))][1-(\lambda_{g2}\Delta t+O(\Delta t))] \\
& [1-\mu_{g2}\Delta t+O(\Delta t)][1-b\lambda_{i1}\Delta t+O(\Delta t)]\} \\
& + P_{0,0}(t)\{[\lambda_{g1}\Delta t+O(\Delta t)]+[\lambda_{g2}\Delta t+O(\Delta t)]\} \\
& + P_{2,0}(t)\{2\mu_{g2}\Delta t+O(\Delta t)\} \\
& + P_{1,1}(t)\{[\mu_{i1}\Delta t+O(\Delta t)]+[\mu_{i2}\Delta t+O(\Delta t)]\}\ for\ n,m\geq 1
\end{aligned} \qquad \ldots (2.3)$$

$$\begin{aligned}
P_{0,1}(t+\Delta t) = {} & P_{n,m}(t)\{[1-(\lambda_{g1}\Delta t+O(\Delta t))] \\
& [1-(\lambda_{g2}\Delta t+O(\Delta t))][1-b\lambda_i\Delta t+O(\Delta t)]\} \\
& + P_{1,1}(t)\{[\mu_{g1}\Delta t+O(\Delta t)+[\mu_{g2}\Delta t+O(\Delta t)]+[\mu_{g3}\Delta t+O(\Delta t)]\} \\
& + P_{0,0}(t)\{b\lambda_i\Delta t+O(\Delta t)\}\ for\ n,m\geq 1
\end{aligned} \qquad \ldots (2.4)$$

After Simplification, it can be written as

$$\begin{aligned}
\frac{d}{dt}P_{n,m}(t) = {} & \{-(\lambda_{g1}+\lambda_{g2}+nm\mu_{g1}+n\mu_{g2}+nm\,\mu_{g3}+b\lambda_i+nm\mu_{i1}+nm\mu_{i2})\}\,P_{n,m}(t) \\
& + \{[\lambda_{g1}+\lambda_{g2}\}P_{n-1,m}(t)+\{(n+1)m\mu_{g1}+(n+1)\mu_{g2} \\
& + (n+1)m\mu_{g3}\}P_{n+1,m}(t)+\{b\lambda_i\}P_{n,m-1}(t) \\
& + \{n(m+1)\mu_{i1}+n(m+1)\mu_{i2}\}P_{n,m+1}(t)\ for\ n,m\geq 1
\end{aligned} \qquad \ldots(2.5)$$

The steady-state equations for the values of n=0, 1 and m=0, 1are

$$\frac{d}{dt}P_{0,0}(t) = -(\lambda_{g1} + \lambda_{g2} + b\lambda_i)\,P_{0,0}(t) + \mu_{g2}P_{1,0}(t) \quad \ldots (2.6)$$

$$\frac{d}{dt}P_{1,0}(t) = \{-(\lambda_{g1} + \lambda_{g2} + \mu_{g2} + b\lambda_i)\}\,P_{1,0}(t) + \{\lambda_{g1} + \lambda_{g2}\}P_{0,0}(t) + 2\mu_{g2}P_{2,0}(t) + \{\mu_{i1} + \mu_{i2}\}P_{1,1}(t) \quad \ldots (2.7)$$

$$\frac{d}{dt}P_{0,1}(t) = -(\lambda_{g1} + \lambda_{g2} + b\lambda_i)\,P_{0,1}(t) + \{\mu_{g1} + \mu_{g2} + \mu_{g3}\}P_{1,1}(t) + \{b\lambda_i\}P_{0,0}(t) \quad \ldots (2.8)$$

The initial conditions of Probability generating is

$$P_{n,m}(0) = 1;\ for\ n = N_0, m = M_0\ \ and\ \ P_{n,m}(0) \neq 1;\ for\ n \neq N_0, m \neq M_0$$

Where N_0 and M_0 are initial values of glucose and insulin.

Let $P(x, y; t)$ be the joint probability generating function of $P_{n,m}(t)$;

Where $P(x, y; t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} x^n y^m P_{n,m}(t)$ … (2.9)

Multiplying the equations (2.1) to (2.8) with $x^n y^m$ and summing overall n and m, we obtain the probability generating function is

$$\begin{aligned}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P'_{n,m}(x, y; t) &= -(\lambda_{g1} + \lambda_{g2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) - \mu_{g1}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nmP_{n,m}(t) \\ &\quad - \mu_{g2}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nP_{n,m}(t) - \mu_{g3}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nmP_{n,m}(t) \\ &\quad - (b\lambda_i)\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) - (\mu_{i1} + \mu_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} nmx^n y^m P_{n,m}(t) \\ &\quad + \{\lambda_{g1} + \lambda_{g2}\}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n-1,m}(t) + \mu_{g1}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m (n+1)mP_{n+1,m}(t) \\ &\quad + \mu_{g2}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} (n+1)x^n y^m P_{n+1,m}(t) + \mu_{g3}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} (n+1)mx^n y^m P_{n+1,m}(t) \\ &\quad + \{b\lambda_i\}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m-1}(t) + (\mu_{i1} + \mu_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} n(m+1)x^n y^m P_{n,m+1}(t)\end{aligned} \quad \ldots (2.10)$$

Simplifying the equation(2.10) will reduces to

$$\frac{\partial P(x,y;t)}{\partial t} = \{(x-1)(\lambda_{g1}+\lambda_{g2})+(y-1)(b\lambda_i)\}P(x,y;t) + \{xy(\mu_{g1}+\mu_{g3}+\mu_{i1}+\mu_{i2})+y(\mu_{g1}+\mu_{g3})+x(\mu_{i1}+\mu_{i2})\}\frac{\partial^2 P(x,y;t)}{\partial x \partial y} + \{(1-x)\mu_{g2}\}\frac{\partial P(x,y;t)}{\partial x} \quad \ldots (2.11)$$

We can obtain the characteristics of the model by using the joint cumulant generating function of $p_{n,m}(t)$. Taking $x=e^u, y=e^v$ and denoting $K(u,v;t)$ as the joint cumulant generating function of $p_{n,m}(t)$, equation (2.11) becomes

$$\begin{aligned}\frac{\partial K(u,v;t)}{\partial t} &= \{(u+\frac{u^2}{2})(\lambda_{g1}+\lambda_{g2})+(v+\frac{v^2}{2})(b\lambda_i)\}\left[uE_x(t)+vE_y(t)+\frac{u^2}{2}V_x(t)+\frac{v^2}{2}V_y(t)+uvE_{xy}(t)\right] \\ &+\{-(\mu_{g1}+\mu_{g3}+\mu_{i1}+\mu_{i2})+e^{-u}(\mu_{g1}+\mu_{g3})+e^{-v}(\mu_{i1}+\mu_{i2})\} \\ &\left[\begin{array}{l}E_{xy}(t)-(E_x(t)+uV_x(t)+vE_{xy}(t))-(E_y(t)+vV_y(t)+uE_{xy}(t)) \\ -(uE_x(t)+vE_y(t)+\frac{u^2}{2}V_x(t)+\frac{v^2}{2}V_y(t)+uvE_{xy}(t))\end{array}\right] \\ &+\{(1-e^u)\mu_{g2}\}\left[(E_x(t)+uV_x(t)+vE_{xy}(t))-(uE_x(t)+vE_y(t)+\frac{u^2}{2}V_x(t)+\frac{v^2}{2}V_y(t)+uvE_{xy}(t))\right]\end{aligned} \quad \ldots (2.12)$$

On comparing the coefficients of u's, v's, $\frac{u^2}{2}$'s, $\frac{v^2}{2}$'s and uv's , arrived to the simultaneous ordinary differential equations.

Differential Equations and Statistical Measures:

Using the notion of probability generating and cumulant generating functions, we can obtain the derivatives with respect to 't',

$$\frac{d}{dt}\left(E_x(t)\right) = -(\mu_{g1}+\mu_{g3})E_{xy}(t)+[\mu_{g1}+\mu_{g3}-\mu_{g2}]E_x(t)+[\mu_{g1}+\mu_{g3}]E_y(t) \quad \ldots (2.13)$$

$$\frac{d}{dt}\left(E_y(t)\right) = -(\mu_{i1}+\mu_{i2})E_{xy}(t)+(\mu_{i1}+\mu_{i2})E_x(t)+(\mu_{i1}+\mu_{i2})E_y(t) \quad \ldots (2.14)$$

$$\frac{d}{dt}\left(V_x(t)\right) = [2(\lambda_{g1}+\lambda_{g2})+(\mu_{g1}+3\mu_{g2}+\mu_{g3})]E_x(t)+[2(\mu_{g1}+\mu_{g3}-\mu_{g2})]V_x(t) + 3(\mu_{g1}+\mu_{g3})E_{xy}(t)-(\mu_{g1}+\mu_{g3})E_y(t) \quad \ldots (2.15)$$

$$\frac{d}{dt}\left(V_y(t)\right) = [2(b\lambda_i)+(\mu_{i1}+\mu_{i2})]E_y(t) + 2(\mu_{i1}+\mu_{i2})V_y(t)-(\mu_{i1}+\mu_{i2})E_x(t)+(\mu_{i1}+\mu_{i2})E_{xy}(t) \quad \ldots (2.16)$$

$$\frac{d}{dt}\left(E_{xy}(t)\right) = \left[(\lambda_{g1} + \lambda_{g2}) + (\mu_{g1} + \mu_{g2} + \mu_{g3})\right] E_y(t)$$
$$+ \left[(b\lambda_i) + (\mu_{i1} + \mu_{i2})\right] E_x(t) + (\mu_{g1} + \mu_{g3}) V_y(t)$$
$$+ (\mu_{i1} + \mu_{i2}) V_x(t) + \left[(\mu_{g1} + \mu_{g3}) + (\mu_{i1} + \mu_{i2}) - \mu_{g2}\right] E_{xy}(t) \quad \text{... (2.17)}$$

where $E_x(t)$ is average level of glucose at time 't'; $E_y(t)$ is average level of insulin at time 't'; $V_x(t)$ is the variance of glucose level at time 't'; $V_y(t)$ is the variance of insulin level at time 't'; $E_{xy}(t)$ is average of glucose and insulin levels at time 't'.

By solving the set of linear simultaneous differential equations from (2.13) to (2.17), we will get the following measures by fixing variability of glucose and insulin levels.

Average number of glucose molecules in the blood stream at a point of time 't' is

$$E_x(t) = d_1 + e^{\alpha t} d_2 \quad \text{... (2.18)}$$

Average number of insulin granules in the blood stream at a point of time 't' is

$$E_y(t) = -\frac{d_3}{a_3} - d_2(1 + b_4)e^{\alpha t} + ke^{a_3 t} \quad \text{... (2.19)}$$

By considering

$$a_1 = (\mu_{g1} + \mu_{g3}); \quad a_2 = (\mu_{g1} + \mu_{g3} - \mu_{g2}); \quad a_3 = \mu_{i1} + \mu_{i2};$$

$$a_4 = 2(\lambda_{g1} + \lambda_{g2}) + (\mu_{g1} + 3\mu_{g2} + \mu_{g3}); \quad a_5 = 2(b\lambda_i) + (\mu_{i1} + \mu_{i2});$$

$$a_6 = (\lambda_{g1} + \lambda_{g2}) + (\mu_{g1} + \mu_{g2} + \mu_{g3}); \quad a_7 = (b\lambda_i) + (\mu_{i1} + \mu_{i2});$$

$$a_8 = \mu_{g1} + \mu_{g3} + (\mu_{i1} + \mu_{i2}) - \mu_{g2}; \quad b_1 = \frac{(2a_2 a_3 V_x - 6a_1 a_3 V_y)}{a_1(a_3 + 3a_5)}; \quad b_2 = \frac{(a_3 a_4 + 3a_1 a_3)}{a_1(a_3 + 3a_5)};$$

$$b_3 = \frac{(2a_2 V_x - a_1 b_1)}{3a_1}; \quad b_4 = \frac{(a_4 - a_1 b_2)}{3a_1}; \quad d_1 = \frac{(a_1 b_1 - a_1 b_3)}{(a_2 + a_1 b_4 + a_1 b_2)};$$

$$d_2 = G_0 + \frac{(a_1 b_1 - a_1 b_3)}{(a_2 + a_1 b_4 + a_1 b_2)};$$

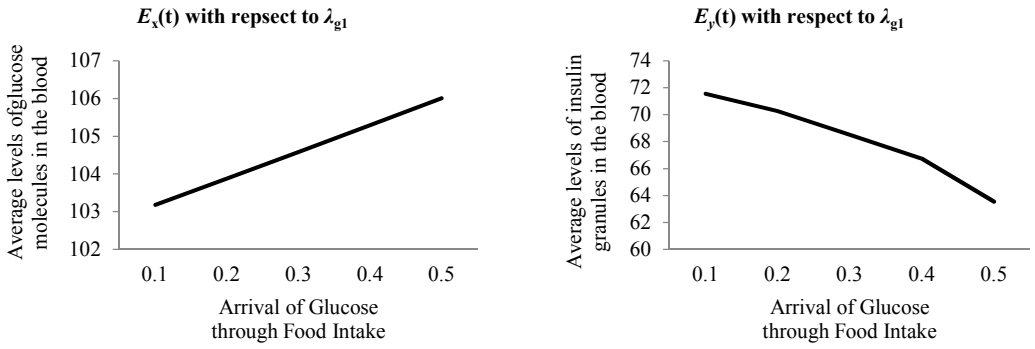
$$d_3 = -a_3 b_3 + (a_3 b_4 + a_3)\mathrm{d}_1; \quad \alpha = a_2 + a_1 b_4 + a_1 b_2; \quad k = I_0 + \frac{d_3}{a_3} + d_2(1 + b_4);$$

G_0 and I_0 are the initial sizes of glucose and insulin respectively.

Numerical Illustration and Sensitivity Analysis:

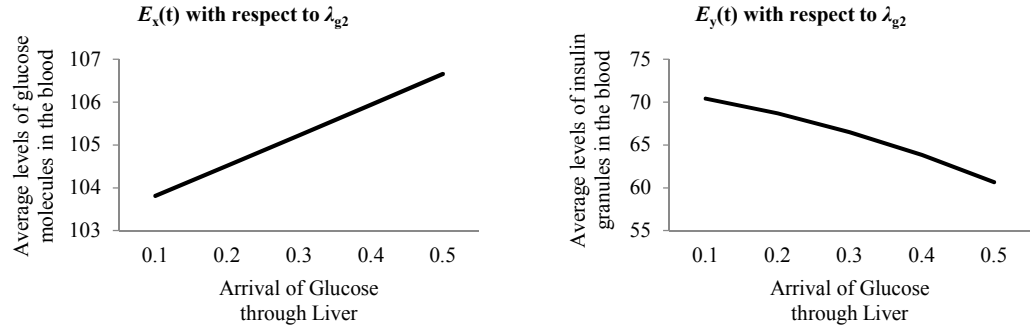
In order to measure the glucose and insulin levels with the developed model, a hypothetical numerical data set was generated for values of average levels of glucose molecules and average levels of insulin granules at a point of time for changing values of one parameter when other parameters are constants. The results were simulated using MATHCAD 8.0 version and presented in Table-2.1. Graphical presentations were given for better understanding of the influencing variables with the respective independent variables.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to λ_{g1}:



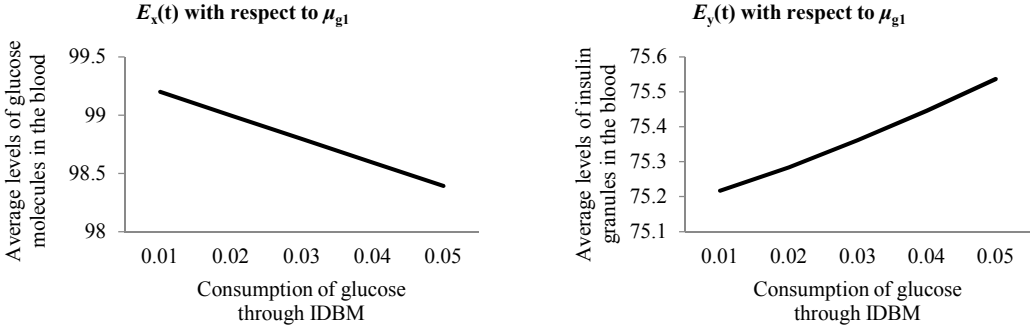
From the above representation it is observed that $E_x(t)$ is an increasing function and $E_y(t)$ is decreasing function of λ_{g1} when the other parameters are constants. It may implies that there is (i) Positive relation between rate of arrival of glucose from food intake and the average levels of glucose in the blood plasma; (ii) Negative relation between rate of arrival of glucose through food intake and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to λ_{g2}:



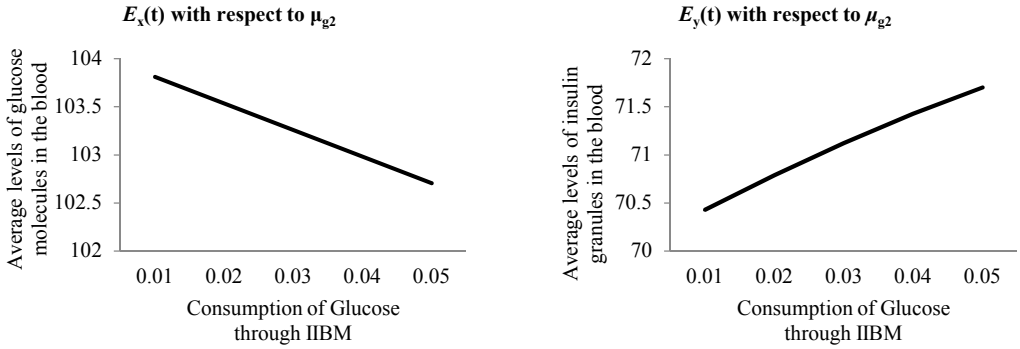
From the above representation, it is observed that $E_x(t)$ is an increasing function and $E_y(t)$ is decreasing function of λ_{g2} when the other parameters are constants. It may implies that there is (i) Positive relation between rate of arrival of glucose through liver and the average levels of glucose in the blood stream. (ii) Negative relation between rate of arrival of glucose through liver and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to μ_{g1}:



From the above representation, it is observed that $E_x(t)$ is decreasing function and $E_y(t)$ is an increasing function of μ_{g1} when the other parameters are constants. It may implies that there is (i)Negative relation between rate of consumption of glucose through Insulin Dependent Body Maintenance (IDBM) and the average levels of glucose in the blood stream. (ii) Positive relation between rate of consumption of glucose through Insulin Dependent Body Maintenance (IDBM) and the average levels of insulin in the blood stream.

