Mathematical Modeling and Bifurcation Analysis of Human Glucose Insulin Regulation System under the Influence of Pancreatic β- Cell

A Thesis Submitted to the Department of Mathematics, Jimma University in Partial Fulfillment for the Requirements of the Degree of Masters of Science (MSc.) in Mathematics.

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DECLARATION

Here, I submit the dissertation entitled "**Mathematical Modeling and Bifurcation Analysis of Human Glucose Insulin Regulation System under the Influence of Pancreatic $\boldsymbol{\beta}$ −Cell**" for the award of degree of Master of Science in Mathematics. I, the undersigned declare that, this study is original and it has not been submitted to any institution elsewhere for the award of any academic degree or the like, where other sources of information have been used, they have been acknowledged.

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The work has been done under the supervision and approval of advisor

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ABSTRACT

Problems in engineering, computational science, physical and biological sciences are using increasingly sophisticated mathematical techniques. The main objective of this study is to formulate mathematical model of human glucose insulin regulation system under the influence of pancreatic β-cell followed by some mathematical manipulation such as stability condition and bifurcation conditions. In order to achieve the stated objective analytic method was employed. The result of the research indicates that the model is analyzed in terms of local stability, backward and Hopf bifurcation. Based on critical points and backward bifurcation, appropriate physiological implication is well spelled out.

Key words: *Model formulation, model analysis, local stability condition, Bifurcation analysis, Beta cell mass, Routh's stability criterion*

TABLE OF CONTENTS

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

Differential equations have a remarkable potential to predict the world around us. They are used in a wide variety of disciplines such as biology, economics, physics, chemistry and engineering. They can describe exponential growth and decay, the population growth of species or the change in investment return over time. Mathematical and theoretical biology is an interdisciplinary scientific research field with a range of applications. The field is sometimes called mathematical biology or biomathematics to stress the mathematical side or to stress the biological side (Barnes, 2010). Theoretical biology focuses more on the development of theoretical principles for biology while mathematical biology focuses on the use of mathematical tools to study biological systems (Israel, 1988).

Nowadays mathematics and biology have a synergistic relationship. There are several types of biological problems which can be treated as mathematical modeling; modeling on Diabetes is one of them. Diabetes is an indication of disordered metabolism, commonly due to a combination of hereditary and environmental bases, resulting in abnormally high or low blood sugar levels etc. Mathematical model is a powerful tool for understanding biologically observed phenomena which cannot be understood by verbal reasoning alone (Alder, 2001). One such example is that of human glucose insulin regulation system.

Bifurcation theory is the mathematical study of changes in the qualitative or topological structure of a given dynamical systems. Bifurcation occurs when a small change made to the parameter values (the bifurcation parameters) of a system causes a sudden qualitative or topological change in its behavior (Blanchard, 2006). The name "bifurcation" was first introduced by Henri Poincaré in 1885 in the first paper in mathematics showing such a behavior (Poincare, 1885). Local bifurcation occurs when a parameter change causes the stability of equilibrium to change.

Glucose concentration in the blood of a normal person lies with narrow range. In normal individuals, high plasma glucose level induces the release of insulin from pancreatic β-cells, which enables the muscle and other cells to take up glucose for energy or to store it as glycogen in liver. On the other hand, at low plasma glucose level, glucagon secreted from α-cells counter regulates the glucose level by inducing the breakdown of glycogen into glucose.

In diabetic individuals, the synchronized mechanism between insulin and glucagon secretion is disrupted. The two most common forms of diabetes are due to either a diminished production of insulin also known as type-1 diabetes or diminished response by the body to insulin also known as type-2 diabetes. Another type of diabetes is Gestational diabetes, which occurred in pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. Some other forms of diabetes are congenital diabetes, which is genetic defects of insulin secretion, cystic fibrosis related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenetic diabetes. Both type-1 and type-2 are chronic conditions those cannot be cured permanently (Wild et al., 2004).

In1961, the first diabetic model was developed by Bolie which consisted differential equation each for glucose and insulin (Bolie, 1961). But this model failed the accountancy distribution of insulin and glucose throughout the body. The real start of mathematical modeling of 'glucose insulin dynamics' was started with the so called 'minimal model' proposed by the team of Bergman and Cobelli in the early eighties (Bergman et al.,1979). Later some drawbacks were found in the minimal model and taking into account these drawbacks De Gaetano and Arino (De Gaetano and Arino, 2000a, 2000b) proposed a delay differential model called Dynamical model. In 2014, Jamal Hussain and Danghmingliani Zadeng studied stability analysis of the mathematical model of human glucose insulin regulatory system consisting two variables (Hussain and Zadeng, 2014).

In 2016, Devi et al. proposed a simple model of human glucose insulin regulatory system incorporating an additional variable to describe human glucose-insulin regulation system under the influence of externally ingested glucose in the form of source of food as follows.

$$\begin{cases} G'(t) = -aG - bI + \alpha E + \delta \\ I'(t) = cG - dI \\ E'(t) = \beta E(1 - \gamma E) \end{cases}, \tag{1.1}$$

where $G(t)$ and $I(t)$ are glucose and insulin concentration in body at time t respectively and $E(t)$ is the externally ingested glucose at time t which is coming from source of food to the body and $\delta, a, b, c, d, \alpha, \beta, \gamma$ are constants. They also studied stability analysis of the model. However, the inclusion of a time delay representing the delayed effect of insulin on inhibiting glucose production is not considered.

In 2015, Minghu Wang studied mathematical model of human glucose-insulin regulatory system given as follows.

$$\begin{cases} G' = G_{in} + f_5(x_3) - f_2(G) - f_3(G)f_4(I_i) \\ I'_p = \beta f_1(G) - R(I_p - I_i) - \frac{I_P}{t_p} \\ I'_i = R(I_p - I_i) - \frac{I_i}{t_i} \\ x'_1 = \frac{3}{t_d}(I_p - x_1) \\ x'_2 = \frac{3}{t_d}(x_1 - x_2) \\ x'_3 = \frac{3}{t_d}(x_2 - x_3) \\ \beta' = \varepsilon\left(P(I_p) - a(I_p, G)\right)\beta \end{cases}, \qquad (1.2)$$

Where $G -$ plasma glucose concentration,

I_p −Plasma insulin concentration,

I_i −Interstitial insulin concentration,

R −is transfer rate constant,

$x_1, x_2, x_3 -$ Represents the relationship between the time delays of insulin in plasma and its effect on the hepatic glucose production,

$\beta -$ beta cell mass,

$t_p -$ is insulin clearance time constant in the plasma,

$t_i -$ is insulin clearance time constant in the interstitial,

$t_d -$ is time delay,

and

$$
\begin{cases}
f_1(G) = \frac{r_1 G^{n_1}}{{K_1}^{n_1} + G^{n_1}} \\
f_2(G) = \frac{r_2 G}{K_2 + G} \\
f_3(G) = c_1 G \\
f_4(I_i) = \frac{r_3 {I_i}^{n_2}}{{K_3}^{n_2} + {I_i}^{n_2}} + c_2 \\
f_5(x_3) = \frac{r_4 {K_4}^{n_3}}{{K_4}^{n_3} + {x_3}^{n_3}} \\
I_p(p) = \frac{p_0 I_p}{r_0 + {I_p}^2} \\
a\left(I_p, G\right) = \frac{a_0 I_p}{r_0 + {I_p}^2}\ (1 - r_a G - r_b G^2),
\end{cases}
\quad , \qquad (1.3)
$$

where $G_{in}, a_0, r_0, r_a, r_b, r_1, r_2, r_3, r_4, K_1, K_2, K_3,\ K_4, p_0, c_1, c_2, n_1, n_2, n_3$ are constants.

Insulin is secreted from beta cells, the only cell which produces insulin. Loss of beta-cells will lead to diabetes over time. Therefore, the control of pancreatic beta-cell function and survival is essential for maintaining glucose homeostasis and preventing diabetes. It has been hypothesized that overworking leads beta-cells to die (Wang, 2015)

Consequently, the main goal of this study is to formulate a generalized mathematical model of human glucose insulin regulation system based on models (1.1) &(1.2) as given above for better understandings of beta-cells in a mathematical context and to investigate the bifurcation analysis of the new model under the influence of pancreatic beta cell.

1.2 Statement of the Problem

Problems in engineering, computational science, physical and biological sciences are using increasingly sophisticated mathematical techniques. Thus, the bridge between the mathematical sciences and other disciplines is heavily traveled. Mathematical biology is a fast-growing, well-recognized, and the most exciting modern application of mathematics. In 2015, Minghu Wang studied mathematical model of human glucose-insulin regulatory system. However, the model did not put externally ingested glucose as a variable into consideration. In 2016, Devi et al. studied stability analysis of the mathematical model of human glucose insulin regulatory system consisting three variables by introducing externally ingested glucose in the form of food as a variable. However, an interesting feature of the system that is the inclusion of a time delay representing the delayed effect of insulin on inhibiting glucose production is not considered. Therefore, it is important to formulate a generalized mathematical model of human glucose

insulin regulation system that incorporate more variables like beta cell mass, externally ingested glucose in the form of food and inclusion of time delay to regulate the distribution of glucose and insulin in the whole body based on models (1.1) and (1.2).
Consequently, this study focuses on the following problems.