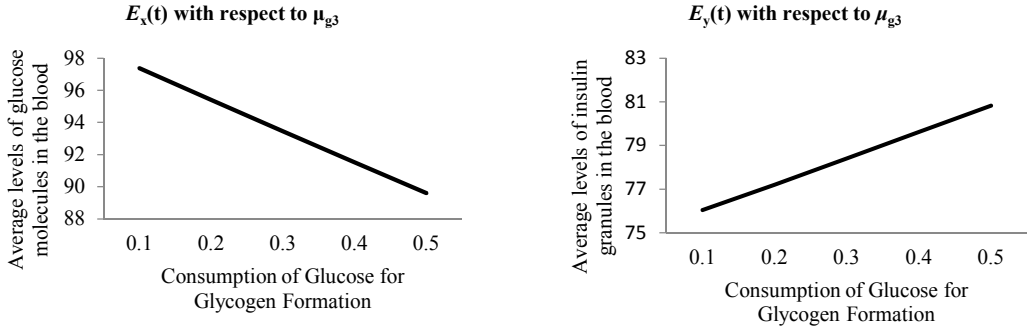
Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to μ_{g2}:



From the above representation, it is observed that $E_x(t)$ is decreasing function and $E_y(t)$ is an increasing function of μ_{g2} when the other parameters are constants. It

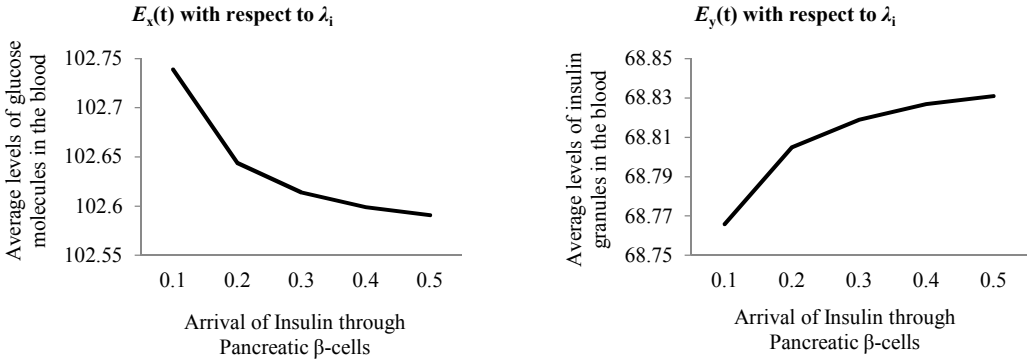
may implies that there is (i) Negative relation between rate of consumption of glucose through Insulin Independent Body Maintenance (IIBM) and the average levels of glucose in the blood stream. (ii) Positive relation between rate of consumption of glucose through Insulin Independent Body Maintenance (IIBM) and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to μ_{g3}:



From the above representation, it is observed that $E_x(t)$ is decreasing function and $E_y(t)$ is an increasing function of μ_{g3} when the other parameters are constants. It may implies that there is (i) Negative relation between rate of consumption of glucose for Glycogen formation and the average levels of glucose in the blood stream. (ii) Positive relation between rate of consumption of glucose for Glycogen formation and the average levels of insulin in the blood stream.

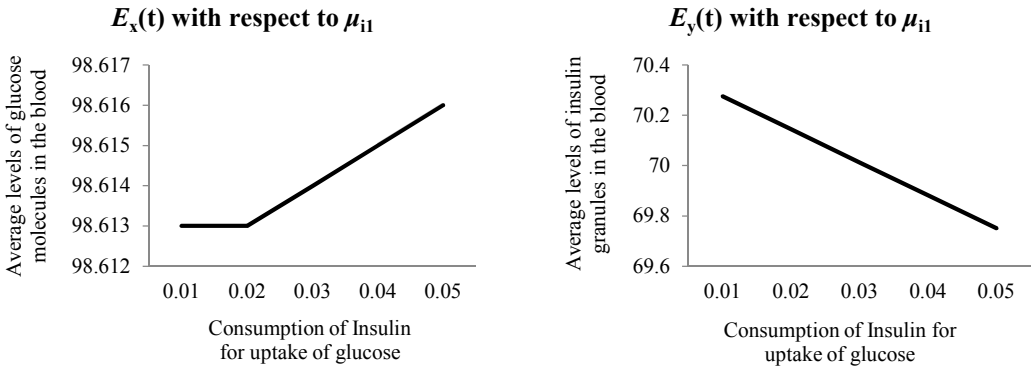
Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to λ_{i1}:



From the above representation, it is observed that $E_x(t)$ is decreasing function and $E_y(t)$ is an increasing function of λ_i when the other parameters are constants. It may imply that there is (i) Negative relation between rate of secretion of insulin from Pancreatic β-cells and the average levels of glucose in the blood stream. (ii) Positive

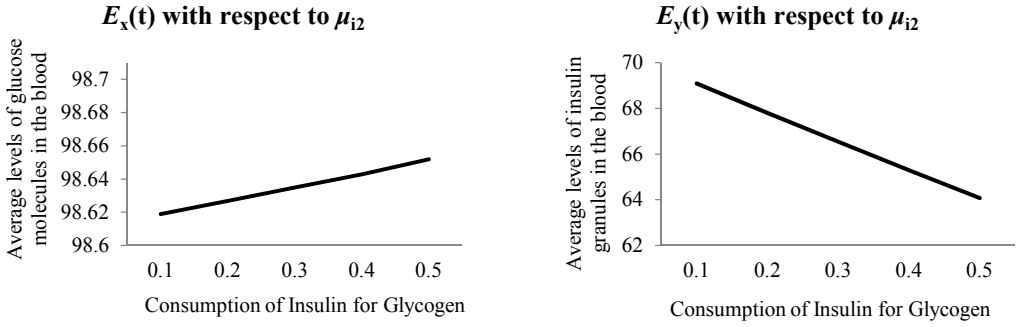
relation between rates of secretion of insulin from Pancreatic β-cells and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to μ_{i1}:



From the above representation, it is observed that $E_x(t)$ is an increasing function and $E_y(t)$ is decreasing function of μ_{i1} when the other parameters are constants. It may implies that there is (i) Positive relation between rate of consumption of insulin for glucose absorption to the muscle cells and adipose tissues and the average levels of glucose in the blood stream. (ii) Negative relation between rate of consumption of insulin for glucose absorption to the muscle cells and adipose tissues and the average levels of insulin in the blood stream.

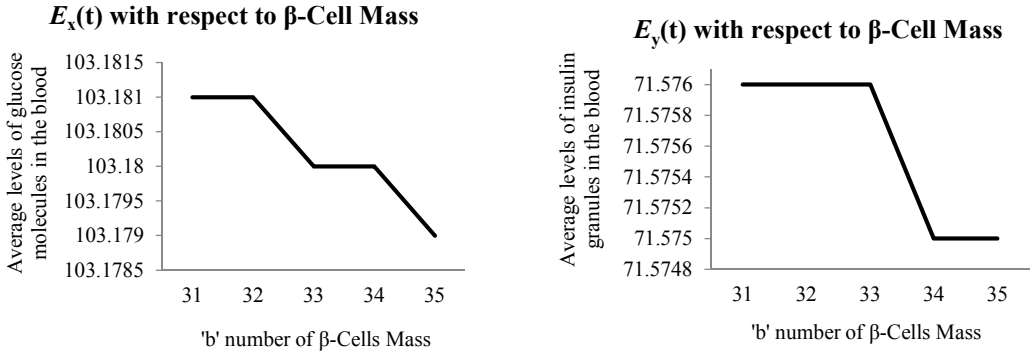
Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to μ_{i2}:



From the above representation, it is observed that $E_x(t)$ is an increasing function and $E_y(t)$ is decreasing function of μ_{i2} when the other parameters are constants. It may implies that there is (i) Positive relation between rate of consumption of insulin for converting the glucose as glycogen and the average levels of glucose in the blood stream. (ii) Negative relation between rate of consumption of

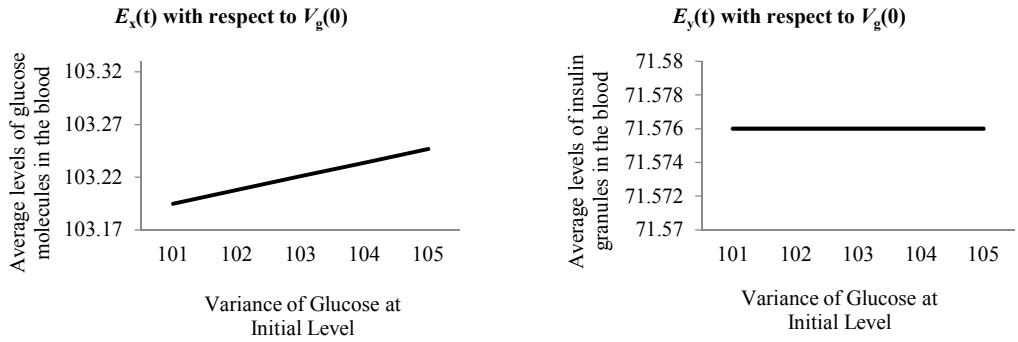
insulin for converting the glucose as glycogen and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to β-cell mass:



From the above representation, it is observed that $E_x(t)$ and $E_y(t)$ are decreasing functions of β-cell mass when the other parameters are constants. It may implies that there is (i) Negative relation between rate of increasing insulin secretion from the pancreatic β-cell mass and the average levels of glucose in the blood stream. (ii) Negative relation between rate increasing insulin secretion from the pancreatic β-cell mass and the average levels of insulin in the blood stream it may be because of simultaneous insulin consumption in the process of glucose metabolism.

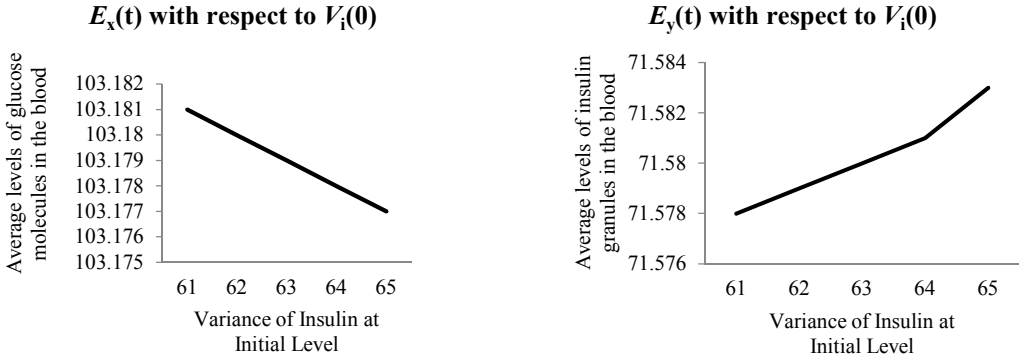
Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to $V_g(0)$:



From the above representation, it is observed that $E_x(t)$ is an increasing function and $E_y(t)$ is invariant function of $V_g(0)$ when the other parameters are constants. It may implies that there is (i) Positive relation between the variance of glucose at initial level and the average levels of glucose in the blood stream. (ii) The

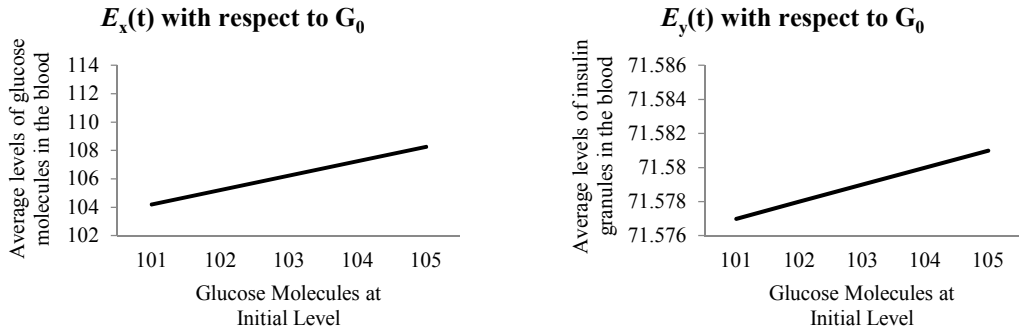
invariant relation between the variance of glucose at initial level and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to $V_i(0)$:



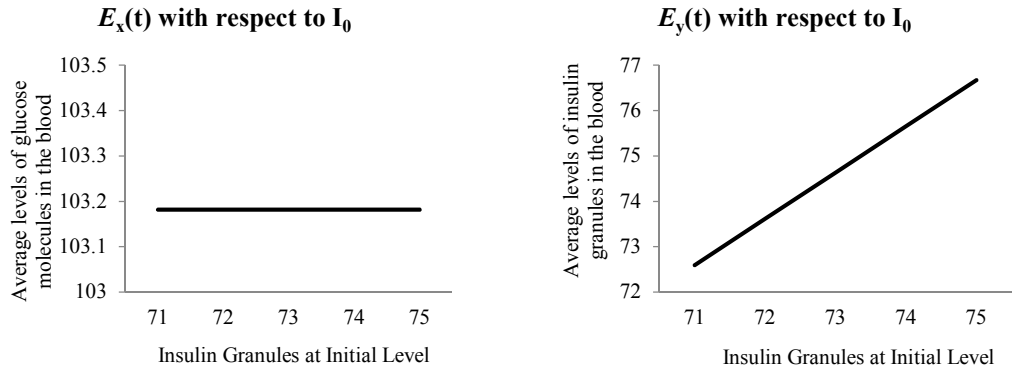
From the above representation, it is observed that $E_x(t)$ is decreasing function and $E_y(t)$ is an increasing function of $V_i(0)$ when the other parameters are constants. It may imply that there is (i) Negative relation between the variance of insulin at initial level and the average levels of glucose in the blood stream. (ii) Positive relation between the variance of insulin at initial level and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to G_0:



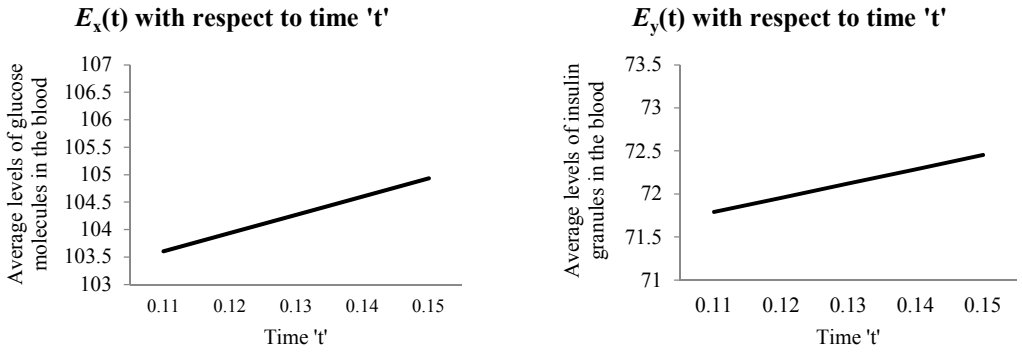
From the above representation, it is observed that $E_x(t)$ is an increasing function and $E_y(t)$ is increasing function of G_0 when the other parameters are constants. It may implies that there is (i) Positive relation between the glucose at initial level and the average levels of glucose in the blood stream. (ii) Positive relation between the glucose at initial level and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to I_0:



From the above representation, it is observed that $E_x(t)$ is an invariant function and $E_y(t)$ is an increasing function of I_0 when the other parameters are constants. It may implies that there is (i) No relation between insulin at initial level and the average levels of glucose in the blood stream. (ii) Positive relation between insulin at initial level and the average levels of insulin in the blood stream.

Graphical Representation of $E_x(t)$ and $E_y(t)$ with respect to $Time't'$:



From the above representation, it is observed that $E_x(t)$ and $E_y(t)$ are increasing functions of $Time't'$ when the other parameters are constants. It may implies that there is (i) Positive relation between the time 't' and the average levels of glucose in the blood stream during glucose arrival time. (ii) Positive relation between the time 't' and the average levels of insulin in the blood stream during glucose arrival time.

Table-2.1: Values of average levels of glucose molecules and average level of insulin granules at a point of time 't' for changing values of one parameter when other parameters are constants.

λ_{g1}	λ_{g2}	μ_{g1}	μ_{g2}	μ_{g3}	λ_i	μ_{i1}	μ_{i2}	b	$V_g(0)$	$V_i(0)$	G_0	I_0	Time 't'	$E_x(t)$	$E_y(t)$
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**103.18**	**71.58**
0.2	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**103.88**	**70.28**
0.3	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**104.59**	**68.51**
0.4	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**105.3**	**66.73**
0.5	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**106.02**	**63.55**
0.1	**0.1**	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**103.81**	**70.43**
0.1	**0.2**	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**104.52**	**68.71**
0.1	**0.3**	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**105.23**	**66.52**
0.1	**0.4**	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**105.94**	**63.85**
0.1	**0.5**	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**106.66**	**60.69**
0.1	0.1	**0.01**	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**99.2**	**75.22**
0.1	0.1	**0.02**	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**98.998**	**75.28**
0.1	0.1	**0.03**	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**98.796**	**75.36**
0.1	0.1	**0.04**	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**98.595**	**75.45**
0.1	0.1	**0.05**	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**98.394**	**75.54**
0.1	0.1	0.1	**0.01**	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**103.81**	**70.43**
0.1	0.1	0.1	**0.02**	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**103.54**	**70.79**
0.1	0.1	0.1	**0.03**	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**103.26**	**71.12**
0.1	0.1	0.1	**0.04**	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**102.98**	**71.43**
0.1	0.1	0.1	**0.05**	0.1	0.1	0.1	0.1	30	100	60	100	70	0.1	**102.71**	**71.7**
0.1	0.1	0.1	0.01	**0.1**	0.1	0.1	0.1	30	100	60	100	70	0.1	**97.393**	**76.05**
0.1	0.1	0.1	0.01	**0.2**	0.1	0.1	0.1	30	100	60	100	70	0.1	**95.409**	**77.2**
0.1	0.1	0.1	0.01	**0.3**	0.1	0.1	0.1	30	100	60	100	70	0.1	**93.452**	**78.4**
0.1	0.1	0.1	0.01	**0.4**	0.1	0.1	0.1	30	100	60	100	70	0.1	**91.521**	**79.62**
0.1	0.1	0.1	0.01	**0.5**	0.1	0.1	0.1	30	100	60	100	70	0.1	**89.614**	**80.83**
0.1	0.1	0.1	0.01	0.1	**0.1**	0.1	0.01	30	100	60	100	70	0.1	**102.74**	**68.77**
0.1	0.1	0.1	0.01	0.1	**0.2**	0.1	0.01	30	100	60	100	70	0.1	**102.64**	**68.81**
0.1	0.1	0.1	0.01	0.1	**0.3**	0.1	0.01	30	100	60	100	70	0.1	**102.61**	**68.82**
0.1	0.1	0.1	0.01	0.1	**0.4**	0.1	0.01	30	100	60	100	70	0.1	**102.6**	**68.83**
0.1	0.1	0.1	0.01	0.1	**0.5**	0.1	0.01	30	100	60	100	70	0.1	**102.59**	**68.83**
0.1	0.01	0.1	0.01	0.01	0.1	**0.01**	0.1	30	100	60	100	70	0.1	**98.613**	**70.28**
0.1	0.01	0.1	0.01	0.01	0.1	**0.02**	0.1	30	100	60	100	70	0.1	**98.613**	**70.15**
0.1	0.01	0.1	0.01	0.01	0.1	**0.03**	0.1	30	100	60	100	70	0.1	**98.614**	**70.01**
0.1	0.01	0.1	0.01	0.01	0.1	**0.04**	0.1	30	100	60	100	70	0.1	**98.615**	**69.88**

λ_{g1}	λ_{g2}	μ_{g1}	μ_{g2}	μ_{g3}	λ_i	μ_{i1}	μ_{i2}	b	$V_g(0)$	$V_i(0)$	G_0	I_0	Time 't'	$E_x(t)$	$E_y(t)$
0.1	0.01	0.1	0.01	0.01	0.1	**0.05**	0.1	30	100	60	100	70	0.1	**98.616**	**69.75**
0.1	0.01	0.1	0.01	0.01	0.1	0.1	**0.1**	30	100	60	100	70	0.1	**98.619**	**69.1**
0.1	0.01	0.1	0.01	0.01	0.1	0.1	**0.2**	30	100	60	100	70	0.1	**98.627**	**67.82**
0.1	0.01	0.1	0.01	0.01	0.1	0.1	**0.3**	30	100	60	100	70	0.1	**98.635**	**66.55**
0.1	0.01	0.1	0.01	0.01	0.1	0.1	**0.4**	30	100	60	100	70	0.1	**98.643**	**65.3**
0.1	0.01	0.1	0.01	0.01	0.1	0.1	**0.5**	30	100	60	100	70	0.1	**98.652**	**64.08**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	**31**	100	60	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	**32**	100	60	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	**33**	100	60	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	**34**	100	60	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	**35**	100	60	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	**101**	60	100	70	0.1	**103.2**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	**102**	60	100	70	0.1	**103.21**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	**103**	60	100	70	0.1	**103.22**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	**104**	60	100	70	0.1	**103.23**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	**105**	60	100	70	0.1	**103.25**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	**61**	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	**62**	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	**63**	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	**64**	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	**65**	100	70	0.1	**103.18**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	**101**	70	0.1	**104.2**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	**102**	70	0.1	**105.22**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	**103**	70	0.1	**106.24**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	**104**	70	0.1	**107.26**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	**105**	70	0.1	**108.28**	**71.58**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	**71**	0.1	**103.18**	**72.6**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	**72**	0.1	**103.18**	**73.62**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	**73**	0.1	**103.18**	**74.64**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	**74**	0.1	**103.18**	**75.66**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	**75**	0.1	**103.18**	**76.68**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	110	100	100	70	**0.11**	**103.61**	**71.79**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	**0.12**	**103.94**	**71.96**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	**0.13**	**104.27**	**72.12**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	**0.14**	**104.61**	**72.29**
0.1	0.01	0.1	0.01	0.1	0.1	0.1	0.1	30	100	60	100	70	**0.15**	**104.94**	**72.46**

Chapter-3

Stochastic Modeling & Numerical Method's Approach for Measuring Glucose/ Insulin Levels in Healthy Individuals

Introduction:

The previous chapter deals with development of stochastic model for dynamics of glucose and insulin using differential difference equations so as getting the differential equations. It is a bivariate linear birth and death process for glucose and insulin mechanics as applications of point processes among diabetic patients. This is purely classical approach to get the proposed statistical measures such as average level of glucose, average level of insulin, variance of glucose level, variance of insulin level and covariance between the levels of glucose and insulin at a point of time. The set of differential equations from 2.13 to 2.17 are expressed as simultaneous linear dependent. In which the influence of previous existing insulin and glucose levels will be on the current levels of glucose and insulin. Moreover, they were formulated in such a way that the differential equation of glucose/ insulin at time t is a function with respect to previous levels of insulin/glucose. The total activity though it is analytical, it has a limitation of non-getting convergent values of expected sizes of glucose and insulin. It is further complicated in finding the second order moments so as variance of glucose size, variance of insulin size and covariance between the glucose and insulin levels. In summary, it is cleared that getting higher order moments for linear dependent differential equations is more complicated. Obtaining the exact and real values of the said statistical measures through classical approaches is a complicated issue. It is appropriate to extract the approximate values of the mentioned statistical measures through numerical methods.

Stochastic Model for Glucose and Insulin Regulatory System among Healthy Individuals:

The model developed on glucose and insulin arrivals or consumptions in the mechanism of their metabolism in healthy individuals will help in measuring the parameters to get the indicators of the status. The following diagram will provide the scheme behind the processes.

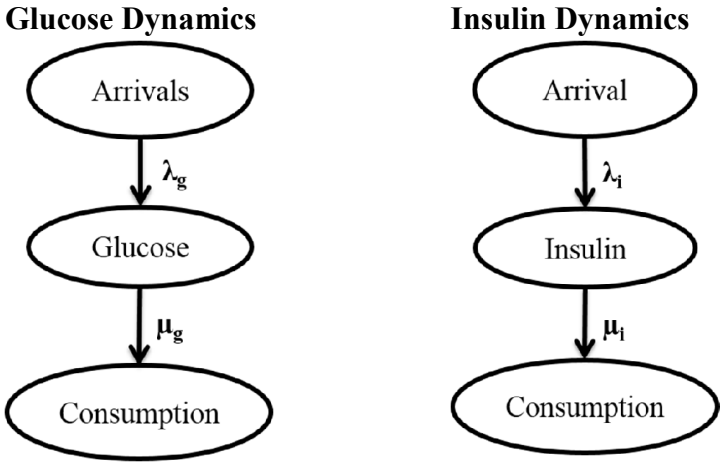


Figure – 3.0: Dynamics of Glucose and Insulin processes.

The assumptions of the model are as follows,

- Let λ_g be the arrival rate of glucose molecules to the blood stream per unit time.
- Let λ_i be the rate of arrivals of insulin granules to the blood stream per unit time.
- Let μ_g be the rate of consumption of glucose molecules from the blood stream per unit time.
- Let μ_i be the rate consumption of insulin granules per unit time from the blood stream.
- Let 'b' be the number/ mass of β-cells in the pancreas, which is responsible for insulin secretion.
- Let 'n' be the number of glucose molecules existed in the blood stream at a point of time.
- Let 'm' be the number of insulin granules existed in the blood stream at a point of time.
- Let the process of accumulation and consumption of both glucose molecules and insulin granules follows Poisson processes.

The postulates of the models are as follows:

- Probability of adding one glucose molecule to the blood stream during Δt is $\lambda_g \Delta t + O(\Delta t)$.
- Probability of usage or consumption of one glucose molecule during Δt, given that there are 'n' glucose molecules and 'm' insulin granules in the blood stream during (0, t) is $nm\mu_g \Delta t + O(\Delta t)$.

- Probability of arrival of one insulin granule during Δt, given that there exists 'b' number of β-cells in the pancreas during (0, t) is $b\lambda_i \Delta t + O(\Delta t)$.
- Probability of usage or consumption of one insulin granule during Δt, provided there exist 'n' glucose molecules in the blood stream during (0, t) is $n\mu_i \Delta t + O(\Delta t)$.

Differential Equations of the Model

The above assumptions and postulates have been used to get the differential difference equations. Let $P_{n,m}(t)$ be the probability of existing of 'n' glucose molecules and 'm' insulin granules in the blood stream during (0,t). Let $P_{n,m}(t+\Delta t)$ be the probability that happening of an event in the infinitesimal interval Δt, when there exists 'n' glucose molecules and 'm' insulin granules in the blood stream during (0,t). The differential difference equations and the respective differential equations of the model are

$$\begin{aligned} P_{n,m}(t+\Delta t) = {} & P_{n,m}(t)[1-(\lambda_g \Delta t + O(\Delta t))][1-nm\mu_g \Delta t + O(\Delta t)] \\ & [1-b\lambda_i \Delta t + O(\Delta t)][1-n\mu_i \Delta t + O(\Delta t)] \\ & + P_{n-1,m}(t)\{\lambda_g \Delta t + O(\Delta t)\} + P_{n+1,m}(t)\{(n+1)m\mu_g \Delta t + O(\Delta t)\} \\ & + P_{n,m-1}(t)\{b\lambda_i \Delta t + O(\Delta t)\} + P_{n,m+1}(t)\{n\mu_i \Delta t + O(\Delta t)\} \\ & + P_{n\pm i,m\pm i}(t)[O(\Delta t)^2] \; for \; i \geq 2 \end{aligned} \quad \ldots (3.1)$$

The other difference equations are

$$P_{0,0}(t+\Delta t) = P_{0,0}(t)\{[1-(\lambda_g \Delta t + O(\Delta t))][1-b\lambda_i \Delta t + O(\Delta t)]\} \quad \ldots (3.2)$$

$$\begin{aligned} P_{1,0}(t+\Delta t) = {} & P_{1,0}(t)[1-(\lambda_g \Delta t + O(\Delta t))][1-b\lambda_i \Delta t + O(\Delta t)][1-\mu_i \Delta t + O(\Delta t)] \\ & + P_{0,0}(t)\{\lambda_g \Delta t + O(\Delta t)\} + P_{1,1}(t)\{\mu_i \Delta t + O(\Delta t)\} \end{aligned} \quad \ldots (3.3)$$

$$\begin{aligned} P_{0,1}(t+\Delta t) = {} & P_{0,1}(t)[1-(\lambda_g \Delta t + O(\Delta t))][1-b\lambda_i \Delta t + O(\Delta t)] \\ & + P_{1,1}(t)\{\mu_g \Delta t + O(\Delta t)\} + P_{0,0}(t)\{b\lambda_i \Delta t + O(\Delta t)\} \end{aligned} \quad \ldots (3.4)$$

Simplifying the above equation (3.2.1), we obtained

$$\begin{aligned} \frac{d}{dt}P_{n,m}(t) = {} & -(\lambda_g + nm\mu_g + b\lambda_i + n\mu_i)P_{n,m}(t) + \lambda_g P_{n-1,m}(t) \\ & + (n+1)m\mu_g P_{n+1,m}(t) + b\lambda_i P_{n,m-1}(t) + n\mu_i P_{n,m+1}(t) \end{aligned} \quad \ldots (3.5)$$

The Steady-state equations for (3.2 to 3.4), the values of n=0, 1 and m=0, 1 are

$$\frac{d}{dt}P_{0,0}(t) = -(\lambda_g + b\lambda_i)P_{0,0}(t) \quad \ldots (3.6)$$

$$\frac{d}{dt}P_{1,0}(t) = -(\lambda_g + b\lambda_i + \mu_i)P_{1,0}(t) + \lambda_g P_{0,0}(t) + \mu_i P_{1,1}(t) \quad \ldots (3.7)$$

$$\frac{d}{dt}P_{0,1}(t) = -(\lambda_g + b\lambda_i)P_{0,1}(t) + b\lambda_i P_{0,0}(t) + \mu_g P_{1,1}(t) \quad \ldots (3.8)$$

The initial conditions of Probability generating is

$$P_{n,m}(0) = 1; \textit{ for } n = N_0, m = M_0 \textit{ and } P_{n,m}(0) \neq 1; \textit{ for } n \neq N_0, m \neq M_0$$

Where N_0 and M_0 are initial values of glucose and insulin.