- Constructing generalized mathematical model that describes human glucose insulin regulation system.
- Local stability analysis of the generalized mathematical model of human glucose insulin regulation system using Routh Hurwitz Criterion.
- Bifurcation analysis of the generalized mathematical model of human glucose insulin regulation system.

1.3 Objective of the Study

1.3.1 General Objective of the Study

The general objective of this study is to formulate generalized mathematical model that describes human glucose insulin regulation system and to investigate bifurcation analysis of the new model under the influence of pancreatic beta cell.

1.3.2 Specific Objectives of the Study

The specific objectives of the study are:

- ✓ To formulate generalized mathematical model that describes human glucose insulin regulation system based on simple models (1.1) and (1.2) under some logical considerations.
- ✓ To make local stability analysis of the generalized mathematical model of human glucose insulin regulation system by Routh Hurwitz stability criterion.
- ✓ To carry out bifurcation analysis of the generalized mathematical model of human glucose insulin regulation system.

1.4. Significance of the Study

The outcomes of this study have the following importance:

- Provides range of individual stability condition based on relative strength of β-cell functionality.
- The model can be used by biologists for further investigation of diabetic.
- To do a little in promoting Interdisciplinary Applied Mathematics.

1.5 Delimitation of the Study

This study is delimited to discussing stability conditions and bifurcation analysis of generalized mathematical model of human glucose insulin regulation system formulated from equations (1.1) and (1.2) under the influence of pancreatic beta cell.

1.6 Basic Definition

Definition 1.1 Let A be a square matrix of order m, its determinant, denoted by $|A|$ or by $detA$, is given by

$$|A| = \sum(-1)^S a_{1j_1}a_{2j_2} \dots a_{mj_m},$$

where $j_1, j_2, \dots, j_m$ is a permutation of the numbers $1,2,3, \dots, m$ and s is zero or one depending on whether the number of transpositions required to restore $j_1, j_2, \dots, j_m$ to the natural sequence $1,2,3, \dots, m$ is even or odd respectively; the sum is taken over all possible such permutations.

Definition 1.2 (Jacobson, 1974) The characteristic polynomial of square matrix A of order n is given by $P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + a_3\lambda^{n-3} + \cdots + a_{n-1}\lambda + a_n$,

where $a_1 = -\sum a_{ii} = -TraA$, $a_i = (-1)^i *$ the sum of i −rowed diagonal minor of A,

$a_n = (-1)^n \det A$.

Definition 1.3 (Krzysztof, 1990) Let x be a real number, the function $sgnx$ is defined as

$$sgnx = \begin{cases} 1, if\ x > 0 \\ -1, if\ x < 0 \\ 0, x = 0 \end{cases}$$

Properties of sgn function: Let X and Y be real numbers, then

$$(i)\ sgn(XY) = sgnX.sgnY\ ,\ (ii)\ sgn\left(\frac{X}{Y}\right) = \frac{sgnX}{sgnY}$$

CHAPTER TWO

LITERATURE REVIEW

2.1 History and Definition of Differential Equations

The subject of differential equation originated in the study of calculus by Isaac Newton (1642-1716) and Gottfried Wilhelm Leibniz (1646-1716) independently in the seventeenth century. Differential equation is a mathematical equation that relates some function with its derivatives. In applications, the functions usually represent physical quantities, the derivatives represent their rates of change, and the equation defines a relationship between the two. Because such relations are extremely common, differential equations play a prominent role in many disciplines including engineering, physics, economics, and biology.

2.2 Diabetes

In 1980, expert committee of WHO proposed classification of diabetes mellitus and named it as IDDM (insulin dependent diabetes mellitus) or type-1 and NIDDM (non-insulin dependent diabetes mellitus) or type-2. But in 1985 type-1 and type-2 names are omitted and only IDDM and NIDDM were known as the types of diabetes mellitus (Wild et al.,2004). Human bodies need to maintain glucose concentration level in a narrow range 70-109 mg/dl (Jaitu et al.,2012).
If one's glucose concentration level is significantly out of the normal range, this person is considered to have the plasma glucose problem. With or without diabetes, monitoring of blood sugar levels is crucial to a person's health. Diabetes is a metabolic illness that can affect other organs of the body. Acquiring diabetes may aggravate a simple disease too. Internal organs like heart, kidney, lungs, liver, pancreas, or even the limbs are the favorite target of this metabolic disease (Sandhya and Kumar, 2011).

2.3 History of Mathematical Model of Glucose Insulin Regulation System

In 1961, the first diabetic model was developed by Bolie which consisted differential equation each for glucose and insulin (Bolie, 1961). A similar model was developed by Ackerman et al. for glucose insulin dynamics (Ackerman et al., 1995). The interaction effects of glucose and insulin were obtained from the first two models. But these models failed the accountancy of distribution of insulin and glucose throughout the body. The minimal model developed by (Bergman et al., 1981) had 3-compartments as lumped representation of human body.

This model lacked the dynamics of glucose transport and distribution in tissues and effects of glucagon, which raises the blood glucose concentration. Cobelli et al. in 1982 utilized 5-compartment models for glucose, insulin and glucagon effects each lumped into its own whole body blood pool (Cobelli and Ruggeri, 1983). This also included the use of threshold functions for saturation. Comparison of the peripheral versus portal route for insulin administration in closed loop glucose control was done by Cobelli and Ruggeri (1983). But they were unable to describe the glucose distribution in the body (Cobelli and Ruggeri, 1983).

Puckett in 1992 developed a modeling study of diabetes mellitus in which a two blood pool system representing insulin and glucose concentrations which were directly affected by metabolic flux terms and exogenous signals (Puckett,1992). With the help of Lightfoot in 1995, Puckett also demonstrated inter and intra patient variability and steady state behavior using his models (Puckett,1995). Sorensen treated glucose and insulin separately with coupling through metabolic effects utilizing threshold functions. A whole body lumped representation was also included to complete the glucose-insulin system with counter regulation. A small inclusion into this model was made by Sorenson to include meal disturbances and parameters for uncertainty analysis. In 2014, Jamal Hussain and Danghmingliani Zadeng studied stability of nonlinear mathematical model of glucose insulin regulatory system by linearizing the model using Jacobian matrix (Hussain and Zadeng, 2014). However, the model has its own drawback due to the fact that only two variables are considered. In 2014, Sandhya and Kumar.D developed a new mathematical model for glucose insulin regulatory system of diabetes mellitus by taking all plasma glucose concentration, generalized insulin and plasma insulin concentration (Sandhya and Kumar, 2011). In 2015, Nagarajan.R, Krshnan.K and Monica. C studied stability analysis of glucose insulin dynamic system using matrix Lambert W function (Nagarajan et al.,2015).In 2014, Marie, J. studied Hopf Bifurcation of two delay mathematical model of glucose insulin during physical activities (Marie, 2014). In 2017, Mahata et al. studied stability analysis of a mathematical model of glucose insulin regulatory system on diabetes mellitus in fuzzy and crisp environment (Mahata et al., 2017).

CHAPTER THREE

METHODOLOGY

3.1. Study Area and Period

The study was conducted in Jimma University under the department of Mathematics from September 2016 to June 2017 G.C.

3.2. Study Design

This study employed analytical method.

3.3. Source of Information

The relevant sources of information for this study were books, published articles & related studies from internet.

3.4. Study Procedures

This study was conducted based on the following procedures.

1) Constructing generalized mathematical model that describe human glucose insulin regulation system.
2) Determining critical points of the generalized mathematical model of human glucose insulin regulation system.
3) Stability analysis of the generalized mathematical model of human glucose insulin regulation system by Routh Hurwitz criterion.
4) Bifurcation analysis of generalized mathematical model of human glucose insulin regulation system.

3.5. Ethical Considerations

Ethical clearance was obtained from Research and Post Graduate program coordinator office of College of Natural Sciences, Jimma University and any concerned body will informed about the purpose of the study.

CHAPTER FOUR

RESULT AND DISCUSSION

4.1 Mathematical Model Formulation

Applying the Mass Conservation Law,

Rate of Change = Input - Output.

The two major factors in the regulatory system to be modeled are glucose and insulin. Let $G(t)$ denote the plasma glucose concentration at time $t \geq 0$. In order to describe the complex mechanism of the regulatory system, we consider the insulin in two compartments. One is plasma insulin and the other is interstitial insulin, which are denoted by $I_p(t)$ and $I_i(t)$, respectively. The transport of insulin between them is assumed to be a passive diffusion process driven by the difference in insulin, with transfer rate R (Polonsky, 1986).

Then we obtain the following

$$\frac{dG(t)}{dt} = glucose\ prduction - glucose\ utilization \tag{4.1}$$

$$\frac{dI_p}{dt} = insulin\ secretion - compartments\ exchange - insulin\ clearance \tag{4.2}$$

$$\frac{dI_i}{dt} = compartment\ exchange - insulin\ clearance \tag{4.3}$$

Further to access the complex mechanism of such regulatory system, we are also interested in the rate of change for beta-cell mass, which is denoted by $\beta(t)$.

$$\frac{d\beta}{dt} = formation - loss \tag{4.4}$$

Glucose production (Tolic et al., 2000) There are two main sources of glucose production.