Let $P(x, y; t)$ be the joint probability generating function of $P_{n,m}(t)$, where

$$P(x, y; t) = \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) \quad \ldots (3.9)$$

Multiplying the (3.6) to (3.8) with $x^n y^m$ and summing overall n and m, we obtain

$$\begin{aligned}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P'_{n,m}(t) = &-\lambda_g \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) - \mu_g \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nm P_{n,m}(t) \\ &- b\lambda_i \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) - \mu_i \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m n P_{n,m}(t) \\ &+ \lambda_g \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n-1,m}(t) + \mu_g \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m (n+1) m P_{n+1,m}(t) \\ &+ b\lambda_i \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m-1}(t) + \mu_i \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} n x^n y^m P_{n,m+1}(t)\end{aligned} \quad \ldots (3.10)$$

Simplifying and rearranging the terms in the equation (3.10) we arrive to the following,

$$\begin{aligned}\frac{\partial P(x, y; t)}{\partial t} = &\{-\lambda_g - b\lambda_i\}P(x, y; t) - \mu_g xy \frac{\partial^2 P(x, y; t)}{\partial x \partial y} \\ &- \mu_i x \frac{\partial P(x, y; t)}{\partial x} + \lambda_g x P(x, y; t) + \mu_g (x+1) y \frac{\partial^2 P(x, y; t)}{\partial x \partial y} \\ &+ b\lambda_i y P(x, y; t) + \mu_i \frac{x}{y} \frac{\partial P(x, y; t)}{\partial x}\end{aligned} \quad \ldots (3.11)$$

We can obtain the characteristics of the model by using the joint cumulant generating function of $P_{n,m}(t)$. Taking $x = e^u$ and $y = e^v$, denoting $K(u, v; t)$ as the joint cumulant generating function of $P_{n,m}(t)$, equation (3.8) becomes

So, the form can be obtain after the transformation is as follows

$$\frac{\partial K(u,v;t)}{\partial t} = \{(e^{u}-1)\lambda_g + (e^{v}-1)b\lambda_i\}\,\mathrm{K}(u,v;t) + \mu_i e^{u}\left(\frac{1}{e^{v}}-1\right)e^{-u}\left[\frac{\partial K(u,v;t)}{\partial u} - K(u,v;t)\right] + e^{v}\mu_g e^{-(u+v)}\left[\frac{\partial^2 K(u,v;t)}{\partial u\partial v} - \frac{\partial K(u,v;t)}{\partial u} - \frac{\partial K(u,v;t)}{\partial v} - K(u,v;t)\right] \quad \ldots (3.12)$$

On comparing the coefficients of u's, v's, $\frac{u^2}{2}$'s, $\frac{v^2}{2}$'s and uv's , we arrived to the simultaneous or coupled differential equations.

Simultaneous Differential Equations and Statistical Measures of the Model

$$\frac{d}{dt}E_x(t) = -\mu_g\{V_x(t) + 2E_{xy}(t) + E_y(t)\} \quad \ldots (3.13)$$

$$\frac{d}{dt}E_y(t) = -\mu_i E_x(t) - \mu_g\{V_y(t) + E_{xy}(t) + E_y(t)\} \quad \ldots (3.14)$$

$$\frac{d}{dt}V_x(t) = 2\lambda_g E_x(t) + \mu_g\{V_x(t) + 3E_{xy}(t) + E_x(t) - E_y(t)\} \quad \ldots (3.15)$$

$$\frac{d}{dt}V_y(t) = 2b\lambda_i E_y(t) + \mu_i\{E_x(t) - 2E_{xy}(t) + 2E_y(t)\} - \mu_g V_y(t) \quad \ldots (3.16)$$

$$\frac{d}{dt}E_{xy}(t) = \lambda_g E_y(t) + b\lambda_i E_x(t) + \mu_i\{E_x(t) - V_x(t)\} + \mu_g\{E_y(t) + V_y(t)\} \quad \ldots (3.17)$$

Solution for Differential Equations using Runge -Kutta Method:

Solving of the above set of differential equations using analytical method has no exact solutions for the glucose and insulin parameters. In order to get the approximate solutions, a numerical method approach is considered using Runge-Kutta method. This method has an added advantage that will provide approximations up to the second order moments such as mean/average levels of glucose, average level of insulin, variance of glucose levels, variance of insulin levels, and the correlation coefficient between insulin and glucose levels. As there is no built in software to handle the above formulated equations, a scientific computer program using FORTRAN was developed.

Numerical Simulations and Statistical Measures:

The proposed model in chapter-2 has the limitations of non-getting analytical solution for all the required statistical measures based on higher order moments. Assuming constant variability of the study variables is a rare phenomenon and quite unnatural. Hence, Runge-Kutta numerical method has been used to get the approximate values of various statistical measures. The study has further focused on getting the indicators of two categories of subjects namely (i) normal/healthy persons and (ii) persons prone to T2DM.

Numerical illustrations based on simulated data sets are provided for understanding the glucose/insulin dynamics. The assumed study is initiated after 90 minutes of food intake and data sets were simulated for a total time of 150 minutes with an interval of 15 minutes. It has given a reasonable number of samples around 10 points per a spell of study. Here, the unit measurement of glucose is in mg/dl and for insulin is in μU/ml.

Case-1: Normal Individuals

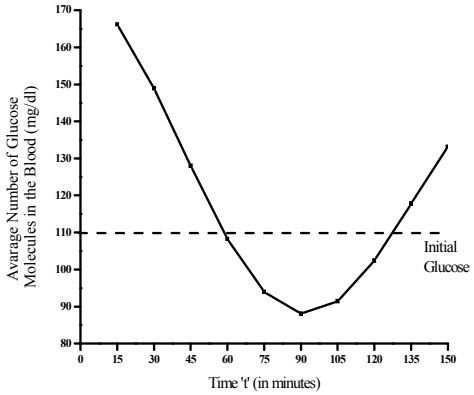
The datasets are calculated by giving the initial values to the system of simultaneous or coupled system in the program. This study mainly focused on observing the patterns of averages, variances and correlation between the glucose molecules and insulin granules.

Table: 3.1. Data Set for Case-1

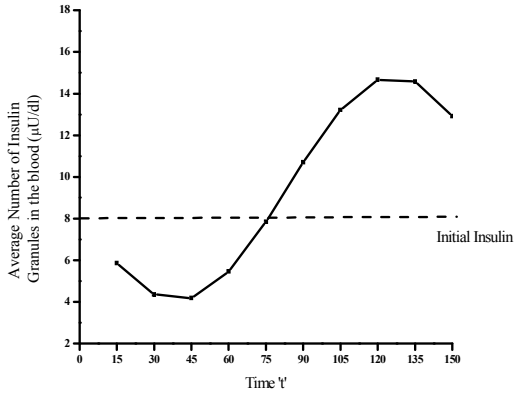
The values of Average glucose level, average insulin level, variance of glucose level, variance of insulin level and correlation coefficient between the average level of glucose and average level of insulin level were calculated for changing values of time period by considering the constant values for the following $E_x(0)=110$, $E_y(0)=8$, $V_x(0)=50$, $V_y(0)=5$, $E_{xy}(0)=80$, $\lambda_g=60$, $\mu_g=0.72$, $b=43.2$, $\lambda_i=6$, $\mu_i=432$

Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
15	166.152	5.864	61.616	5.458	-0.527
30	148.897	4.357	68.284	5.654	-0.326
45	128.019	4.182	73.712	5.775	-0.256
60	108.232	5.455	76.842	5.987	-0.272
75	93.931	7.849	77.142	6.406	-0.329
90	88.065	10.705	74.733	7.072	-0.408
105	91.410	13.217	70.360	7.935	-0.509

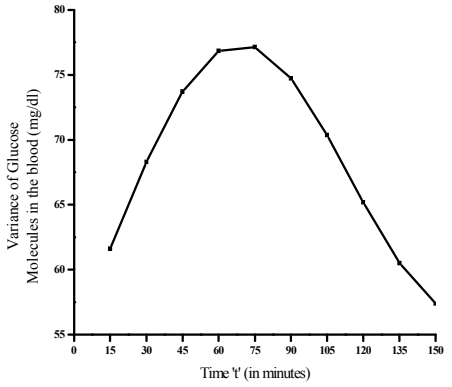
Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
120	102.434	14.658	65.189	8.877	-0.622
135	117.765	14.579	60.506	9.738	-0.705
150	133.122	12.917	57.390	10.368	-0.703



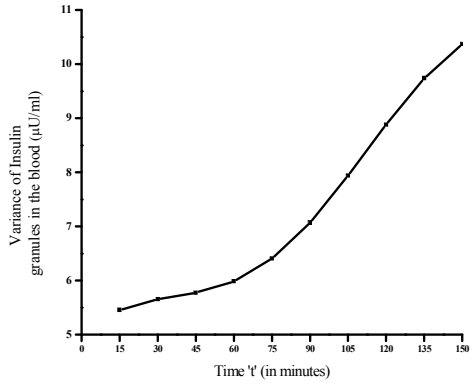
Average levels of Glucose molecules



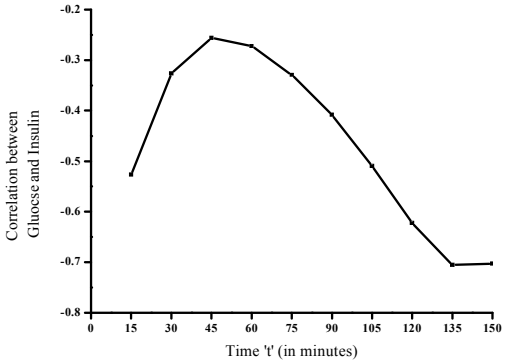
Average levels of Insulin Granules



Variance of Glucose



Variance of Insulin



Correlation between Glucose and Insulin

Figure 3.1: *Graphical presentation on Averages, Variances and Correlation Coefficients based on Case-1*

Discussion for Case-1:

The data sets in table: (3.1), and the graphs (3.1), revealed that the plasma glucose level rises to a peak level up to approximately 166.15 mg/dl after following food intake. The study was initiated after 90 minutes of the food intake, the maximum record is observed at 15^{th} minute after study process. As the time proceeds the glucose level drops below the upper limit of normal range (110 mg/dl) at 60^{th} minute, further it has reached to the lowest basal level (88 mg/dl) at the 90^{th} minute. It has gaining the momentum in increasing glucose levels from 90^{th} minute to 135^{th} minute to reach the basal range (110 mg/dl). Further it is increased 133 mg/dl up to the end of study period at 150^{th} minute.

These fluctuated phenomena of glucose in plasma may be the reasons due to food intake (the level is from 166 mg/dl to 88 mg/dl) from 15^{th} minute to 90^{th} minute. And subsequent levels of minimum to the increased levels (from 88 mg/dl to 133 mg/dl) form time during 90th minute to 150^{th} minute may be due to the contribution of stored glycogen in liver to convert it as glucose. The fluctuations of insulin levels are may be due to healthy consumption levels of glucose.

It is also observed that there is cyclical movement in average level of insulin around 5.455μU/ml. The initial insulin level at 15^{th} minute is 5.9 μU/ml and the lowest level (4.18 μU/ml) is observed at 45^{th} minute. Further the flux is continuing to increase the insulin level up to 120^{th} minute (14.66 μU/ml). It indicates the points of inflexion are observed at the time points of 45 and 120 minutes.

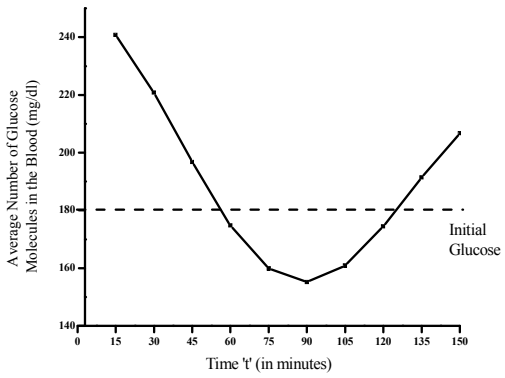
Regarding the variance of glucose levels, it rises up to 75 minutes and it will be decreasing after 75^{th} minute. Meanwhile it is observed that the variances of insulin levels are increasing consistently throughout the study period. These happenings may be due to regularized consumption of glucose. Further it indicates that there is increased variability of insulin over a period of time. Very interesting observation regarding the correlation between the level of glucose and the level of insulin is negative throughout the study period. It indicates that the increased level of insulin leads to decreased levels of glucose and vice versa. It is a wanted phenomenon regarding the glucose insulin regulatory systems.

Case-2: Persons prone to T2DM

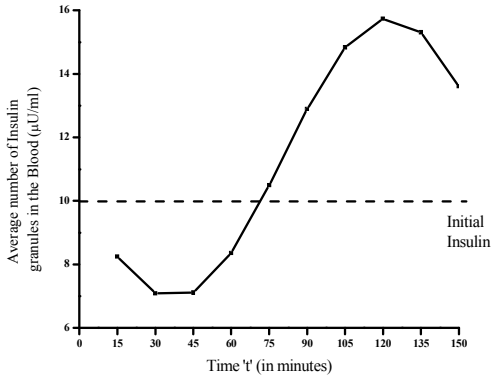
Table: 3.2. Data Set for Case-2

The values of Average levels of glucose, average levels of insulin, variance of glucose level, variance of insulin level and correlation coefficient between the average level of glucose and average level of insulin level were calculated for changing values of time period (150 minutes) by considering the constant values for the following $E_x(0)=180,\ E_y(0)=10,\ V_x(0)=80,\ V_y(0)=5,\ E_{xy}(0)=100,\ \lambda_g=80,\ \mu_g=0.72,$ $b=43.2,\ \lambda_i=6,$ and $\mu_i=432$

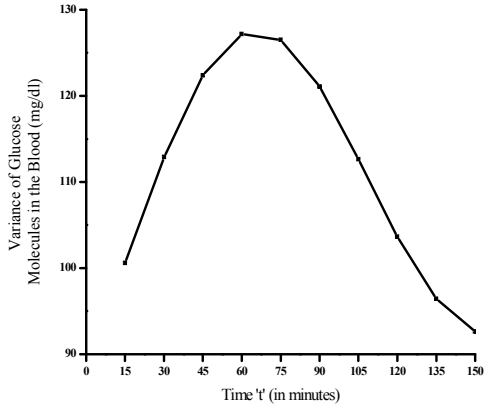
Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
15	240.797	8.24367	100.596	5.73788	-0.1610
30	220.768	7.09226	112.911	6.0816	-0.1670
45	196.812	7.11214	122.391	6.34401	-0.2460
60	174.797	8.36122	127.15	6.79984	-0.3708
75	159.896	10.4956	126.487	7.62673	-0.5102
90	155.187	12.8899	121.053	8.85461	-0.6371
105	160.899	14.8328	112.639	10.3612	-0.7322
120	174.483	15.7369	103.649	11.9125	-0.7807
135	191.458	15.3055	96.4289	13.234	-0.7666
150	206.752	13.6091	92.6425	14.0922	-0.6806



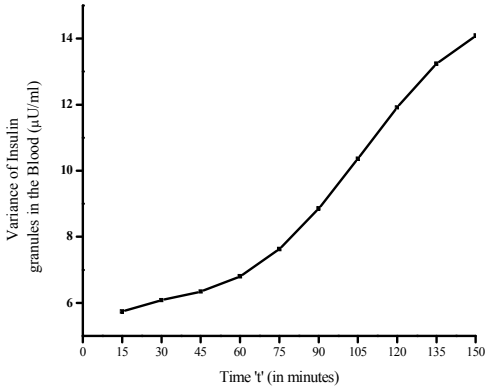
Average levels of Glucose molecules



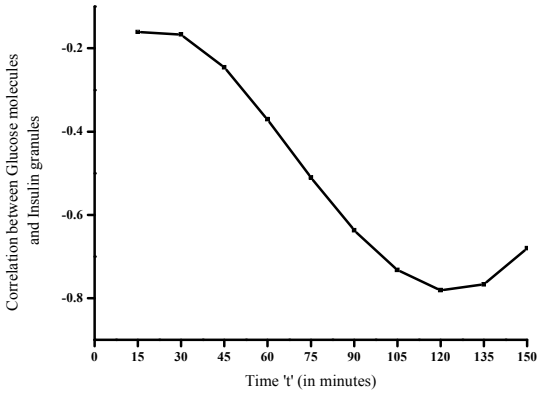
Average levels of Insulin Granules



Variance of Glucose



Variance of Insulin



Correlation between Glucose and Insulin

Figure 3.2: *Graphical presentation on Averages, Variances and Correlation Coefficients based on Case-1*

Discussion for Case-2

The data sets in table: (3.2), and the graphs (3.2), revealed that the plasma glucose level rises to a peak level up to approximately 240 mg/dl after following food intake. The study was initiated after 90 minutes of the food intake, the maximum record is observed at 15^{th} minute after study process. As the time proceeds the glucose level drops below the range (180 mg/dl) for patients who prone to diabetes at 75^{th} minute, further it has reached to the lowest level (155 mg/dl) at the 90^{th} minute. It has gaining the momentum in increasing glucose levels from 90^{th} minute to 135^{th} minute to reach the basal range (180 mg/dl). Further it is increased 206.75 mg/dl up to the end of study period at 150^{th} minute.

These fluctuated phenomena of glucose in plasma may be the reasons due to food intake (the level is from 240.80 mg/dl to 155.18 mg/dl) from 15^{th} minute to 90^{th}minute. And subsequent levels of minimum to the increased levels (from 155.18

mg/dl to 206.75 mg/dl) from 90th minute to 150th minute may be due to the contribution of stored glycogen in liver to convert it as glucose.

It is also observed that there is cyclical movement in average level of insulin around 8.36 μU/ml. The initial insulin level at 15th minute is 8.24 μU/ml and the lowest level (7.11 μU/ml) is observed at 45th minute. Further the flux is continuing to increase the insulin level up to 120th minute (15.73 μU/ml). It indicates the points of inflexion are observed at the time points of 45 and 120 minutes. Further it is decreased 13.60 μU/ml up to the end of study period at 150th minute.

Regarding the variance of glucose levels, it rises 126.48 up to 75thminutes and it will be decreasing after 75th minute. Meanwhile it is observed that the variances of insulin levels are increasing consistently throughout the study period. These happenings may be due to regularized consumption of glucose. Further it indicates that there is increased variability of insulin over a period of time. The correlation between the level of glucose and the level of insulin is negative throughout the study. And it is observed decrement up to120th minute after that there is an increment up to end of the study period due to fluctuations of consumption of both glucose and insulin.

Chapter-4

Stochastic Model for Glucose & Insulin Levels in Acute Hyperglycemic T2DM Patients on Insulin Intervention

Introduction

In this chapter, a bivariate stochastic model for glucose/insulin regulatory system in acute hyperglycemic conditions of T2DM with the intervention of insulin through external sources is proposed on the similar lines of chapter-2. The pathophysiology related to glucose metabolism is modeled with proposed postulates of the processes behind glucose and insulin dynamics. This model has given the set of simultaneous linear differential equations regarding the levels of glucose and insulin in blood plasma under the influence of induced insulin through external sources. If the secreted insulin is not enough to meet the requirements of glucose conversion into energy, then external source of inducing insulin is required. In this chapter, we considered the arrival of insulin through external induced sources as an intervention of the treatment. The proposed model has provided the set of differential equations for measuring the averages and variances of glucose and insulin levels. This set of equations has also provided the covariance function so as to measure the correlation coefficient between the levels of glucose and insulin levels. This model has addressed the dynamics of glucose/insulin among the T2DM patients who are in heavy glycemic conditions and under the treatment of external induced insulin. The model behavior was analyzed to get the indicators of glucose and insulin levels and to monitor the wanted levels of them.

Stochastic Model

The set of proposed linear differential equations in this model are on similar lines of assumptions and postulates of the model developed in chapter-2, which describes that the arrival of insulin to blood stream is through pancreas only. The additional feature of the model includes the intervention of insulin to T2DM patients. This chapter is on developing a stochastic model for measuring various statistical values of the acute hyperglycemic patients, where the intervention of insulin through induced external sources in addition to the contribution of pancreas. Solving the developed equations for deriving all the five measures through classical or analytical

approach is quite tedious and cumbersome. More over the results obtained through analytical methods shall not provide the exact solutions for all the times. The limitations behind getting the measures such as average number glucose molecules, average number of insulin granules, variance of level of glucose, variance of insulin level and covariance between the levels of glucose and insulin at point of time, is that all the five equations are related as one is dependent on the other measures. Linear dependent differential equations are the real bottle neck of the problem to break. That is the reason why the classical solutions for chapter-2 are provided only for average number of glucose molecules and average number of insulin granules, under the assumption that the variances and co-variances are known and constant. But, in real life situations, assuming the existence of known variance and that too it is constant has no relevance. Hence there is a need of getting all the statistical measures by treating all the developed five equations by accepting the truth that the variances or co-variances are not constants. The values of statistical measures in the model are explored with Runge-Kutta numerical method.

The following schematic diagram will explain the arrival and disposal of both Glucose and Insulin in acute hyperglycemic patients who are under treatment of intervention of induced insulin through external sources.

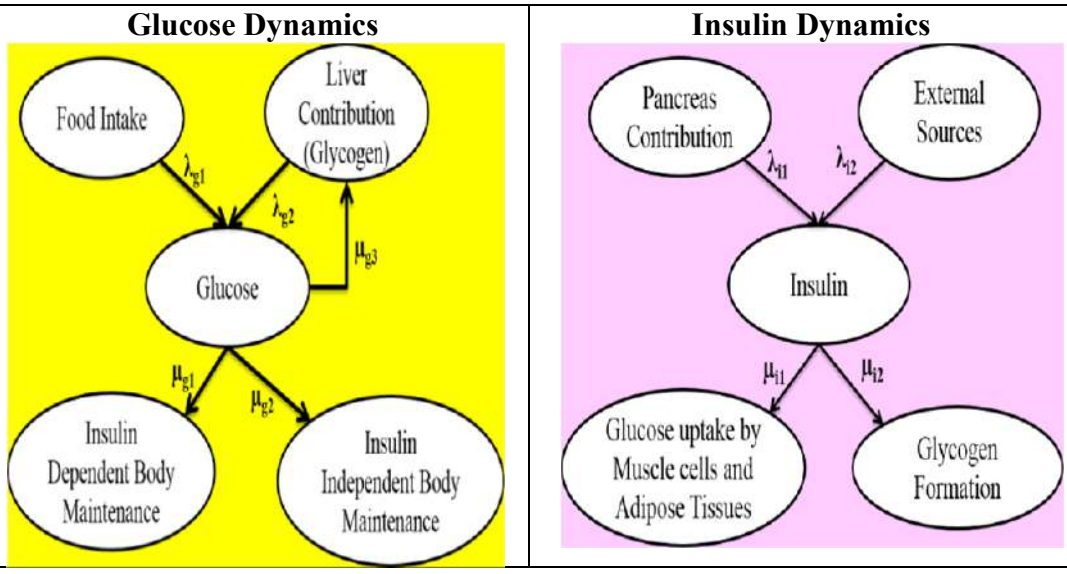


Figure 4.0: Schematic Diagram for Glucose and Insulin arrivals and disposals

Assumptions and Postulates of the Stochastic Model

All most all assumptions of the model in chapter-2 are considered here except the arrival of insulin through external sources. The additional assumptions in this model are

- Let λ_{i1} be the rate of arrival of insulin granules from the β-cells with the involvement of Pancreas.
- Let λ_{i2} be the rate of arrival of insulin granules with the induced external sources respectively per unit time.

Basing on the additional assumptions, the relates extended postulates are

- Probability of arrival of one insulin granule during Δt, given that the arrival of insulin granules molecules based on 'b' number of β-cells in the pancreas during (0, t) is $b.\lambda_{i1}.\Delta t + O(\Delta t)$.
- Probability of arrival of one insulin granule from external sources during Δt is $\lambda_{i2}.\Delta t + O(\Delta t)$.

Differential- Difference Equations of the Model

As $P_{n,m}(t)$ is the probability of existing of 'n' glucose molecules and 'm' insulin granules in the blood stream at a point of time't', the difference equation is

$$\begin{aligned}
P_{n,m}(t+\Delta t) = {} & P_{n,m}(t)[1-(\lambda_{g1}\Delta t + O(\Delta t))] \\
& [1-(\lambda_{g2}\Delta t + O(\Delta t))][1-nm\mu_{g1}\Delta t + O(\Delta t)] \\
& [1-n\mu_{g2}\Delta t + O(\Delta t)][1-nm\,\mu_{g3}\Delta t + O(\Delta t)] \\
& [1-b\lambda_{i1}\Delta t + O(\Delta t)][1-\lambda_{i2}\Delta t + O(\Delta t)] \\
& [1-nm\mu_{i1}\Delta t + O(\Delta t)][1-nm\mu_{i2}\Delta t + O(\Delta t)] \\
& + P_{n-1,m}(t)\{[\lambda_{g1}\Delta t + O(\Delta t)] + [\lambda_{g2}\Delta t + O(\Delta t)]\} \\
& + P_{n+1,m}(t)\{[(n+1)m\mu_{g1}\Delta t + O(\Delta t) + [(n+1)\mu_{g2}\Delta t + O(\Delta t)] + [(n+1)m\mu_{g3}\Delta t + O(\Delta t)] \\
& + P_{n,m-1}(t)\{[b\lambda_{i1}\Delta t + O(\Delta t)] + [\lambda_{i2}\Delta t + O(\Delta t)]\} \\
& + P_{n,m+1}(t)\{[n(m+1)\mu_{i1}\Delta t + O(\Delta t)] + [n(m+1)\mu_{i2}\Delta t + O(\Delta t)] \\
& + P_{n\pm i,m\pm i}(t)[O(\Delta t)^2]\ for\ i \geq 2
\end{aligned}$$

…(4.1)

The other difference equations for m = 0,1 and n = 0,1 are

$$P_{0,0}(t+\Delta t) = P_{0,0}(t)[1-(\lambda_{g1}\Delta t + O(\Delta t))][1-(\lambda_{g2}\Delta t + O(\Delta t))]$$
$$[1-b\lambda_{i1}\Delta t + O(\Delta t)][1-\lambda_{i2}\Delta t + O(\Delta t)] \quad \ldots (4.2)$$
$$+ P_{1,0}(t)\{(n+1)\mu_{g2}\Delta t + O(\Delta t)$$

$$P_{1,0}(t+\Delta t) = P_{1,0}(t)[1-(\lambda_{g1}\Delta t + O(\Delta t))]$$
$$[1-n\mu_{g2}\Delta t + O(\Delta t)][1-b\lambda_{i1}\Delta t + O(\Delta t)][1-\lambda_{i2}\Delta t + O(\Delta t)]$$
$$+ P_{0,0}(t)\{[\lambda_{g1}\Delta t + O(\Delta t)] + [\lambda_{g2}\Delta t + O(\Delta t)]\}$$
$$+ P_{2,0}(t)\{[2\mu_{g2}\Delta t + O(\Delta t)] + P_{1,1}(t)\{[\mu_{i1}\Delta t + O(\Delta t)] + [\mu_{i2}\Delta t + O(\Delta t)]$$

… (4.3)

$$P_{0,1}(t+\Delta t) = P_{0,1}(t)[1-(\lambda_{g1}\Delta t + O(\Delta t))]$$
$$[1-b\lambda_{i1}\Delta t + O(\Delta t)][1-\lambda_{i2}\Delta t + O(\Delta t)]$$
$$+ P_{1,1}(t)\{[\mu_{g1}\Delta t + O(\Delta t)] + [\mu_{g2}\Delta t + O(\Delta t)] + [\mu_{g3}\Delta t + O(\Delta t)]$$
$$+ P_{0,0}(t)\{[b\lambda_{i1}\Delta t + O(\Delta t)] + [\lambda_{i2}\Delta t + O(\Delta t)]\}$$

… (4.4)

The Differential equations are

$$\frac{d}{dt}P_{n,m}(\mathrm{t}) = \{-(\lambda_{g1}+\lambda_{g2}+nm\mu_{g1}+n\mu_{g2}+nm\,\mu_{g3}+b\lambda_{i1}+\lambda_{i2}+nm\mu_{i1}+nm\mu_{i2})\}P_{n,m}(t)$$
$$+\{[\lambda_{g1}+\lambda_{g2}\}P_{n-1,m}(t)+\{(n+1)m\mu_{g1}+(n+1)\mu_{g2}$$
$$+(n+1)m\mu_{g3}\}P_{n+1,m}(t)+\{b\lambda_{i1}+\lambda_{i2}\}P_{n,m-1}(t)$$
$$+\{n(m+1)\mu_{i1}+n(m+1)\mu_{i2}\}P_{n,m+1}(t)\ for\ n,m\geq 1$$

…(4.5)

The other differential equations of the model for the values of n=0, 1 and m=0, 1are

$$\frac{d}{dt}P_{0,0}(t) = -(\lambda_{g1}+\lambda_{g2}+b\lambda_{i1}+\lambda_{i2})P_{0,0}(t)+\mu_{g2}P_{1,0}(t) \quad \ldots (4.6)$$

$$\frac{d}{dt}P_{1,0}(t) = \{-(\lambda_{g1}+\lambda_{g2}+\mu_{g2}+b\lambda_{i1}+\lambda_{i2})\}P_{1,0}(t)+\{\lambda_{g1}+\lambda_{g2}\}P_{0,0}(t)$$
$$+2\mu_{g2}P_{2,0}(t)+\{\mu_{i1}+\mu_{i2}\}P_{1,1}(t) \quad \ldots (4.7)$$

$$\frac{d}{dt}P_{0,1}(t) = -(\lambda_{g1}+\lambda_{g2}+b\lambda_{i1}+\lambda_{i2})P_{0,1}(t)+\{\mu_{g1}+\mu_{g2}+\mu_{g3}\}P_{1,1}(t) \quad \ldots (4.8)$$
$$+\{b\lambda_{i1}+\lambda_{i2}\}P_{0,0}(t)$$

The Initial conditions of Probability generating is

$$P_{n,m}(0)=1;\ for\ n=N_0,m=M_0\ \ and\ \ P_{n,m}(0)\neq 1;\ for\ n\neq N_0,m\neq M_0$$

Where N_0 and M_0 are initial values of glucose and insulin.

Let $P(x,y;t)$ be the joint probability generating function of $p_{n,m}(t)$;

Where $P(x,y;t)=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m p_{n,m}(t)$ … (4.9)

Multiplying the equations (4.5) to (4.8) with $x^n y^m$ and summing overall n and m, we obtain the probability generating function is

$$\begin{aligned}
P_{n,m}(x,y:\mathrm{t}) &= -(\lambda_{g1}+\lambda_{g2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m P_{n,m}(t)-\mu_{g1}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m nmP_{n,m}(t)\\
&-\mu_{g2}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m nP_{n,m}(t)-\mu_{g3}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m nmP_{n,m}(t)\\
&-(b\lambda_{i1}+\lambda_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m P_{n,m}(t)-(\mu_{i1}+\mu_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}nmx^n y^m P_{n,m}(t)\\
&+\{\lambda_{g1}+\lambda_{g2}\}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m P_{n-1,m}(t)+\mu_{g1}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m (n+1)mP_{n+1,m}(t)\\
&+\mu_{g2}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}(n+1)x^n y^m P_{n+1,m}(t)+\mu_{g3}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}(n+1)mx^n y^m P_{n+1,m}(t)\\
&+\{b\lambda_{i1}+\lambda_{i2}\}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}x^n y^m P_{n,m-1}(t)+(\mu_{i1}+\mu_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}n\,(m+1)x^n y^m P_{n,m+1}(t)
\end{aligned}$$

… (4.10)

Simplifying the equation(4.10), then the reduces to

$$\begin{aligned}
\frac{\partial P(x,y;t)}{\partial t} &= \{(x-1)(\lambda_{g1}+\lambda_{g2})+(y-1)(b\lambda_{i1}+\lambda_{i2})\}P(x,y;t)\\
&+\{xy(\mu_{g1}+\mu_{g3}+\mu_{i1}+\mu_{i2})+y(\mu_{g1}+\mu_{g3})+x(\mu_{i1}+\mu_{i2})\}\frac{\partial^2 P(x,y;t)}{\partial x\partial y}\\
&+\{(1-x)\mu_{g2}\}\frac{\partial P(x,y;t)}{\partial x}
\end{aligned}$$

… (4.11)

We can obtain the characteristics of the model by using the joint cumulant generating function of $p_{n,m}(t)$. Taking $x=e^u, y=e^v$ and denoting $c(u,v;t)$ as the joint cumulant generating function of $p_{n,m}(t)$, equation (4.11) becomes

$$\frac{\partial K(u,v;t)}{\partial t} = \{(u+\frac{u^2}{2})(\lambda_{g1}+\lambda_{g2})+(v+\frac{v^2}{2})(b\lambda_{i1}+\lambda_{i2})\}\left[uE_x(t)+vE_y(t)+\frac{u^2}{2}V_x(t)+\frac{v^2}{2}V_y(t)+uvE_{xy}(t)\right]$$
$$+\{-(\mu_{g1}+\mu_{g3}+\mu_{i1}+\mu_{i2})+e^{-u}(\mu_{g1}+\mu_{g3})+e^{-v}(\mu_{i1}+\mu_{i2})\}$$
$$\begin{bmatrix} E_{xy}(t)-(E_x(t)+uV_x(t)+vE_{xy}(t)) \\ -(E_y(t)+vV_y(t)+uE_{xy}(t)) \\ -(uE_x(t)+vE_y(t)+\frac{u^2}{2}V_x(t)+\frac{v^2}{2}V_y(t)+uvE_{xy}(t)) \end{bmatrix}$$
$$+\{(1-e^u)\mu_{g2}\}\left[(E_x(t)+uV_x(t)+vE_{xy}(t))-(uE_x(t)+vE_y(t)+\frac{u^2}{2}V_x(t)+\frac{v^2}{2}V_y(t)+uvE_{xy}(t))\right]$$

… (4.12)

On comparing the coefficients of u's, v's, $\frac{u^2}{2}$'s, $\frac{v^2}{2}$'s and uv's , arrived to the simultaneous ordinary differential equations.