1) Glucose is released from dietary carbohydrates, subsequently being absorbed into the blood.
2) The liver is the other source of glucose production.

Glucose utilization (Tolic et al., 2000) Glucose utilization also consists of two parts, namely,

1) Insulin-independent utilization and
2) Insulin- dependent utilization.

The main insulin-independent glucose consumers are brain and nerve cells. The insulin-dependent glucose uptake is mostly due to muscle, fat cells and other tissues. These cells consume the glucose and convert it into energy for the body.

Insulin production (Ahren, 2002) Insulin can only be produced through beta-cell secretion, mainly in response to elevated blood glucose level.

Insulin clearance (Duckworth et al., 1998) Insulin is cleared by all insulin sensitive tissues.

β -cell proliferation: The proliferation of beta-cells is not surprisingly assumed to be proportional to beta-cell mass itself.

β-cell apoptosis: Beta-cell apoptosis has been shown to vary nonlinearly with glucose.

Interstitial insulin comes from plasma, so its rate of change is the difference between the exchange with plasma insulin and its degradation. The rate of change of beta-cell mass is a combining effect of proliferation and apoptosis, but could be much slower than that of glucose and insulin.

We use the following state variables.

G −Plasma glucose concentration,

I_p −Plasma insulin concentration,

I_i −Interstitial insulin concentration,

E −Externally ingested glucose in the form of food which is assumed to follow logistic growth model (Davi, et al.,2016),

x_1, x_2, x_3 − Represents the relationship between the time delays of insulin in plasma and its effect on the hepatic glucose production,

β - beta cell mass.

$$\text{Glucose Production} = \delta + mE + f_5(x_3) \quad , \tag{4.5}$$

where δ is constant amount of glucose in the body,
m is rate constant representing increase of glucose level due to ingested glucose,
$f_5(x_3)$ is the effect of insulin on glucose production such that

$f_5(0) > 0, f_5(x_3) > 0$ and $f'_5(x_3) < 0$.

$$\text{Glucose Utilization} = f_2(G) + f_3(G)f_4(I_i) \quad , \tag{4.6}$$

where $f_2(G)$ is insulin independent glucose utilization such that

$$f_2(0) = 0, f_2(G) > 0 \text{ and } f'_2(G) > 0 \, , \tag{4.7}$$

$f_3(G) -$ the glucose utilization by the muscles and fat cells,

$f_4(I_i) -$ the relationship between the plasma insulin concentration and the cellular glucose uptake and satisfies all conditions of (4.7).

Plugging equations (4.5) and (4.6) into (4.1),

$$\frac{dG(t)}{dt} = \delta + mE + f_5(x_3) - f_2(G) - f_3(G)f_4(I_i) \tag{4.8}$$

$$\text{Plasma insulin production} = \beta f_1(G) \, , \tag{4.9}$$

where β is beta cell mass and $f_1(G)$ is the effect of glucose on insulin secretion such that it satisfies all conditions of (4.7).

$$\text{Compartment exchange} = R(I_p - I_i) \, , \tag{4.10}$$

where R is glucose transfer rate.

$$\text{Insulin clearance} = \frac{I_P}{t_p}, \tag{4.11}$$

where t_p is insulin clearance time constant in the plasma.

Plugging equations (4.9), (4.10) and (4.11) into (4.2),

$$\frac{dI_p}{dt} = \beta f_1(G) - R(I_p - I_i) - \frac{I_P}{t_p} \tag{4.12}$$

$$\text{Insulin clearance in interstitial} = \frac{I_i}{t_i} \tag{4.13}$$

Plugging equations (4.10) and 4.13) into (4.3),

$$\frac{dI_i}{dt} = R(I_p - I_i) - \frac{I_i}{t_i} \quad , \tag{4.14}$$

Since, externally ingested glucose in the form of food follow logistic growth model, we have

$$E'(t) = \alpha E(1 - \gamma E) \, , \tag{4.15}$$

where α is intrinsic growth constant of ingested source of glucose,

$\frac{1}{\gamma}$ is Carrying capacity of ingested source of glucose.

Time delay

An interesting feature of the system is the inclusion of a time delay representing the delayed effect of insulin on inhibiting glucose production. The effect of insulin on glucose production is not immediate but involves a substantial time delay (Jiatu,2006).

$$\begin{cases} x'_1 = \frac{3}{t_d}\left(I_p - x_1\right) \\ x'_2 = \frac{3}{t_d}(x_1 - x_2) \\ x'_3 = \frac{3}{t_d}(x_2 - x_3) \end{cases} \tag{4.16}$$

Beta cell formation= $I_p(p) = \frac{p_0 I_p}{r_0 + {I_p}^2}$, (4.17)

where p_0 is the rate of beta cell formation and $\frac{I_p}{r_0 + {I_p}^2}$ reflects insulin signaling.

Beta cell loss= $a\left(I_p, G\right) = \frac{a_0 I_p}{r_0 + {I_p}^2}\ (1 - r_a G - r_b G^2)$, (4.18)

where a_0 is the rate of beta cell loss and r_a, r_b are constants.

$$\beta' = \varepsilon(P\left(I_p\right) - a\left(I_p, G\right))\beta\ , \tag{4.19}$$

Combining equations (4.8), (4.12), (4.14), (4.15), (4.16) and (4.19) the desired model is formulated as follows.

$$\begin{cases} G' = f_5(x_3) - f_2(G) - f_3(G) f_4(I_i) + mE + \delta \\ I'_p = \beta f_1(G) - R\left(I_p - I_i\right) - \frac{I_P}{t_p} \\ I'_i = R\left(I_p - I_i\right) - \frac{I_i}{t_i} \\ E' = \alpha E(1 - \gamma E) \\ x'_1 = \frac{3}{t_d}\left(I_p - x_1\right) \\ x'_2 = \frac{3}{t_d}(x_1 - x_2) \\ x'_3 = \frac{3}{t_d}(x_2 - x_3) \\ \beta' = \varepsilon\left(P\left(I_p\right) - a\left(I_p, G\right)\right)\beta \end{cases} , \tag{4.20}$$

where f_1, f_2, f_3, f_4 and f_5 are defined as follows (Wang, 2015)

$$f_1(G) = \frac{r_1 G^{n_1}}{{K_1}^{n_1} + G^{n_1}}, \qquad f_2(G) = \frac{r_2 G}{K_2 + G}, \qquad f_3(G) = c_1 G$$

$$f_4(I_i) = \frac{r_3 {I_i}^{n_2}}{{K_3}^{n_2} + {I_i}^{n_2}} + c_2, \qquad f_5(x_3) = \frac{r_4 {K_4}^{n_3}}{{K_4}^{n_3} + {x_3}^{n_3}}$$

K_1 is half saturation glucose concentration in pancreatic insulin production,

K_2 is half saturation glucose concentration in insulin independent glucose utilization,

K_3 is half saturation glucose concentration in insulin dependent glucose utilization,

K_4 is half saturation glucose concentration when liver produce glucose,

r_1 is maximum secretion rate of insulin stimulated by glucose,

r_2 is maximum insulin independent glucose consumption rate,

r_3 is maximum insulin dependent glucose consumption rate,

r_4 is maximum glucose production rate by liver,

n_1, n_2, n_3 are constants.

System (4.20) is FAST-SLOW dynamic system.

4.2 Model Analysis

By the general fast-slow system, we write the original model in simplified form.

$$\begin{cases} \frac{dY}{dt} = F(Y, \beta) \\ \frac{d\beta}{dt} = \varepsilon g(Y, \beta) \end{cases}, \tag{4.21}$$

where $Y = (G, I_p, I_i, E, x_1, x_2, x_3)^T$ are considered as the fast variables and β is the slow variable. To analyze such fast-slow system, we refer to Fenichel's theorem (Fenichel, 1979)

Theorem 1 (Fenichel theorem). Suppose $M_0 \subset \{Y / F(Y, \beta) = 0\}$ is compact, possibly with boundary, and normally hyperbolic, that is, the eigenvalues λ of the Jacobian all satisfy $Re(\lambda) \neq 0$. Suppose F and G are smooth. Then for $\epsilon > 0$ and sufficiently small, there exists a manifold $M_\epsilon, O(\epsilon)$ close and diffeomorphic to M_0 that is locally invariant under the flow of the full problem (4.20). This theorem gives us an approach to understand the dynamics of the full system by knowing the dynamics on its critical manifold, which is usually of lower dimension.

The critical manifold of the model (4.20) is given by

$$M_0 = \{Y/F(Y,\beta) = 0\} \quad (4.22)$$

The dynamics on this manifold can give us a good approximation of the dynamics of full system by Fenichel's theorem. Thus the next step is to do analyses on the critical Manifold M_0.

Consider the fast sub-system as follows.

$$\begin{cases} G' = f_5(x_3) - f_2(G) - f_3(G)f_4(I_i) + mE + \delta \\ I'_p = \beta f_1(G) - R(I_p - I_i) - \frac{I_P}{t_p} \\ I'_i = R(I_p - I_i) - \frac{I_i}{t_i} \\ E' = \alpha E(1-\gamma E) \\ x'_1 = \frac{3}{t_d}(I_p - x_1) \\ x'_2 = \frac{3}{t_d}(x_1 - x_2) \\ x'_3 = \frac{3}{t_d}(x_2 - x_3) \end{cases}, \quad (4.23)$$

where we view β as a parameter of the fast sub-system.

4.2.1 Equilibrium Point of the System

We set the right hand side of all equations of system (4.23) to zero. The resulting system of equations to be solved is:

$$\begin{aligned} & f_5(x_3) - f_2(G) - f_3(G)f_4(I_i) + mE + \delta = 0 \\ & \beta f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p} = 0 \\ & R(I_p - I_i) - \frac{I_i}{t_i} = 0 \\ & \alpha E(1-\gamma E) = 0 \quad , \\ & \frac{3}{t_d}(I_p - x_1) = 0 \\ & \frac{3}{t_d}(x_1 - x_2) = 0 \\ & \frac{3}{t_d}(x_2 - x_3) = 0 \end{aligned} \quad (4.24)$$

By the last three equation of system (4.24) we have

$$\frac{3}{t_d}\left(I_p - x_1\right) = 0 \Rightarrow I_P - x_1 = 0 \quad \left(\frac{3}{t_d} \neq 0\right) \quad \Rightarrow I_p = x_1$$

$$\frac{3}{t_d}(x_1 - x_2) = 0 \Rightarrow x_1 - x_2 = 0 \quad \Rightarrow x_1 = x_2$$

$$\frac{3}{t_d}(x_2 - x_3) = 0 \Rightarrow x_2 - x_3 = 0 \quad \Rightarrow x_2 = x_3$$

$$\therefore I_p = x_1 = x_2 = x_3$$

The fourth equation results in

$$\alpha E(1-\gamma E) = 0 \Rightarrow \alpha E = 0 \text{ or } 1-\gamma E = 0 \Rightarrow E = 0 \ (\alpha \neq 0) \ or \ E = \frac{1}{\gamma}$$

The third equation results in

$$R\left(I_p - I_i\right) - \frac{I_i}{t_i} = 0 \Rightarrow RI_p - RI_i - \frac{I_i}{t_i} = 0$$

$$\Rightarrow RI_p = RI_i + \frac{I_i}{t_i} \Rightarrow I_p = I_i + \frac{I_i}{Rt_i} \quad \Rightarrow I_p = \left(1+\frac{1}{Rt_i}\right) I_i$$

$$I_i = \left(1+\frac{1}{Rt_i}\right)^{-1} I_p, \quad \text{Let } c = \left(1+\frac{1}{Rt_i}\right)^{-1}, \text{then } I_i = cI_p$$

Plugging it into the first two equations (4.24)

$$\begin{cases} f_5(x_3) - f_2(G) - f_3(G) f_4(I_i) + mE + \delta = 0 \\ \beta f_1(G) - R\left(I_p - cI_p\right) - \frac{I_p}{t_p} = 0 \end{cases} \tag{4.25}$$

The second equation of (4.24) gives,

$$\beta f_1(G) - R(1-c)I_p - \frac{I_p}{t_p} = 0 \Rightarrow \beta f_1(G) - (R(1-c) + \frac{1}{t_p})I_p = 0$$

$$\beta f_1(G) = (R(1-c) + \frac{1}{t_p})I_p \Rightarrow I_P = \beta f_1(G)[R(1-c) + \frac{1}{t_p}]^{-1}$$

$$I_p = \beta f_1(G)(R(1-\frac{1}{1+\frac{1}{Rt_i}}) + \frac{1}{t_p})^{-1} \Rightarrow I_p = \beta f_1(G)[R\left(\frac{1}{1+R_{ti}}\right) + \frac{1}{t_p}]^{-1}$$

$$I_p = \beta f_1(G)[\frac{1}{R^{-1}+t_i} + \frac{1}{t_p}]^{-1}, \quad \text{let } c' = [\frac{1}{R^{-1}+t_i} + \frac{1}{t_p}]^{-1}, \text{ then } \quad I_p = c'\beta f_1(G)$$

Plugging it into the first equation of (4.24),

$$f_5(x_3) - f_2(G) - f_3(G)f_4\big(cc'\beta f_1(G)\big) + mE + \delta = 0 \tag{4.26}$$

To solve equation (4.26) we consider two cases.

Case 1: Glucose free case ($E = 0$)

$$f_5(x_3) - f_2(G) - f_3(G)f_4\big(cc'\beta f_1(G)\big) + \delta = 0$$

$$\delta + f_5(I_p) = f_2(G) + f_3(G)f_4(cc'f_1\,(G))$$

$$\delta + f_5(c'\beta f_1(G)) = f_2(G) + f_3(G)f_4(cc'f_1\,(G)) \tag{4.27}$$

Notice that the function $f_1, f_2, f_{3,} f_4$ are increasing with respect to $G\ on\ (0, \infty)$, while f_5 is decreasing. Thus, the left side of equation (4.27) is decreasing on $(0, \infty)$ with lower bound δ, and the right side is increasing on $((0, \infty)$ with no upper bound. Thus, equation (4.27) has unique solution G^* on $(0, \infty)$, with no upper bound (Wang, 2015). Further, we are able to find the solution of system (4.24) as

$$(G^*, c'\beta f_1(G^*), cc'f_1(G^*), 0, c'\beta f_1(G^*), c'\beta f_1(G^*), c'\beta f_1(G^*) \tag{4.28}$$

Note, we view β as varying parameter in the fast sub-system. Hence, we refer to the solution as

$$E^*{}_\beta = (G^*(\beta), I_p^*(\beta), cI_p{}^*(\beta), 0,\ I_p{}^*(\beta), I_p{}^*(\beta), I_p^*(\beta)) \tag{4.29}$$

For each $\beta > 0$, moreover, we can find the equilibria of the whole system (4.20) by solving

$$\varepsilon\left(p(I_p) - a(G, I_p)\right)\beta = 0 \tag{4.30}$$

Restricted on the critical manifold M_0 ,

Since $p(I_p) = \frac{p_{0\,I_p}}{r_0 + I_p^2}$, $a(G, I_p) = \frac{a_0 I_p}{r_0 + I_p^2}\,[1 - r_a G + r_b\, G^2]$ equation (4.30) can be simplified as,

$$\varepsilon(pI_p) - a(G, I_p))\beta = \varepsilon[\frac{p_o I_p}{r_o + I_p^2} - \frac{a_o I_p}{r_o + I_p^2}(1 - r_a G + r_b G^2)]_\beta = 0$$

$$= \frac{\varepsilon I_p}{r_o + I_p^2}[\,p_{0-}\, a_0(1 - r_a G + r_b G^2)\beta = 0$$

Since $\varepsilon > 0$ *and* $\frac{I_p}{r_0+I_p^2} > 0$, Equation (4.30) is equivalent to

$$[p_0 - a_0(1 - r_a G + r_b G^2)]\beta = 0, \text{ Then } \beta = 0 \text{ or } \left(p_0 - a_0(1 - r_a\, G + r_b G^2)\right) = 0$$

The latter equation can be written as

$$-r_b\, G^2 + r_a G + \left(\frac{p_0}{a_0} - 1\right) = 0 \tag{4.31}$$

Solving equation (4.31) using quadratic formula,

$$G = \frac{r_a \pm \sqrt{r_a^2 + 4r_b(\frac{p_0}{a_0} - 1)}}{2r_b}$$

1) If $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) < 0$, then the complete model (4.20) has only one trivial equilibrium point. This trivial equilibrium point is found by letting $\beta = 0$ and substituting it into equation (4.29)

$$E(0) = (G^*(0), o.c'f_1\,(G^*), 0.cc'f_1(G^*), 0, 0.c'f_1(G^*), 0.c'f_1(G^*), 0.c'f_1(G^*), 0)$$

$$E_0^* = (G^*(0), 0,0,0,0,0,0,0)$$

2) If $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) = 0$, then the complete model (4.20) has two equilibrium points. One of which is trivial. when $\beta = 0$, $E_0^* = (G^*(0), 0,0,0,0,0,0,0)$

when, $G_1^* = \frac{r_a}{2r_b}$, $E_1^* = (G_1^*,\, {I_p}_1^*, c\, {I_p}_1^*, 0,\, {I_p}_1^*,\, {I_p}_1^*,\, {I_p}_1^*, \beta_1^*)$

Therefore, we have two equilibrium points.

3) If $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) > 0$ then, the complete model (4.20) has three equilibrium points. One of which is trivial.

$$G = \frac{r_a \pm \sqrt{r_a^2 + 4r_b\,(\frac{p_0}{a_0} - 1)}}{-2r_b}$$

$$G_1^* = \frac{r_a - \sqrt{r_a^2 + 4r_b\,(\frac{p_0}{a_0} - 1)}}{2r_b} \quad \text{or} \quad G_2^* = \frac{r_a + \sqrt{r_a^2 + 4r_b\,(\frac{p_0}{a_0} - 1)}}{2r_b}$$

Thus we end up with three equilibrium points of the complete model as follows.

$$E_0^* = (G^*(0), 0,0,0,0,0,0,0),$$

$$E_1^* = (G_{1,}^* \, I_{p_1}{}^*, c\, I_{p_1}{}^*, 0,\, I_{p_1}{}^*,\, I_{p_1}{}^*,\, I_{p_1}{}^*, \beta_1^*)$$

$$E_2^* = (G_{2,}^* \, I_{p_2}{}^*, c\, I_{p_2}{}^*, 0,\, I_{p_2}{}^*,\, I_{p_2}{}^*,\, I_{p_2}{}^*, \beta_2^*)$$

Note: The superscript * represent equilibrium point in case one.