$$\frac{d}{dt}\left(E_x(t)\right) = -(\mu_{g1}+\mu_{g3})E_{xy}(t)+[\mu_{g1}+\mu_{g3}-\mu_{g2}]E_x(t)+[\mu_{g1}+\mu_{g3}]E_y(t) \quad \text{... (4.13)}$$

$$\frac{d}{dt}\left(E_y(t)\right) = -(\mu_{i1}+\mu_{i2})E_{xy}(t)+(\mu_{i1}+\mu_{i2})E_x(t)+(\mu_{i1}+\mu_{i2})E_y(t) \quad \text{... (4.14)}$$

$$\frac{d}{dt}\left(V_x(t)\right) = [2(\lambda_{g1}+\lambda_{g2})+(\mu_{g1}+3\mu_{g2}+\mu_{g3})]E_x(t)+[2(\mu_{g1}+\mu_{g3}-\mu_{g2})]V_x(t)$$
$$+3(\mu_{g1}+\mu_{g3})E_{xy}(t)-(\mu_{g1}+\mu_{g3})E_y(t)$$

... (4.15)

$$\frac{d}{dt}\left(V_y(t)\right) = [2(b\lambda_{i1}+\lambda_{i2})+(\mu_{i1}+\mu_{i2})]E_y(t)$$
$$+2(\mu_{i1}+\mu_{i2})V_y(t)-(\mu_{i1}+\mu_{i2})E_x(t)+(\mu_{i1}+\mu_{i2})E_{xy}(t) \quad \text{... (4.16)}$$

$$\frac{d}{dt}\left(E_{xy}(t)\right) = \left[(\lambda_{g1}+\lambda_{g2})+(\mu_{g1}+\mu_{g2}+\mu_{g3})\right]E_y(t)$$
$$+\left[(b\lambda_{i1}+\lambda_{i2})+(\mu_{i1}+\mu_{i2})\right]E_x(t)+(\mu_{g1}+\mu_{g3})V_y(t)$$
$$+(\mu_{i1}+\mu_{i2})V_x(t)+\left[(\mu_{g1}+\mu_{g3})+(\mu_{i1}+\mu_{i2})-\mu_{g2}\right]E_{xy}(t)$$
... (4.17)

Solution for Differential Equations using Runge-Kutta Method

A bivariate stochastic model for glucose/insulin regulatory system in acute hyperglycemic conditions of T2DM with the intervention of insulin through external sources is developed to get the set of simultaneous linear differential equations. Runge-Kutta method has been considered for getting various statistical measures on

glucose and insulin levels from the developed differential equations to address the dynamics of glucose/insulin among the T2DM patients who are in heavy glycemic conditions. Usual methods of diabetes management include three fold actions namely (i) minimizing the excess food intake, (ii) sufficient physical activity and (iii) proper medication and insulin intervention (if necessary). Since the intervention of insulin is the third and last resort of diabetes management, the focus of study is given on comparative analysis among two groups of patients who are with at least mean glucose levels of 250 mg/dl and 300 mg/dl respectively. Approximate solutions to the said set of equations are obtained by developing FORTRAN code and its running with supportive operating systems. The detailed numerical and sensitivity analysis has been done to get the alarming indicators of the diabetes conditions. Patterns of all statistical measures are explored by executing the developed FOTRAN code. The extracted results were presented in tabular form as well as graphical means.

Numerical Illustration on Simulation of Statistical Measures and Analysis

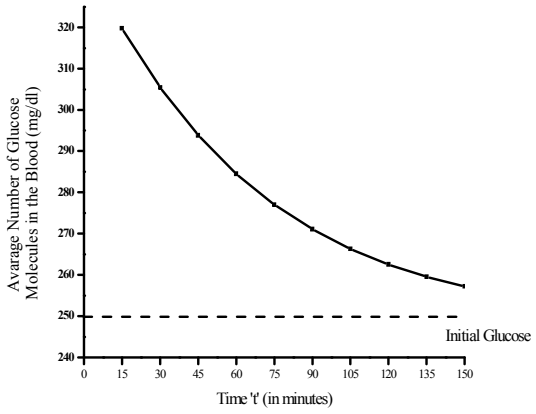
In order to get the approximate values of statistical measures such as average glucose level, average insulin level, variances of glucose and insulin levels, correlation coefficient between the glucose level and insulin level with the differential equations obtained from 4.13 through 4.17, then numerical method namely Runge-Kutta method has been used. The study has further focused on getting the indicators of two categories of subjects namely (i) Patients with Mean Glucose level at 250 mg/dl and (ii) Patients with Mean Glucose level at 300 mg/dl.

Case-I: Patients with Mean Glucose level at 250 mg/dl:

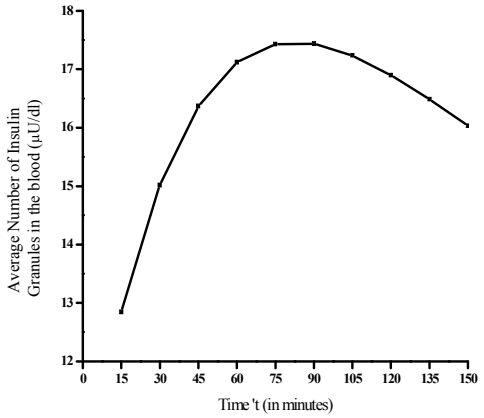
The values of Average glucose level, average insulin level, variance of glucose level, variance of insulin level and correlation coefficient between the average level of glucose and average level of insulin level were calculated for changing values of time period by considering the constant values for the following $E_x(0) = 250$, $E_y(0) = 8$, $V_x(0) = 80$, $V_y(0) = 7$, $E_{xy}(0) = 80$, $\lambda_{g1} = 0.5$, $\lambda_{g2} = 0.2$, $\mu_{g1} = 0.1$, $\mu_{g2} = 1$, $\mu_{g3} = 0.001$, $\lambda_{i1} = 1$, $\lambda_{i2} = 0.5$, $\mu_{i1} = 0.03$, $\mu_{i2} = 0.001$ and $b = 20$.

Table: 4.1. Values of $E_x(t), E_y(t), V_x(t), V_y(t)$ and correlation coefficient for case-1 patients:

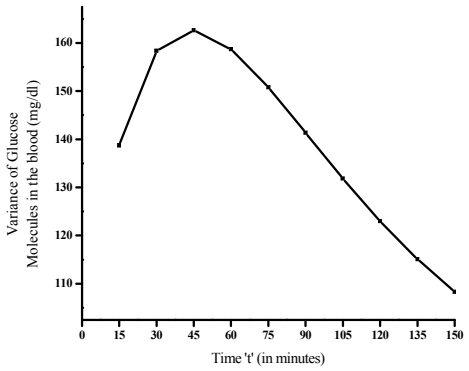
Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
15	319.7704	12.8466	138.7173	7.4647	-0.5916
30	305.4220	15.0159	158.3560	7.7317	-0.5764
45	293.8386	16.3697	162.6320	7.3499	-0.5893
60	284.5145	17.1193	158.6734	7.4863	-0.5829
75	277.0339	17.4320	150.7444	8.6280	-0.5427
90	271.0543	17.4375	141.3323	9.9632	-0.5053
105	266.2934	17.2352	131.8318	11.4094	-0.4730
120	262.5190	16.8996	122.9741	12.9074	-0.4456
135	259.5405	16.4856	115.0946	14.4157	-0.4225
150	257.2016	16.0329	108.2996	15.9065	-0.4028



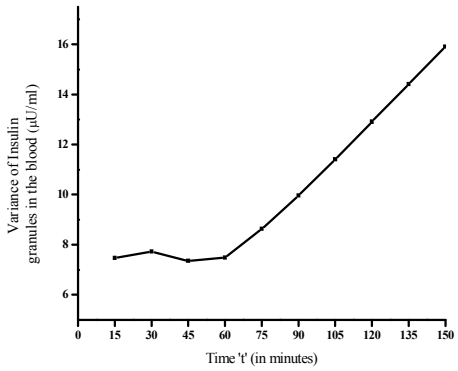
Average levels of Glucose molecules



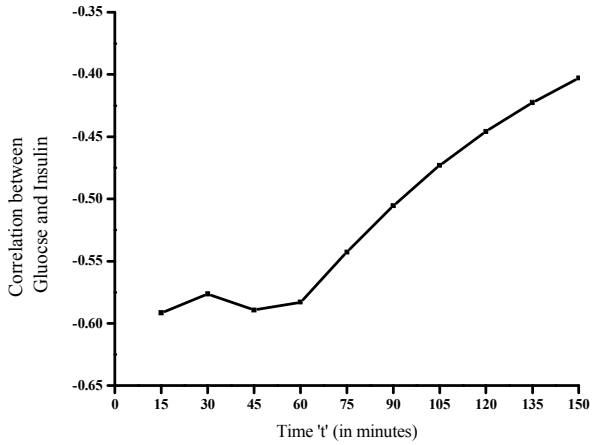
Average levels of Insulin Granules



Variance of Glucose



Variance of Insulin



Correlation between Glucose and Insulin

Figure 4.1: *Graphical presentation on Averages, Variances and Correlation Coefficients based on Case-1*

Discussion for Case-1:

Observing the patterns of average glucose levels in the patients of acute hyperglycemia who have an average glucose level around 250 mg/dl during a50 minutes of study, there is a gradual decline from initial level around 320 mg/dl at 15^{th} minute to 257 mg/dl at 150^{th} minute. It gives an indicator that the gradual declining may be due to induced insulin level 0.5 μ/dl and the existing average insulin levels 12.85 μ/dl at 15^{th} minute and gradual increase in average insulin level up to 17.4375 μ/dl at 90^{th} minute and decreased average insulin up to 16.0329 μ/dl at 150^{th} minute. Hence, we may conclude that the gradual decrement in glucose levels among hyperglycemic patients can be achieved by intervention of induced insulin from external sources.

Regarding the patterns of variance levels of glucose, the distribution is positively skewed during 150 minutes of study period. There is a steep increment in variance of glucose level from 138.72 μ/dl at 15^{th} minute to 162.63 μ/dl at 45^{th} minute and gradual and slow decrement in variance up to 108.2996 μ/dl at 150^{th} minute. However, the variance pattern of insulin levels reveals there is gradual increment throughout study period. Hence we may conclude that the increased volatility in insulin leads to gradual decrement in average glucose levels.

The indicators of correlation coefficient between the average level of glucose and the average level of insulin reveal that there is a negative relation between these two variables. It further communicating that the increased levels of glucose will be

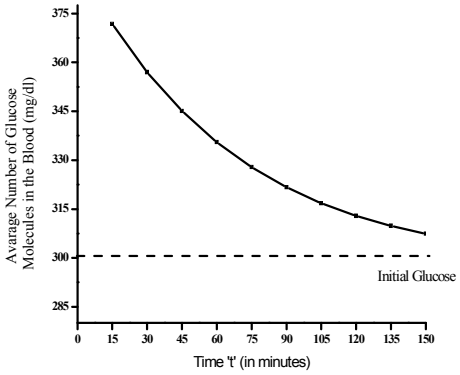
observed with the decreased levels of insulin and vice versa. Hence, the wanted levels of glucose decrement can be achieved by increasing the required levels of insulin. Further it is observed that the highest linear intensity relationship is at initial time of study at 15th minute and the least relationship is observed at 150th minute. It is also indicating that the more intensity of relationship is observed at the initial study period and the lesser the intensity is observed during fag end periods.

Case-2: Patients with Mean Glucose level at 300 mg/dl

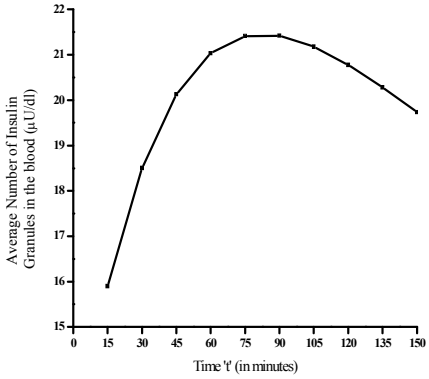
The values of Average glucose level, average insulin level, variance of glucose level, variance of insulin level and correlation coefficient between the average level of glucose and average level of insulin level were calculated for changing values of time period by considering the constant values for the following $E_x(0) = 300$, $E_y(0) = 10$, $V_x(0) = 80$, $V_y(0) = 7$, $E_{xy}(0) = 80$, $\lambda_{g1} = 0.5$, $\lambda_{g2} = 0.2$, $\mu_{g1} = 0.1$, $\mu_{g2} = 1$, $\mu_{g3} = 0.001$, $\lambda_{i1} = 1$, $\lambda_{i2} = 0.5$, $\mu_{i1} = 0.03$, $\mu_{i2} = 0.001$ and $b = 20$.

Table: 4.2. Values of $E_x(t), E_y(t), V_x(t), V_y(t)$ and correlation coefficient for case-2 patients:

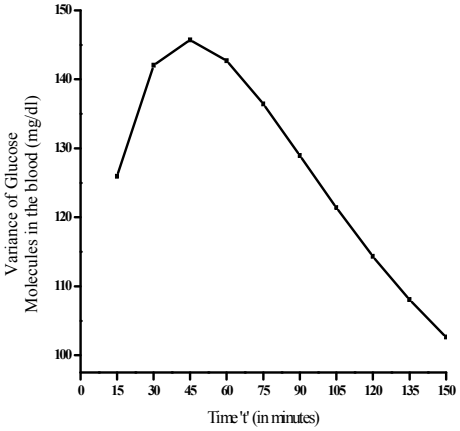
Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
15	371.7645	15.8975	125.9526	7.6894	-0.5872
30	357.0071	18.5029	142.0330	8.0016	-0.5807
45	345.0934	20.1300	145.6899	7.5348	-0.6041
60	335.5035	21.0320	142.6740	7.4778	-0.6110
75	327.8095	21.4094	136.4275	8.8575	-0.5646
90	321.6592	21.4179	128.9598	10.4701	-0.5216
105	316.7621	21.1767	121.3992	12.2164	-0.4843
120	312.8797	20.7751	114.3384	14.0254	-0.4527
135	309.8158	20.2793	108.0510	15.8473	-0.4259
150	307.4097	19.7366	102.6252	17.6487	-0.4030



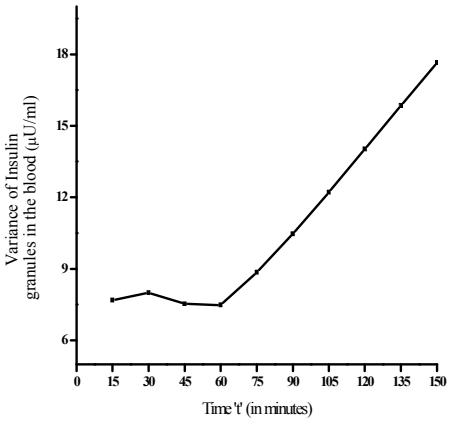
Average levels of Glucose molecules



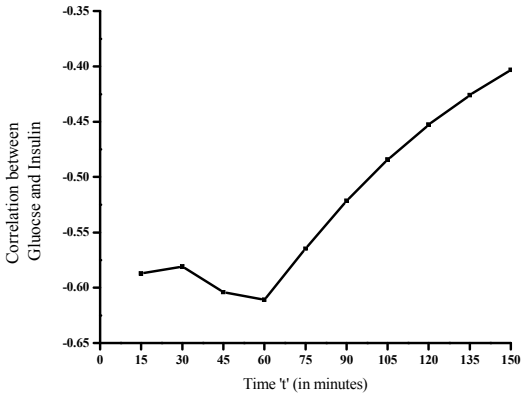
Average levels of Insulin Granules



Variance of Glucose



Variance of Insulin



Correlation between Glucose and Insulin

Figure 4.2: *Graphical presentation on Averages, Variances and Correlation Coefficients based on Case-2*

Discussion for Case-2:

Observing the patterns of average glucose levels in the patients of acute hyperglycemia who have an average glucose level around 300 mg/dl during a150 minutes of study, there is a gradual decline from initial level around 371.8 mg/dl at 15^{th} minute to 307.4 mg/dl at 150^{th} minute. It gives an indicator that the gradual declining may be due to induced insulin level 0.5 μ/dl and the existing average insulin levels 15.9 μ/dl at 15^{th} minute and gradual increase in average insulin level up to 21.41 μ/dl at 90^{th} minute and decre*a*sed average insulin up to 19.73 μ/dl at 150^{th} minute. Hence, we may conclude that the gradual decrement in glucose levels among hyperglycemic patients can be achieved by intervention of induced insulin from external sources.

Regarding the patterns of variance levels of glucose, the distribution is positively skewed during 150 minutes of study period. There is a steep increment in variance of glucose level from 125.95 μ/dl at 15^{th} minute to 145.68 μ/dl at 45^{th} minute and gradual and slow decrement in variance up to 102.6252 μ/dl at 150^{th} minute. However, the variance pattern of insulin levels reveals there is gradual increment throughout study period. Hence we may conclude that the increased volatility in insulin leads to gradual decrement in average glucose levels.