Case 2: Glucose existing case($E = \frac{1}{\gamma}$), Plugging $E = \frac{1}{\gamma}$ in equation (4.26),

$$f_5(I_p) - f_2(G) - f_3(G) f_4\,(cc'\beta\, f_1(G)) + \frac{1}{\gamma} m + \delta = 0$$

$$\Rightarrow \frac{1}{\gamma} m + \delta + f_5(I_p) = f_2(G) + f_3(G) f_4\big(cc'\beta f_1(G)\big)$$

$$\Rightarrow \frac{1}{r} m + \delta + f_5(c'\beta f_1(G)) = f_2(G) + f_3(G) f_4\big(cc'\beta f_1(G)\big) \tag{4.32}$$

$$(G^{\#}, c'\beta f_1(G^{\#}), cc'\beta f_1(G^{\#}), \frac{1}{\gamma}, c'\beta f_1(G^{\#}), c'\beta f_1(G^{\#}), c'\beta f_1(G^{\#})) \tag{4.33}$$

Note, we view β as a varying parameter in the fast sub-system. Hence, we refer to the solution as $E_\beta^{\#} = (G^{\#}(\beta), I_p{}^{\#}(\beta), cI_p{}^{\#}(\beta), \frac{1}{\gamma}, I_p{}^{\#}(\beta), I_p{}^{\#}(\beta), I_p{}^{\#}(\beta))$ (4.34)

Equations (4.30) and (4.31) also hold in this case. Solving equation (4.31),

1) If $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) < 0$, then complete model (4.20) has only one trivial equilibrium point. This trivial equilibrium point is found by letting $\beta = 0$ and substituting it into equation (4.33),

$$E_0^{\#} = (G^{\#}(0), c'.0.f_1(G^{\#}), cc'.0.f_1(G^{\#}), \frac{1}{\gamma}, c'.0.f_1(G^{\#}), c'.0.f_1(G^{\#}), c'.0.f_1(G^{\#}))$$

$$E_0^{\#} = (G^{\#}(0), 0{,}0, \frac{1}{\gamma}, 0{,}0{,}0{,}0)$$

2. If $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) = 0$, then the complete model has two equilibrium points ,one of which is trivial when $\beta = 0$

$$E_0^{\#} = (G^{\#}(0), 0{,}0, \frac{1}{\gamma}, 0{,}0{,}0{,}0), \text{ when } G_1^{\#} = \frac{r_a}{2r_b}$$

$$E_1^{\#} = (G_{1,}^{\#} \, I_{p_1}{}^{\#}, c\, I_{p_1}{}^{\#}, \frac{1}{\gamma},\, I_{p_1}{}^{\#},\, I_{p_1}{}^{\#},\, I_{p_1}{}^{\#}, \beta_1^{\neq})$$

3. If $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) > 0$, then complete model (4.20) has three equilibrium points one of which is trivial.

Thus we end up with three equilibrium points of the complete model under glucose existing case as follows.

$$E_0^{\#} = (G^{\#}(0), 0,0, \frac{1}{\gamma}, 0,0,0,0)$$

$$E_1^{\#} = (G_1^{\#}, {I_{p_1}}^{\#}, c\,{I_{p_1}}^{\#}, \frac{1}{\gamma}, {I_{p_1}}^{\#}, {I_{p_1}}^{\#}, {I_{p_1}}^{\#}, \beta_1^{\#})$$

$$E_2^{\#} = (G_2^{\#}, {I_{p_2}}^{\#}, c\,{I_{p_2}}^{\#}, \frac{1}{\gamma}, {I_{p_2}}^{\#}, {I_{p_2}}^{\#}, {I_{p_2}}^{\#}, \beta_2^{\#})$$

Note: The superscript # represents equilibrium point in case two.

Physiological implication of the equilibrium points

Based on the discriminate of equation (4.31) if $r_a^2 + 4r_b\left(\frac{p_0}{a_0} - 1\right) < 0$

$$4r_b\left(\frac{p_0}{a_0} - 1\right) < -r_a^2 \Rightarrow \frac{p_0}{a_0} - 1 < \frac{-r_a^2}{4r_b} \Rightarrow \frac{p_0}{a_0} < 1 - \frac{r_a^2}{4r_b}$$

In the model p_0 is the proliferation parameter and a_0 is the apoptosis parameter

Hence we consider the ratio value , $w = \frac{p_0}{a_0}$, as relative strength of beta cell functionality. The above condition becomes $w < 1 - \frac{r_a^2}{4r_b}$. In physiological context if the relative strength of beta cell functionality is too weak, the body will develop the pathological state, which in our model is the trivial equilibrium points i.e E_0^* and $E_0^{\#}$. However if the relative strength of beta cell functionality is strong, with $w > 1 - \frac{r_a^2}{4r_b}$, the body could have healthy states which in the model are are represented by the interior equilibrium points.

4.2.2 Local Stability Conditions of the Equilibrium

Based on the fast sub- system (4.23) with varying β we can obtain the Jacobian of the fast sub-system (4.23) through linearization process as follows.

$$J\left|E_\beta^{*,\#} = \left[\frac{\partial F_i}{\partial Y_j}\right]_{ij}\right|E_\beta^{*,\#} \qquad 4.35)$$

$$\frac{\partial F_1}{\partial Y_1} = \frac{\partial F_1}{\partial G} \Rightarrow \frac{\partial F_1}{\partial G} = \frac{\partial}{\partial G}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta]$$

$$\frac{\partial F_1}{\partial Y_1} = -\frac{\partial}{\partial G} f_2(G) - \frac{\partial}{\partial G} f_3(G) f_4\,(I_i) \Rightarrow \frac{\partial F_1}{\partial Y_1} = \frac{-\partial}{\partial G}\left[\frac{r_2\, G}{k_2+G}\right] - \frac{\partial}{\partial G}[c_1\, G] f_4(I_i)$$

$$\frac{\partial F_1}{\partial Y_1} = \frac{-r_2\, k_2}{(k_2+G)^2} - c_1\left(\frac{r_3 {I_i}^{n_2}}{k_3^{n2}+{I_i}^{n_2}} + c_2\right) \Rightarrow \frac{\partial F_1}{\partial Y_1} = -[\frac{r_2\, k_2}{(k_2+G)^2} + c_1(\frac{r_3 {I_i}^{n_2}}{k_3^{n2}+{I_i}^{n_2}} + c_2)$$

Let $q_{11} = \frac{r_2\, k_2}{(k_2+G)^2} + c_1(\frac{r_3\, {I_i}^{n_2}}{k_3^{n2}+{I_i}^{n_2}} + c_2) \Rightarrow \frac{\partial F_1}{\partial Y_1} = -q_{11}$

$$\frac{\partial F_1}{\partial Y_2} = \frac{\partial F_1}{\partial I_p} \Rightarrow \frac{\partial F_1}{\partial I_p} = \frac{\partial}{\partial I_p}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta] = 0$$

$$\frac{\partial F_1}{\partial Y_3} = \frac{\partial F_1}{\partial I_i} \Rightarrow \frac{\partial F_1}{\partial I_i} = \frac{\partial}{\partial I_i}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta]$$

$$\frac{\partial F_1}{\partial Y_3} = -f_3(G)\frac{\partial}{\partial I_i} f_4\,(I_i) \Rightarrow \frac{\partial F_1}{\partial Y_3} = -f_3(G)\frac{\partial}{\partial I_i}[\frac{r_3\, {I_i}^{n_2}}{k_3^{n_2}+{I_i}^{n_2}} + c_2]$$

$$\frac{\partial F_1}{\partial Y_3} = -\, c_1 r_3 n_2 K_3^{n_2}\; \frac{G\, {I_i}^{n_2-1}}{(k_3^{n_2}+{I_i}^{n_2})^2}$$

Let $q_{13} = c_1 r_3 n_2 K_3^{n_2}\; \frac{G\, {I_i}^{n_2-1}}{(k_3^{n_2}+{I_i}^{n_2})^2} \Rightarrow \frac{\partial F_1}{\partial Y_3} = -q_{13}$

$$\frac{\partial F_1}{\partial Y_4} = \frac{\partial F_1}{\partial E} \Rightarrow \frac{\partial F_1}{\partial E} = \frac{\partial}{\partial E}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta] = m$$

$$\frac{\partial F_1}{\partial Y_5} = \frac{\partial F_1}{\partial x_1} \Rightarrow \frac{\partial F_1}{\partial x_1} = \frac{\partial}{\partial x_1}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta] = 0$$

$$\frac{\partial F_1}{\partial Y_6} = \frac{\partial F_1}{\partial x_2} \Rightarrow \frac{\partial F_1}{\partial x_2} = \frac{\partial}{\partial x_2}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta] = 0$$

$$\frac{\partial F_1}{\partial Y_7} = \frac{\partial F_1}{\partial x_3} \Rightarrow \frac{\partial F_1}{\partial x_3} = \frac{\partial}{\partial x_3}[\, f_5(x_3) - f_2(G) - f_3(G)f_4\,(I_i) + mE + \delta]$$

$$\frac{\partial F_1}{\partial Y_7} = \frac{\partial}{\partial x_3} f_3(x_3) = \frac{\partial}{\partial x_3}\left[\frac{r_4\, {I_4}^{n_3}}{k_4^{n_3}+{x_3}^{n_3}}\right] = -\, r_4 n_3 k_4^{n_3}\, \frac{{x_3}^{n_3-1}}{(k_4^{n_3}+{x_3}^{n_3})^2}$$

Let $q_{17} = r_4 n_3 k_4^{n_3}\, \frac{{x_3}^{n_3-1}}{(k_4^{n_3}+{x_3}^{n_3})^2} \Rightarrow \frac{\partial F_1}{\partial Y_7} = -q_{17}$

$$\frac{\partial F_2}{\partial Y_1} = \frac{\partial F_2}{\partial G} = \frac{\partial}{\partial \mathrm{G}}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = \beta \frac{\partial}{\partial \mathrm{G}}\, f_1(G) = \beta \frac{\partial}{\partial G}\left[\frac{r_1 G^{n_1}}{{k_1}^{n_1} + G^{n_1}}\right]$$

$$\frac{\partial F_2}{\partial Y_1} = \beta n_1 r_1 K_1^{n_1} \frac{G^{n_1 - 1}}{(K_1^{n_1} + G^{n_1})^2}$$, let $q_{21} = \beta n_1 r_1 K_1^{n_1} \frac{G^{n_1 - 1}}{(K_1^{n_1} + G^{n_1})^2} \Rightarrow \frac{\partial F_2}{\partial Y_1} = q_{21}$

$$\frac{\partial F_2}{\partial Y_2} = \frac{\partial F_2}{\partial I_p} = \frac{\partial}{\partial I_p}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = -R - \frac{1}{t_p} = -(R + \frac{1}{t_p})$$

Let $q_{22} = R + \frac{1}{t_p} \Rightarrow \frac{\partial F_2}{\partial Y_2} = -q_{22}$

$$\frac{\partial F_2}{\partial Y_3} = \frac{\partial F_2}{\partial I_i} = \frac{\partial}{\partial I_i}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = R$$

$$\frac{\partial F_2}{\partial Y_4} = \frac{\partial F_2}{\partial E} = \frac{\partial}{\partial E}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = 0$$

$$\frac{\partial F_2}{\partial Y_5} = \frac{\partial F_2}{\partial x_1} = \frac{\partial}{\partial x_1}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = 0$$

$$\frac{\partial F_2}{\partial Y_6} = \frac{\partial F_2}{\partial x_2} = \frac{\partial}{\partial x_2}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = 0$$

$$\frac{\partial F_2}{\partial Y_7} = \frac{\partial F_2}{\partial x_3} = \frac{\partial}{\partial x_3}[\beta\, f_1(G) - R(I_p - I_i) - \frac{I_p}{t_p}] = 0$$

$$\frac{\partial F_3}{\partial Y_1} = \frac{\partial F_3}{\partial G} = \frac{\partial}{\partial G}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = 0$$

$$\frac{\partial F_3}{\partial Y_2} = \frac{\partial F_3}{\partial I_p} = \frac{\partial}{\partial I_p}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = R$$

$$\frac{\partial F_3}{\partial Y_3} = \frac{\partial F_3}{\partial I_i} = \frac{\partial}{\partial I_i}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = -R - \frac{I_i}{t_i} = -(R + \frac{I_i}{t_i})$$

Let $q_{33} = R + \frac{I_i}{t_i} \Rightarrow \frac{\partial F_3}{\partial Y_3} = -q_{33}$, $\quad \frac{\partial F_3}{\partial Y_4} = \frac{\partial F_3}{\partial E} = \frac{\partial}{\partial E}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = 0$

$\frac{\partial F_3}{\partial Y_5} = \frac{\partial F_3}{\partial x_1} = \frac{\partial}{\partial x_1}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = 0$, $\quad \frac{\partial F_3}{\partial Y_6} = \frac{\partial F_3}{\partial x_2} = \frac{\partial}{\partial x_2}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = 0$

$\frac{\partial F_3}{\partial Y_7} = \frac{\partial F_3}{\partial x_3} = \frac{\partial}{\partial x_3}\left[R(I_p - I_i) - \frac{I_i}{t_i}\right] = 0$, $\quad \frac{\partial F_4}{\partial Y_1} = \frac{\partial F_4}{\partial G} = \frac{\partial}{\partial G}[\alpha E(1 - \gamma E)] = 0$,

$\frac{\partial F_4}{\partial Y_2} = \frac{\partial F_4}{\partial I_p} = \frac{\partial}{\partial I_p}[\alpha E(1 - \gamma E)] = 0$, $\quad \frac{\partial F_4}{\partial Y_3} = \frac{\partial F_4}{\partial I_i} = \frac{\partial}{\partial I_i}[\alpha E(1 - \gamma E)] = 0$

$$\frac{\partial F_4}{\partial Y_4} = \frac{\partial F_4}{\partial E} = \frac{\partial}{\partial E}[\alpha E(1-\gamma E)] = -\alpha(2\gamma E - 1)$$

Let $q_{44} = \alpha(2\gamma E - 1) \Rightarrow \frac{\partial F_4}{\partial Y_4} = -q_{44}$, $\quad \frac{\partial F_4}{\partial Y_5} = \frac{\partial F_4}{\partial x_1} = \frac{\partial}{\partial x_1}[\alpha E(1-\gamma E)] = 0$

$$\frac{\partial F_4}{\partial Y_6} = \frac{\partial F_4}{\partial x_2} = \frac{\partial}{\partial x_2}[\alpha E(1-\gamma E)] = 0, \qquad \frac{\partial F_4}{\partial Y_7} = \frac{\partial F_4}{\partial x_3} = \frac{\partial}{\partial x_3}[\alpha E(1-\gamma E)] = 0$$

$$\frac{\partial F_5}{\partial Y_1} = \frac{\partial F_5}{\partial G} = \frac{\partial}{\partial G}\left[\frac{3}{t_d}(I_p - x_1)\right] = 0, \qquad \frac{\partial F_5}{\partial Y_2} = \frac{\partial F_5}{\partial I_p} = \frac{\partial}{\partial I_p}\left[\frac{3}{t_d}(I_p - x_1)\right] = \frac{3}{t_d}$$

$$\frac{\partial F_5}{\partial Y_3} = \frac{\partial F_5}{\partial I_i} = \frac{\partial}{\partial I_i}\left[\frac{3}{t_d}(I_p - x_1)\right] = 0, \qquad \frac{\partial F_5}{\partial Y_4} = \frac{\partial F_5}{\partial E} = \frac{\partial}{\partial E}\left[\frac{3}{t_d}(I_p - x_1)\right] = 0$$

$$\frac{\partial F_5}{\partial Y_5} = \frac{\partial F_5}{\partial x_1} = \frac{\partial}{\partial x_1}\left[\frac{3}{t_d}(I_p - x_1)\right] = -\frac{3}{t_d}, \qquad \frac{\partial F_5}{\partial Y_6} = \frac{\partial F_5}{\partial x_2} = \frac{\partial}{\partial x_2}\left[\frac{3}{t_d}(I_p - x_1)\right] = 0$$

$$\frac{\partial F_5}{\partial Y_7} = \frac{\partial F_5}{\partial x_3} = \frac{\partial}{\partial x_3}\left[\frac{3}{t_d}(I_p - x_1)\right] = 0, \qquad \frac{\partial F_6}{\partial Y_1} = \frac{\partial F_6}{\partial G} = \frac{\partial}{\partial G}\left[\frac{3}{t_d}(x_1 - x_2)\right] = 0$$

$$\frac{\partial F_6}{\partial Y_2} = \frac{\partial F_6}{\partial I_P} = \frac{\partial}{\partial I_P}\left[\frac{3}{t_d}(x_1 - x_2)\right] = 0, \qquad \frac{\partial F_6}{\partial Y_3} = \frac{\partial F_6}{\partial I_i} = \frac{\partial}{\partial I_i}\left[\frac{3}{t_d}(x_1 - x_2)\right] = 0$$

$$\frac{\partial F_6}{\partial Y_4} = \frac{\partial F_6}{\partial E} = \frac{\partial}{\partial E}\left[\frac{3}{t_d}(x_1 - x_2)\right] = 0, \qquad \frac{\partial F_6}{\partial Y_5} = \frac{\partial F_6}{\partial x_1} = \frac{\partial}{\partial x_1}\left[\frac{3}{t_d}(x_1 - x_2)\right] = \frac{3}{t_d}$$

$$\frac{\partial F_6}{\partial Y_6} = \frac{\partial F_6}{\partial x_2} = \frac{\partial}{\partial x_2}\left[\frac{3}{t_d}(x_1 - x_2)\right] = -\frac{3}{t_d}, \qquad \frac{\partial F_6}{\partial Y_7} = \frac{\partial F_6}{\partial x_3} = \frac{\partial}{\partial x_3}\left[\frac{3}{t_d}(x_1 - x_2)\right] = 0$$