The indicator of correlation coefficient between the average level of glucose and the average level of insulin reveals that there is a negative relation between these two variables. It further communicating that the increased levels of glucose will be observed with the decreased levels of insulin and vice versa. Hence, the wanted levels of glucose decrement can be achieved by increasing the required levels of insulin. Further it is observed that the linear intensity relationship is at initial time of study is -0.5872 at 15^{th} minute and declining up to 60^{th} minute and after that increment relation observed at 150^{th} minute.

Chapter-5

Stochastic Model for Glucose & Insulin Levels in Acute Hyperglycemic T2DM Patients with Induced Insulin and Physical Activity

Introduction

The previous chapter deals with development of model to study the insulin and glucose levels of blood at a point of time under the environment of insulin intervention. However, this chapter deals with stochastic model's development for getting the dynamics of glucose and insulin among acute hyperglycemic T2DM patients when they are in the treatment of two simultaneous interventions namely (i) insulin inducing through external sources and (ii) excess consumption of glucose through physical activities or exercises. The structure of this work consists of the steps like (i) understanding the glucose metabolism with insulin dependent and insulin independent environments; (ii) considering the suitable Pathophysiology assumptions of glucose metabolism to formulate a model; (iii) defining the postulates by relating the biological processes linked with point process experimentation; (iv) development of difference equations for the bivariate stochastic process of simultaneous arrival and consumptions of both glucose and insulin; (v) deriving the differential equations for the functions of average levels of glucose, average size of insulin, variance of glucose level, variance of insulin level and covariance between the levels of insulin and glucose; (vi) solving the differential equations and exploring the approximate values of mentioned statistical measures through numerical methods; (vii) and analyzing the model behaviour through numerical illustrations and graphical devices. This model has addressed the empirical means of exploring the indicators on glucose and insulin levels by a FORTRAN program for soft computations. The developed differential equations were solved through Runge-Kutta method. This approach is more practically adoptable to get the numerical values through simulation techniques as there are limitations in getting the analytical solutions. The linear dependency between several differential equations of the statistical measures leads to search the alternative of numerical method rather than the classical methods.

Stochastic Model for Glucose & Insulin Regulatory System in T2DM Patients

The model developed on glucose and insulin arrivals/consumptions in the mechanism of their metabolism in healthy individuals will help in measuring the parameters of them to get the indicators of the status. The following diagram will provide the scheme behind the processes.

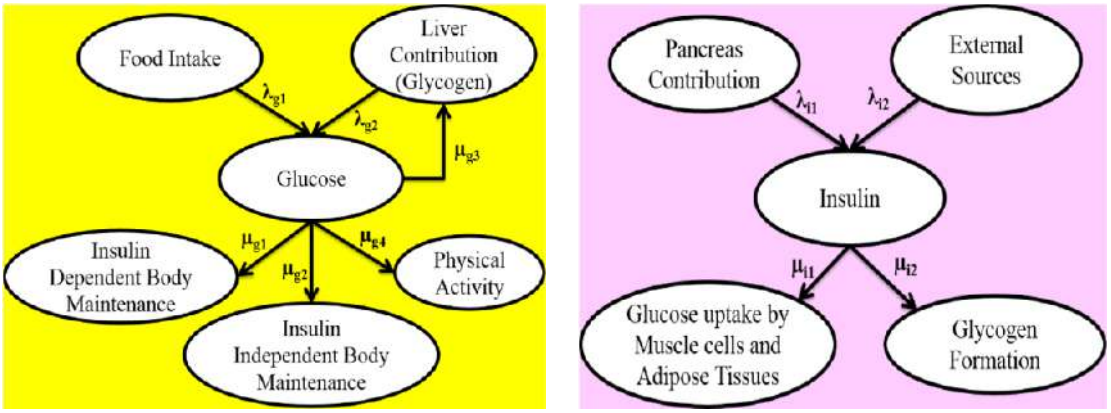


Figure – 5.0: Dynamics of Glucose and Insulin Mechanism

Differential Equations of the Model

Observing the above schematic diagram, the intervention of physical activity as a treatment method is an additional component when compared to the previous chapter's model.

- Let the added physical activity will result in excess consumption of glucose.
- Let μ_{g4} be the rate of consumption of glucose per unit time through the intervention namely physical activity.
- The additional postulate of this models (to chapter-4) is that the Probability of disappearing of one glucose molecule during Δt, provided there exists 'n' glucose molecules and 'm' insulin granules during (0,t) in the blood stream as a reason for physical activity is $n.m.\mu_{g4}.\Delta t + O(\Delta t)$.
- Let $P_{n,m}(t)$ be the probability of existing 'n' glucose molecules and 'm' insulin granules in the blood stream at a point of time't'.
- Let $P_{n,m}(t+\Delta t)$ be the probability that happening of an event in the infinitesimal interval Δt, when there exists 'n' glucose molecules and 'm' insulin granules in the blood stream up to time't',

The difference equation for $P_{n,m}(t)$ is as below.

$$\begin{aligned}
P_{n,m}(t+\Delta t) = {} & P_{n,m}(t)[1-(\lambda_{g1}\Delta t + O(\Delta t))][1-(\lambda_{g2}\Delta t + O(\Delta t))] \\
& [1-nm\,\mu_{g1}\Delta t + O(\Delta t)][1-n\mu_{g2}\Delta t + O(\Delta t)] \\
& [1-nm\ \mu_{g3}\Delta t + O(\Delta t)][1-nm\ \mu_{g4}\Delta t + O(\Delta t)] \\
& [1-b\lambda_{i1}\Delta t + O(\Delta t)][1-\lambda_{i2}\Delta t + O(\Delta t)] \\
& [1-nm\,\mu_{i1}\Delta t + O(\Delta t)][1-nm\,\mu_{i2}\Delta t + O(\Delta t)] \\
& + P_{n-1,m}(t)\{[\lambda_{g1}\Delta t + O(\Delta t)] + [\lambda_{g2}\Delta t + O(\Delta t)]\} \\
& + P_{n+1,m}(t)\{[nm\,\mu_{g1}\Delta t + O(\Delta t) + [n\mu_{g2}\Delta t + O(\Delta t)] \\
& + [nm\,\mu_{g3}\Delta t + O(\Delta t)] + [nm\,\mu_{g4}\Delta t + O(\Delta t)]\} \\
& + P_{n,m-1}(t)\{[b\lambda_{i1}\Delta t + O(\Delta t)] + [\lambda_{i2}\Delta t + O(\Delta t)]\} \\
& + P_{n,m+1}(t)\{[nm\,\mu_{i1}\Delta t + O(\Delta t)] + [nm\,\mu_{i2}\Delta t + O(\Delta t)] \\
& + P_{n\pm i,m\pm i}(t)[\mathrm{O}(\Delta t)^2]\ for\ i \geq 2
\end{aligned} \qquad \ldots (5.1)$$

After Simplification, the above differential difference equation is reduced to

$$\begin{aligned}
\frac{d}{dt}(P_{n,m}(t)) = {} & \{-(\lambda_{g1}+\lambda_{g2}+nm\mu_{g1}+n\mu_{g2}+nm\,\mu_{g3}+nm\,\mu_{g4}+b\lambda_{i1}+\lambda_{i2}+nm\mu_{i1}+nm\mu_{i2})\}P_{n,m}(t) \\
& + \{\lambda_{g1}+\lambda_{g2}\}P_{n-1,m}(t) + \{(n+1)m\mu_{g1}+(n+1)\mu_{g2}+(n+1)m\mu_{g3}+(n+1)m\mu_{g4}\}P_{n+1,m}(t) \\
& + \{b\lambda_{i1}+\lambda_{i2}\}P_{n,m-1}(t) + \{n(m+1)\mu_{i1}+n(m+1)\mu_{i2}\}P_{n,m+1}(t)\ for\ n,m \geq 1
\end{aligned} \qquad \ldots (5.2)$$

With the similar process environments, the differential equations for specific values of n=0, 1 and m=0, 1 are

$$\frac{d}{dt}P_{0,0}(t) = -(\lambda_{g1}+\lambda_{g2}++b\lambda_{i1}+\lambda_{i2})\,P_{0,0}(t) + \mu_{g2}P_{1,0}(t) \qquad \ldots (5.3)$$

$$\begin{aligned}
\frac{d}{dt}P_{1,0}(t) = {} & \{-(\lambda_{g1}+\lambda_{g2}+\mu_{g2}+b\lambda_{i1}+\lambda_{i2})\}\,P_{1,0}(t) + \{\lambda_{g1}+\lambda_{g2}\}P_{0,0}(t) \\
& + 2\mu_{g2}P_{2,0}(t) + \{\mu_{i1}+\mu_{i2}\}P_{1,1}(t)
\end{aligned} \qquad \ldots (5.4)$$

$$\begin{aligned}
\frac{d}{dt}P_{0,1}(t) = {} & -(\lambda_{g1}+\lambda_{g2}+b\lambda_{i1}+\lambda_{i2})\,P_{0,1}(t) + \{\mu_{g1}+\mu_{g2}+\mu_{g3}+\mu_{g4}\}P_{1,1}(t) \\
& + \{b\lambda_{i1}+\lambda_{i2}\}P_{0,0}(t)
\end{aligned} \qquad \ldots (5.5)$$

The initial conditions of Probability are

$P_{n,m}(0) = 1;\ for\ n = N_0, m = M_0\ and\ P_{n,m}(0) \neq 1;\ for\ n \neq N_0, m \neq M_0$

Where N_0 and M_0 are initial values of glucose and insulin.

Let $P(x,y;t)$ be the joint probability generating function of $P_{n,m}(t)$, where

$$P(x,y;t) = \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) \qquad \ldots (5.6)$$

Multiplying the (5.3) to (5.5) with $x^n y^m$ and summing overall n and m, we obtain

$$\begin{aligned}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P'_{n,m}(t) &= -(\lambda_{g1}+\lambda_{g2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t) - \mu_{g1}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nmP_{n,m}(t)\\ &- \mu_{g2}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nP_{n,m}(t) - \mu_{g3}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nmP_{n,m}(t)\\ &- \mu_{g4}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m nmP_{n,m}(t) - (b\lambda_{i1}+\lambda_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m}(t)\\ &- (\mu_{i1}+\mu_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} nmx^n y^m P_{n,m}(t) + \{\lambda_{g1}+\lambda_{g2}\}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n-1,m}(t)\\ &+ \mu_{g1}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m (n+1)mP_{n+1,m}(t) + \mu_{g2}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} (n+1)x^n y^m P_{n+1,m}(t)\\ &+ \mu_{g3}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} (n+1)mx^n y^m P_{n+1,m}(t) + \mu_{g4}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} (n+1)mx^n y^m P_{n+1,m}(t)\\ &+ \{b\lambda_{i1}+\lambda_{i2}\}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} x^n y^m P_{n,m-1}(t) + (\mu_{i1}+\mu_{i2})\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} n(m+1)x^n y^m P_{n,m+1}(t)\end{aligned} \quad \ldots (5.7)$$

Simplifying and rearranging the terms in the equation (5.7), we arrive to the following,

$$\begin{aligned}\frac{\partial P(x,y;t)}{\partial t} &= \{(x-1)(\lambda_{g1}+\lambda_{g2}) + (y-1)(b\lambda_{i1}+\lambda_{i2})\}P(x,y;t)\\ &+ \{-xy(\mu_{g1}+\mu_{g3}+\mu_{g4}+\mu_{i1}+\mu_{i2}) + y(\mu_{g1}+\mu_{g3}+\mu_{g4})\\ &+ x(\mu_{i1}+\mu_{i2})\}\frac{\partial^2 P(x,y;t)}{\partial x\partial y} + \{(1-x)\mu_{g2}\}\frac{\partial P(x,y;t)}{\partial x}\end{aligned} \quad \ldots (5.8)$$

Taking $x = e^u$ and $y = e^v$, denoting $K(u,v;t)$ as the joint cumulant generating function of $P_{n,m}(t)$, equation (5.8) becomes

$$\begin{aligned}\frac{\partial K(u,v;t)}{\partial t} &= \{(e^u-1)(\lambda_{g1}+\lambda_{g2}) + (e^v-1)(b\lambda_{i1}+\lambda_{i2})\}\mathrm{K}(u,v;t)\\ &+ \{-e^{(u+v)}(\mu_{g1}+\mu_{g3}+\mu_{g4}+\mu_{i1}+\mu_{i2}) + e^v(\mu_{g1}+\mu_{g3}+\mu_{g4}) + e^u(\mu_{i1}+\mu_{i2})\}e^{-(u+v)}\\ &\left[\frac{\partial^2 K(u,v;t)}{\partial u\partial v} - \frac{\partial K(u,v;t)}{\partial u} - \frac{\partial K(u,v;t)}{\partial v} - K(u,v;t)\right]\\ &+ \{(1-e^u)\mu_{g2}\}\mathrm{e}^{-u}\left[\frac{\partial K(u,v;t)}{\partial u} - K(u,v;t)\right]\end{aligned} \quad \ldots (5.9)$$

On comparing the coefficients of u's, v's, $\frac{u^2}{2}$'s, $\frac{v^2}{2}$'s and uv's, we arrived to the system of simultaneous differential equations.

Simultaneous Differential Equations and Statistical Measures of the Model

Solving the partial derivation of cumulant generating function in 5.9, the following sets of linear dependent differential equations are obtained.

$$\frac{d}{dt}E_x(t) = -(\mu_{g1}+\mu_{g3}+\mu_{g4})E_{xy}(t)+[\mu_{g1}+\mu_{g3}+\mu_{g4}-\mu_{g2}]E_x(t)+[\mu_{g1}+\mu_{g3}+\mu_{g4}]E_y(t) \quad ...(5.10)$$

$$\frac{d}{dt}E_y(t) = -(\mu_{i1}+\mu_{i2})E_{xy}(t)+(\mu_{i1}+\mu_{i2})E_x(t)+(\mu_{i1}+\mu_{i2})E_y(t) \quad ... (5.11)$$

$$\frac{d}{dt}V_x(t) = [2(\lambda_{g1}+\lambda_{g2})+(\mu_{g1}+3\mu_{g2}+\mu_{g3})]E_x(t)+[2(\mu_{g1}+\mu_{g3}+\mu_{g4}-\mu_{g2})]V_x(t) + 3(\mu_{g1}+\mu_{g3})E_{xy}(t)-(\mu_{g1}+\mu_{g3}+\mu_{g4})E_y(t) \quad ... (5.12)$$

$$\frac{d}{dt}V_y(t) = [2(b\lambda_{i1}+\lambda_{i2})+(\mu_{i1}+\mu_{i2})]E_y(t) + 2(\mu_{i1}+\mu_{i2})V_y(t)-(\mu_{i1}+\mu_{i2})E_x(t)+(\mu_{i1}+\mu_{i2})E_{xy}(t) \quad ... (5.13)$$

$$\frac{d}{dt}E_{xy}(t) = \left[(\lambda_{g1}+\lambda_{g2})+(\mu_{g1}+\mu_{g2}+\mu_{g3}+\mu_{g4})\right]E_y(t) + \left[(b\lambda_{i1}+\lambda_{i2})+(\mu_{i1}+\mu_{i2})\right]E_x(t)+(\mu_{g1}+\mu_{g3}+\mu_{g4})V_y(t) + (\mu_{i1}+\mu_{i2})V_x(t)+\left[(\mu_{g1}+\mu_{g2}+\mu_{g3}+\mu_{g4})+(\mu_{i1}+\mu_{i2})\right]E_{xy}(t) \quad ... (5.14)$$

Solution for Differential Equations using Runge -Kutta Method

The objective of the above mentioned activity is to develop a bivariate stochastic model for glucose/insulin regulatory system in acute hyperglycemic conditions of T2DM patients. These patients may be treated with two parallel interventions namely inducing insulin through external sources and consuming glucose through physical activity. The ultimate purpose of this work is to derive the statistical measures with the help of formulated linear dependent differential equations. As obtaining an analytical solution to the set of equations have a limitation of not getting exact real values, an alternative method namely Runge-Kutta numerical technique has been considered for getting the approximate solutions.

Usually the protocol of diabetes management includes the activities like minimizing the excess food intake, making enough physical exercise to the body and administering proper medication/insulin intervention (if necessary). This study has focused on the latter two activities. A comparative analysis was carried out among two groups of patients who are with at least mean glucose levels of 250 mg/dl and 300

mg/dl respectively. Both groups are in the proposed interventions namely excess physical activity and induced insulin to the body. Soft computing solutions to the developed equations are obtained through FORTRAN programming. Patterns of all statistical measures are explored by executing the developed FOTRAN code through a hypothetical numerical illustration. The extracted results were presented in tabular form as well as graphical means.