$$\frac{\partial F_7}{\partial Y_1} = \frac{\partial F_7}{\partial G} = \frac{\partial}{\partial G}\left[\frac{3}{t_d}(x_2 - x_3)\right] = 0, \qquad \frac{\partial F_7}{\partial Y_2} = \frac{\partial F_7}{\partial I_p} = \frac{\partial}{\partial I_p}\left[\frac{3}{t_d}(x_2 - x_3)\right] = 0$$

$$\frac{\partial F_7}{\partial Y_3} = \frac{\partial F_7}{\partial I_i} = \frac{\partial}{\partial I_i}\left[\frac{3}{t_d}(x_2 - x_3)\right] = 0, \qquad \frac{\partial F_7}{\partial Y_4} = \frac{\partial F_7}{\partial E} = \frac{\partial}{\partial E}\left[\frac{3}{t_d}(x_2 - x_3)\right] = 0$$

$$\frac{\partial F_7}{\partial Y_5} = \frac{\partial F_7}{\partial x_1} = \frac{\partial}{\partial x_1}\left[\frac{3}{t_d}(x_2 - x_3)\right] = 0, \qquad \frac{\partial F_7}{\partial Y_6} = \frac{\partial F_7}{\partial x_2} = \frac{\partial}{\partial x_2}\left[\frac{3}{t_d}(x_2 - x_3)\right] = \frac{3}{t_d}$$

$$\frac{\partial F_7}{\partial Y_7} = \frac{\partial F_7}{\partial x_3} = \frac{\partial}{\partial x_3}\left[\frac{3}{t_d}(x_2 - x_3)\right] = -\frac{3}{t_d}$$

Therefore, from equation (4.35) the Jacobian matrix is given as follows.

$$J=\begin{bmatrix} -q_{11} & 0 & -q_{13} & m & 0 & 0 & -q_{17} \\ q_{21} & -q_{22} & R & 0 & 0 & 0 & 0 \\ 0 & R & -q_{33} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -q_{44} & 0 & 0 & 0 \\ 0 & 3/t_d & 0 & 0 & -3/t_d & 0 & 0 \\ 0 & 0 & 0 & 0 & 3/t_d & -3/t_d & 0 \\ 0 & 0 & 0 & 0 & 0 & 3/t_d & -3/t_d \end{bmatrix}$$

By the Jacobian of sub-system (4.23), we obtain its characteristic equation as follows.

$$P(\lambda)=\lambda^7+a_1\lambda^6+a_2\lambda^5+a_3\lambda^4+a_4\lambda^3+a_5\lambda^2+a_6\lambda+a_7 \qquad (4.36)$$

The main target here is that to calculate $a_i, i=1,2,\dots,7$ based on definition (1.2).

$$a_1=-traJ \Rightarrow a_1=q_{11}+q_{22}+q_{33}+q_{44}+3(3/t_d)$$

$a_2 -$ is the sum of two rowed diagonal minors of J. The two rowed diagonal minors of J are formed by deleting five rows and five identical columns of J. There are 21 two rowed diagonal minors of J. To obtain all these determinants we delete five identical rows and columns alternatively as follows

$$M_1=\begin{vmatrix} -3/t_d & 0 \\ 3/t_d & -3/t_d \end{vmatrix}=\left(3/t_d\right)^2, \qquad M_2=\begin{vmatrix} -3/t_d & 0 \\ 0 & -3/t_d \end{vmatrix}=\left(3/t_d\right)^2$$

$$M_3=\begin{vmatrix} -3/t_d & 0 \\ 3/t_d & -3/t_d \end{vmatrix}=\left(3/t_d\right)^2, \qquad M_4=\begin{vmatrix} -q_{44} & 0 \\ 0 & -3/t_d \end{vmatrix}=q_{44}\left(3/t_d\right)$$

$$M_5=\begin{vmatrix} -q_{44} & 0 \\ 0 & -3/t_d \end{vmatrix}=q_{44}\left(3/t_d\right), \qquad M_6=\begin{vmatrix} -q_{44} & 0 \\ 0 & -3/t_d \end{vmatrix}=q_{44}\left(3/t_d\right)$$

$$M_7=\begin{vmatrix} -q_{33} & 0 \\ 0 & -3/t_d \end{vmatrix}=q_{33}\left(3/t_d\right), \qquad M_9=\begin{vmatrix} -q_{33} & 0 \\ 0 & q_{44} \end{vmatrix}=q_{33}\left(3/t_d\right)$$

Performing the same operation for the remaining determinants and adding all the values of $M_i, i = 1,2,3, \dots ,21$, we obtain a_2 as follows.

$$a_2 = M_1 + M_2 + \cdots + M_{21}$$

$$a_2 = 3\left(3/t_d\right)^2 + 3\left(3/t_d\right)[q_{11} + q_{22} + q_{33} + q_{44}]$$
$$+ q_{11}q_{22} + q_{11}q_{33} + q_{11}q_{44} + q_{22}q_{33} + q_{22}q_{44} - R^2$$

a_3 −is the sum of three rowed diagonal minors of J times – 1. The three rowed diagonal minors of J are formed by deleting four rows and four identical columns of J.

There are 35 three rowed diagonal minors of *J*. To obtain all these determinants we delete four identical rows and columns alternatively as follows.

$$M_1 = \begin{vmatrix} -3/t_d & 0 & 0 \\ 3/t_d & -3/t_d & 0 \\ 0 & 3/t_d & -3/t_d \end{vmatrix} = -(3/t_d)^3, \qquad M_2 = \begin{vmatrix} -q_{44} & 0 & 0 \\ 0 & -3/td & 0 \\ 0 & 3/td & -3/td \end{vmatrix} = -q_{44}(3/t_d)^2$$

$$M_3 = \begin{vmatrix} -q_{44} & 0 & 0 \\ 0 & -3/t_d & 0 \\ 0 & 0 & -3/t_d \end{vmatrix} = -q_{44}(3/t_d)^2, \qquad M_4 = \begin{vmatrix} -q_{44} & 0 & 0 \\ 0 & -3/t_d & 0 \\ 0 & 0 & -3/t_d \end{vmatrix} = -q_{44}(3/t_d)^2$$

$$M_5 = \begin{vmatrix} -q_{33} & 0 & 0 \\ 0 & -3/t_d & 0 \\ 0 & 3/t_d & -3/t_d \end{vmatrix} = -q_{33}(3/t_d)^{2,}$$

Performing the same operation for the remaining determinants and adding all the values of $M_i, i = 1,2,3, \dots ,35$, and multiplying by -1, we obtain a_3 as follows.

$$a_3 = -1[M_1 + M_2 + M_3 + \cdots + M_{35}]$$

$$\begin{aligned} a_3 &= (\tfrac{3}{t_d})^3 + 3(\tfrac{3}{t_d})^2[q_{11} + q_{22} + q_{33} + q_{44}] \\ &+ 3(\tfrac{3}{t_d})[q_{11}q_{22} + q_{11}q_{33} + q_{11}q_{44} + q_{22}q_{44} + q_{22}q_{33} - R^2] \\ &+ q_{11}q_{22}q_{33} - R^2 q_{11} + Rq_{13}q_{12} + q_{11}q_{22}q_{44} \\ &+ q_{11}q_{33}q_{44} + q_{22}q_{33}q_{44} - R^2 q_{44} \end{aligned}$$

$a_4 -$ is the sum four rowed diagonal minors of J. The four rowed diagonal minors of J are formed by deleting three rows and three identical columns of J.

There are 35 four rowed diagonal minors of J. To obtain all these determinants we delete three identical rows and columns alternatively as follows.

$$M_1 = \begin{vmatrix} -q_{33} & 0 & 0 & 0 \\ 0 & -q_{44} & 0 & 0 \\ 0 & 0 & -\frac{3}{t_d} & 0 \\ 0 & 0 & 0 & -\frac{3}{t_d} \end{vmatrix} = q_{44}(\tfrac{3}{t_d})^3$$

$$M_2 = \begin{vmatrix} -q_{33} & 0 & 0 & 0 \\ 0 & -\frac{3}{t_d} & 0 & 0 \\ 0 & \frac{3}{t_d} & -\frac{3}{t_d} & 0 \\ 0 & 0 & \frac{3}{t_d} & -\frac{3}{t_d} \end{vmatrix} = q_{33}(\tfrac{3}{t_d})^3$$

$$M_3 = \begin{vmatrix} -q_{33} & 0 & 0 & 0 \\ 0 & -q_{44} & 0 & 0 \\ 0 & 0 & -\frac{3}{t_d} & 0 \\ 0 & 0 & \frac{3}{t_d} & -\frac{3}{t_d} \end{vmatrix} = q_{33}q_{44}(\tfrac{3}{t_d})^2$$

$$M_4 = \begin{vmatrix} -q_{33} & 0 & 0 & 0 \\ 0 & -q_{44} & 0 & 0 \\ 0 & 0 & -3/t_d & 0 \\ 0 & 0 & 0 & -3/t_d \end{vmatrix} = q_{33}q_{44}(3/t_d)^2$$

Performing the same operation for the remaining determinants and adding all the values of $M_i, i = 1,2,3,\ldots,35$, we obtain a_4 as follows.