Numerical Simulations and Statistical Measures

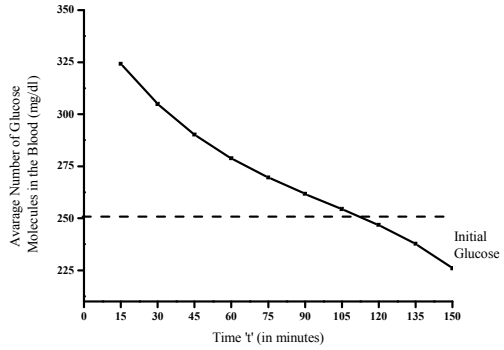
The study has further focused on getting the indicators of two categories of subjects namely (i) Patients with Mean Glucose 250 mg/dl and (ii) Patients with Mean Glucose 300 mg/dl.

Case-I: Patients with Mean Glucose 250 mg/dl

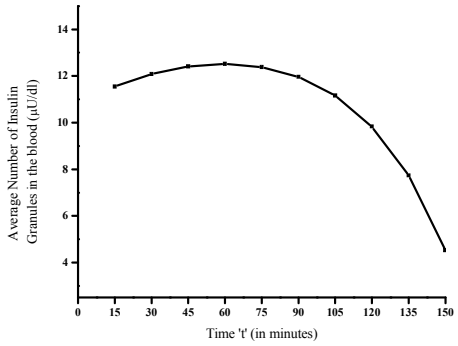
The values of Average glucose level, average insulin level, variance of glucose level, variance of insulin level and correlation coefficient between the average level of glucose and average level of insulin level were calculated for changing values of time period by considering the constant values for the following $E_x(0) = 250$, $E_y(0) = 10$, $V_x(0) = 20$, $V_y(0) = 7$, $E_{xy}(0) = 30$, $\lambda_{g1} = 0.01$, $\lambda_{g2} = 0.01$, $\mu_{g1} = 0.1$, $\mu_{g2} = 1.4$, $\mu_{g3} = 0.1$, $\mu_{g4} = 0.01$, $\lambda_{i1} = 0.01$, $\lambda_{i2} = 0.1$, $\mu_{i1} = 0.01$, $\mu_{i2} = 0.01$, $b = 40$.

Table: 5.1 Values of $E_x(t), E_y(t), V_x(t), V_y(t)$ &Cor. Coefficient. for case-1 patients

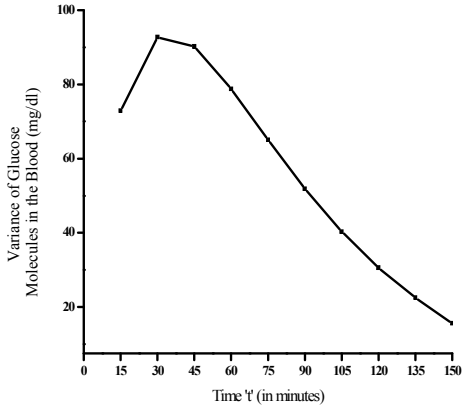
Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
15	324.2065	11.5486	72.8949	5.2683	-0.1905
30	304.8356	12.0933	92.7206	5.8520	-0.1572
45	290.1282	12.4139	90.2022	6.1061	-0.1515
60	278.7348	12.5170	78.8163	6.0539	-0.1562
75	269.5824	12.3832	65.0714	5.6850	-0.1672
90	261.7655	11.9621	51.8730	5.0505	-0.1817
105	254.4482	11.1617	40.3082	6.2529	-0.1607
120	246.7654	9.8321	30.5785	8.0912	-0.1266
135	237.7107	7.7403	22.4737	10.8322	-0.0760
150	225.9933	4.5318	15.5994	14.8847	-0.0029



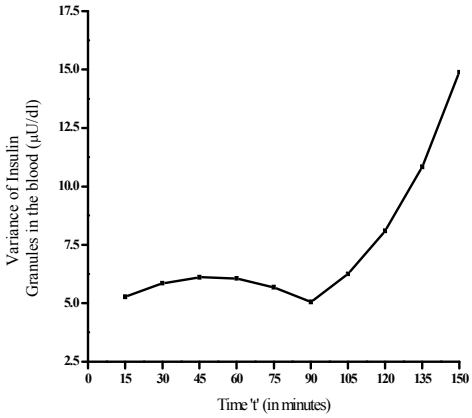
Average levels of Glucose molecules



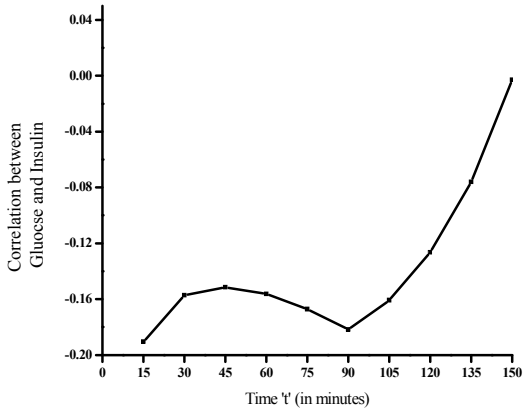
Average levels of Insulin Granules



Variance of Glucose



Variance of Insulin



Correlation between Glucose and Insulin

Figure 5.1: *Graphical presentation on Averages, Variances and Correlation Coefficients based on Case-1*

Discussion for Case-1

Regarding the patients under parallel interventions of excess consumption of glucose through physical activity and induced insulin through external sources, the patterns in the average glucose levels among acute hyperglycemic patients (who have an average glucose level around 250 mg/dl) during a50 minutes of study, there is a

gradual decline from initial level around 324 mg/dl at 15th minute to 224 mg/dl at 150th minute. This is may be the indication of gradual declining in glucose levels are due to the effect of both excess physical activity (leads to consumption of glucose around 0.01 mg/dl) and induced insulin level 0.1 μ/dl. Further it indicates that the existing average insulin level is 11.55 μ/dl at 15th minute and gradual increase in average insulin level up to 12.517 μ/dl at 60th minute and decreased average insulin up to 4.5318 μ/dl at 150th minute. Therefore the summarized information may reveal that the gradual decrement in glucose levels among hyperglycemic patients can be achieved with the interventions of both excess utilization of existing glucose levels through physical activity and also with induced insulin from external sources. It is more realistic approach when compared to the proposed model in chapter-4.

Observations of variances related to glucose levels and insulin levels, the distribution is positively skewed during 150 minutes of study period. There is a steep increment in variance of glucose level from 72.8949 mg/dl at 15th minute to 92.7206 mg/dl at 30th minute and gradual and slow decrement in variance of glucose level up to 15.5994 mg/dl at 150th minute. Whereas, the variance pattern of insulin levels reveals that there is overall increment during the total study period. The initial variance of insulin level is 5.26 μ/dl at 15th minute, increased up to 6.1061μ/dl at 45thminute, decreased to 5.0505 μ/dl at 90th minute, and then gradually increased up to 14.8847 μ/dl at 159th minute. Hence it may conclude that the overall increased volatility in insulin levels leads to gradual decrement in average insulin levels as well as average glucose levels.

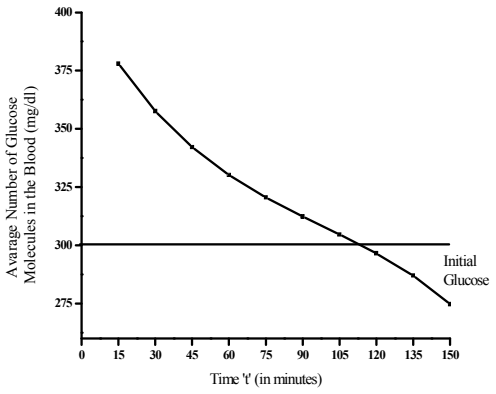
The value of correlation coefficient between the average levels of glucose and insulin reveals that there is a negative relation throughout the study period. The highest negative correlation is observed at the initial study time of 15th minute and the least negative correlation at 150th minute. These are the indicators that the increased levels insulin will contributing in decreasing the glucose levels and vice versa. The strong relation in the initial time and the weak relation at the end period of time also supporting the same justification. Therefore, the required glucose levels can be monitored by regulating the interventions of Physical activity and induced insulin.

Case-2: Patients with Mean Glucose 300 mg/dl:

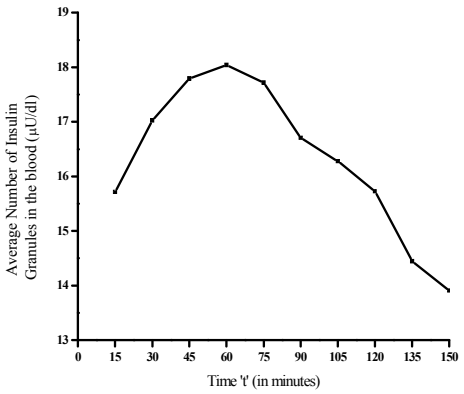
The values of Average glucose level, average insulin level, variance of glucose level, variance of insulin level and correlation coefficient between the average level of glucose and average level of insulin level were calculated for changing values of time period by considering the constant values for the following $E_x(0) = 300$, $E_y(0) = 12$, $V_x(0) = 30$, $V_y(0) = 9$, $E_{xy}(0) = 30$, $\lambda_{g1} = 0.01$, $\lambda_{g2} = 0.01$, $\mu_{g1} = 0.1$, $\mu_{g2} = 1.4$, $\mu_{g3} = 0.1$, $\mu_{g4} = 0.01$, $\lambda_{i1} = 0.01$, $\lambda_{i2} = 0.1$, $\mu_{i1} = 0.01$, $\mu_{i2} = 0.01$ and $b = 40$.

Table: 5.2 Values of $E_x(t), E_y(t), V_x(t), V_y(t)$ &Cor. Coefficient. for case-2 patients

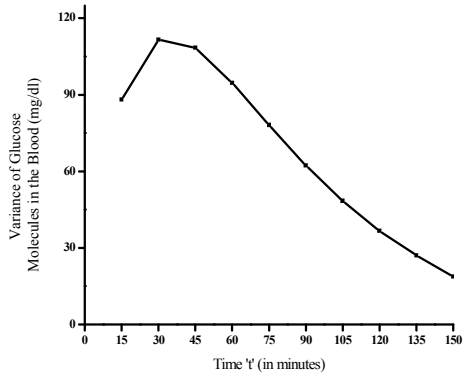
Time (in Minutes)	$E_x(t)$	$E_y(t)$	$V_x(t)$	$V_y(t)$	Correlation Coefficient
15	377.9167	15.7166	88.1333	4.2614	-0.3058
30	357.5767	17.0237	111.6275	4.9609	-0.2574
45	342.1329	17.7925	108.4425	5.2648	-0.2524
60	330.1683	18.0388	94.6898	5.2010	-0.2642
75	320.5561	17.7163	78.1464	4.7568	-0.2869
90	312.3451	16.7034	62.2808	4.1278	-0.3112
105	304.6571	16.2789	48.3874	5.5734	-0.2809
120	296.5831	15.7246	36.7027	7.7832	-0.2450
135	287.0651	14.4457	26.9709	11.0776	-0.1944
150	274.7461	13.9081	18.7171	15.9483	-0.1530



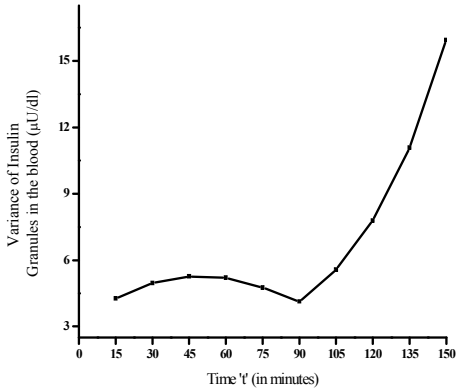
Average levels of Glucose molecules



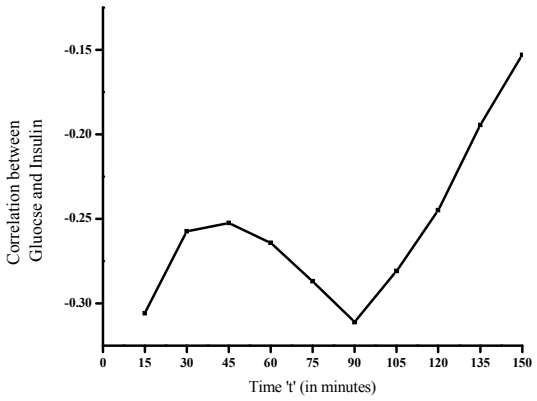
Average levels of Insulin Granules



Variance of Glucose



Variance of Insulin



Correlation between Glucose and Insulin

Figure 5.2: *Graphical presentation on Averages, Variances and Correlation Coefficients based on Case-2*

Discussion for Case-2

The above numerical illustrations and table have given many indicators on the average and variances of insulin and glucose levels. It also provides the indicators on the relationship between the existing levels of insulin and glucose levels. With respect to the expected level of glucose, it is observed that there is gradual decrement throughout study period initiating at 377.9167 mg/dl at 15^{th} minute and the ending at 274.7461 mg/dl at 150^{th} minute. The gradual decline in glucose levels may be due to the effect of additional physical activity (leads to consumption of glucose around 0.01 mg/dl) and induced insulin level 0.1 μ/dl. It also indicates that the existing average insulin level is 15.7166 μ/dl at 15^{th} minute and gradual increase in average insulin level up to 18.0388 μ/dl at 60^{th} minute and decreased levels of average insulin up to 13.9081 μ/dl at 150^{th} minute. Hence the overall above mentioned information may reveal that the gradual decrement in glucose levels among hyperglycemic patients can

be achieved with excessive consumption of glucose through the intervention of physical activity and increased presence of insulin through the intervention of induced insulin to the body through external sources.

According to the variance of glucose levels, the distribution is positively skewed during the study period. There is a steep increment in variance of glucose level from 88.1333 mg/dl at 15^{th} minute to 111.6275 mg/dl at 30^{th} minute and gradual and slow decrement up to 18.7171 mg/dl at 150^{th} minute. Whereas, the variance of insulin indicates that there is overall increment during the total study period. The initial variance of insulin level is 4.2614 μ/dl at 15^{th} minute, increased up to 5.2648μ/dl at 45^{th} minute, decreased to 4.1278 μ/dl at 90^{th} minute, and then gradually increased up to 15.9483 μ/dl at 150^{th} minute. These information may communicate that the overall increased volatility in insulin levels leads to gradual decrement in average insulin levels and average glucose levels.

The value of correlation coefficient between the average levels of glucose and insulin reveals that there is a negative relation throughout the study period. The initial correlation is -0.3058 at 15^{th} minute, increased up to -0.2642 at 45^{th} minute, decreased to -0.3112 at 90^{th} minute, and then gradually increased up to -0.1530 at 150^{th} minute. This indicates that the increased or additional levels of insulin in the blood stream may decrease the glucose levels and vice versa. The fluctuations of correlation between glucose and insulin are fluctuating up to the 90^{th} minute of the study and then it is observed decrement throughout the study period and also justifying the propositions of the model. Hence, monitoring of glucose consumption through the intervention of physical activity and adding of insulin to the blood through the intervention of inducing external insulin will make the healthy maintenance of wanted levels of glucose and insulin.

Summary and Future Scope

This book is dedicated to develop stochastic models by considering bivariate stochastic processes of glucose and insulin regulatory system in patients with Type-2 diabetes mellitus. The mechanism of glucose metabolism was modeled through mathematical notions. The postulates were developed with the assumption on the dynamics of various parameters related to glucose and insulin arrival/consumption which follows Poisson processes. As the issues behind the data acquisition on the said parameters through the manual methods in clinical protocols and due to the complexity in understanding the arrivals/consumptions mechanism of glucose and insulin levels of type-2 diabetes, it is considered that the mathematical modeling is suitable option for studying the parameters which influence the glucose levels in the blood. However, as the rates of parameters of glucose and insulin are random and subject to the uncertainty, it is rational to expedite the glucose metabolic process through stochastic modeling.

Scope of Future Research Work

This work can be extended with compound Poisson processes for more efficient assessment of glucose and insulin levels. Discussion and derivation of various probability distribution‘s properties with reference to some special cases. Estimating the parameters using other than moment’s methods such as MLE, MVUE, etc. can be carried out. Development of Integro-Differential Equations and Inventory management applications will give new vistas for diabetes studies. Multivariate stochastic processes by involving glucose metabolism, insulin secretion, β-cell mass etc., are also a worthy model for study. Extending this work as user interface for health care industry by collaborating inter-disciplinary efforts with theoreticians from mathematics and statistics, diabetes exports and dieticians, developing necessary software and standard operating procedures (SOP’s) will provide more effective and accessible devices to diabetes health care industry. Development of user interface with suitable computer software will generate more effective decision support systems for the diabetes health care management.

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