$$a_4 = M_1 + M_2 + M_3 + \cdots + M_{35}$$

$$a_4 = 3(3/t_d)^2 [q_{11}q_{22} + q_{11}q_{33} + q_{11}q_{44} + q_{22}q_{33} + q_{22}q_{44} + q_{33}q_{44} - R^2]$$
$$+ \left(3/t_d\right)^3 [q_{11} + q_{22} + q_{44} + q_{33}] + q_{13}q_{21}q_{44}R$$
$$+ 3(3/t_d)\ [q_{11}q_{22}q_{33} + q_{11}q_{22}q_{44} + q_{22}q_{33}q_{44} + q_{11}q_{33}q_{44} + q_{13}q_{21}R - R^2 q_{11}]$$

$a_5 -$ is the sum of five rowed diagonal minors of *J* multiplied by – 1. The five rowed diagonal minors of *J* are formed by deleing two rows and two identical columns of *J*. There are 21 five rowed diagonal minors of *J*. To obtain all these determinants we delete two identical rows and columns alternatively as follows.

$$M_1 = \begin{vmatrix} -q_{33} & 0 & 0 & 0 & 0 \\ 0 & -q_{44} & 0 & 0 & 0 \\ 0 & 0 & -3/td & 0 & 0 \\ 0 & 0 & 3/td & -3/td & 0 \\ 0 & 0 & 0 & 3/td & -3/td \end{vmatrix} = -q_{33}q_{44}\left(3/t_d\right)^3$$

$$M_2 = \begin{vmatrix} -q_{22} & 0 & 0 & 0 & 0 \\ 0 & -q_{44} & 0 & 0 & 0 \\ 3/t_d & 0 & -3/t_d & 0 & 0 \\ 0 & 0 & 3/t_d & -3/t_d & 0 \\ 0 & 0 & 0 & 3/t_d & -3/t_d \end{vmatrix} = -q_{22}q_{44}\left(3/t_d\right)^3$$

$$M_3 = \begin{vmatrix} -q_{22} & R & 0 & 0 & 0 \\ R & -q_{44} & 0 & 0 & 0 \\ 3/t_d & 0 & -3/t_d & 0 & 0 \\ 0 & 0 & 3/t_d & -3/t_d & 0 \\ 0 & 0 & 0 & 3/t_d & -3/t_d \end{vmatrix} = -q_{22}q_{33}(3/t_d)^3 + R^2(3/t_d)^3$$

Performing the same operation for the remaining determinants and adding all the values of $M_i, i = 1,2,3,\ldots,21$ and multiplying by -1, we obtain $a_5$as follows.

$$a_5 = -1[M_1 + M_2 + M_3 + \cdots + M_{21}]$$

$$a_5 = 3(3/td)^2 \begin{bmatrix} q_{11}q_{22}q_{33} + q_{11}q_{22}q_{44} + q_{11}q_{33}q_{44} + q_{22}q_{33}q_{44} \\ -R^2q_{44} - R^2q_{11} + q_{13}q_{21}R \end{bmatrix}$$
$$+3(3/td)\begin{bmatrix} q_{11}q_{22}q_{33}q_{44} + q_{13}q_{21}q_{44}R - R^2q_{11}q_{44} \\ \end{bmatrix}$$
$$+(3/td)^3 \begin{bmatrix} q_{11}q_{22} + q_{11}q_{33} + q_{11}q_{44} + q_{22}q_{33} + q_{22}q_{44} \\ +q_{33}q_{44} + q_{17}q_{21} - R^2 \end{bmatrix}$$

$a_6 -$ is the sum of six rowed diagonal minors of *J*. The six rowed diagonal minor of *J* is formed by deleting one row and one identical column of *J*. There are 7 six rowed diagonal minors of *J*.

$$M_1 = \begin{vmatrix} -q_{22} & R & 0 & 0 & 0 & 0 \\ R & -q_{33} & 0 & 0 & 0 & 0 \\ 0 & 0 & -q_{44} & 0 & 0 & 0 \\ 3/t_d & 0 & 0 & -3/t_d & 0 & 0 \\ 0 & 0 & 0 & 3/t_d & -3/t_d & 0 \\ 0 & 0 & 0 & 0 & 3/t_d & -3/t_d \end{vmatrix} = -R^2q_{44}\left(3/t_d\right)^3 + q_{22}q_{33}q_{44}\left(3/t_d\right)^3$$

$$M_2 = \begin{vmatrix} -q_{11} & -q_{13} & m & 0 & 0 & -q_{17} \\ 0 & -q_{33} & 0 & 0 & 0 & 0 \\ 0 & 0 & -q_{44} & 0 & 0 & 0 \\ 3/t_d & 0 & 0 & -3/t_d & 0 & 0 \\ 0 & 0 & 0 & 3/t_d & -3/t_d & 0 \\ 0 & 0 & 0 & 0 & 3/t_d & -3/t_d \end{vmatrix} = q_{11}q_{33}q_{44}\left(3/t_d\right)^3$$

Performing the same operation for the remaining determinants and adding all the values of $M_i, i = 1,2,3,\ldots,7$, we obtain a_6 as follows.

$$a_6 = M_1 + M_2 + M_3 + M_4 + M_5 + M_6 + M_7$$

$$\begin{aligned} a_6 = {} & 3\left(3/t_d\right)^2\left[q_{11}q_{22}q_{33}q_{44} - R^2 q_{11}q_{44} + q_{13}q_{21}q_{44}R\right] \\ & + \left(3/t_d\right)^3 [q_{11}q_{22}q_{33} + q_{11}q_{33}q_{44} + q_{22}q_{33}q_{44} - R^2 q_{44} - R^2 q_{11} \\ & + q_{11}q_{22}q_{44} + q_{13}q_{21}R + q_{17}q_{21}q_{33} + q_{17}q_{21}q_{44}] \end{aligned}$$

$$a_7 = (-1)^7 detJ$$

$$\begin{aligned} a_7 = {} & \left(3/t_d\right)^3\begin{bmatrix} q_{11}q_{22}q_{33}q_{44} - R^2 q_{11}q_{44} + q_{11}q_{22}q_{13}q_{44} + q_{13}q_{17}q_{21}q_{44} \\ +mq_{11}q_{22}q_{33} - mR^2 q_{11} + mq_{17}q_{21}q_{33} + mq_{13}q_{21}R \end{bmatrix} \\ & + \left(3/t_d\right)^2\left[q_{11}q_{22}q_{33}q_{44}q_{17} - R^2 q_{11}q_{44}q_{17} + q_{17}q_{13}q_{21}q_{44}R\right] \end{aligned}$$

Note: q_{ij} and a_i are constant numbers evaluated at $E_\beta^{*,\#}$. Consequently, the following property shows that all of them are non-negative.

Property1. For parameter expression q_{ij} and $a_i, i, j = 1,2,\ldots,7$

(a) $q_{ij} \geq 0$ for all i, j and (b) $a_i \geq 0$ for all i

Proof: (a) Since all the parameters in the model are non-negative, by definition of above q_{ij}, it is clear that $q_{ij} \geq 0$ when evaluated at $E_\beta^{*,\#}$. The equal sign holds for some q_{ij} at $E_0^{*,\#}$.

(b) To obtain $a_i \geq 0$, $a_1 = q_{11} + q_{22} + q_{33} + q_{44} + 3(3/t_d) \Rightarrow a_1 > 0$. To avoid any negative expression in the remaining $a_i's, i = 2,3,\ldots,7$ It is helpful to notice that

$$q_{22}q_{33} - R^2 = \left(R + \frac{1}{t_p}\right)\left(R + \frac{1}{t_i}\right) - R^2$$

$$= R^2 + \left(\frac{1}{t_p} + \frac{1}{t_i}\right)R + \frac{1}{t_p t_i} - R^2$$

$$= \left(\frac{1}{t_p} + \frac{1}{t_i}\right)R + \frac{1}{t_p t_i} > 0$$

Hence, in all expression $q_{22}q_{33} - R^2 > 0$. And it is easy to observe that for every negative term in the expression of $a_i, i = 2,3,\dots,7,$ it can be rearranged and factored out $q_{22}q_{33} - R^2$. Thus, $a_i > 0$ for all $i = 1,2,\dots,7$.

Conditions for Local Stability

The local stability of the equilibria of the fast sub- system is determined by varying β as follows. Applying Routh's stability criteria to the characteristic equation (4.36)

$$P(\lambda) = \lambda^7 + a_1\lambda^6 + a_2\lambda^5 + a_3\lambda^4 + a_4\lambda^3 + a_5\lambda^2 + a_6\lambda + a_7$$

$$\begin{array}{c|cccc} \lambda^7 & 1 & a_2 & a_4 & a_6 \\ \lambda^6 & a_1 & a_3 & a_5 & a_7 \\ \lambda^5 & b_1 & b_2 & b_3 & \\ \lambda^4 & c_1 & c_2 & c_3 & \\ \lambda^3 & d_1 & d_2 & & \\ \lambda^2 & e_1 & e_2 & & \\ \lambda & f_1 & & & \\ \lambda^0 & g_1 & & & \end{array} , \qquad (4.37)$$

where $b_1 = \frac{a_1a_2 - a_3}{a_1}$, $b_2 = \frac{a_1a_4 - a_5}{a_1}$, $b_3 = \frac{a_1a_6 - a_7}{a_1}$

$c_1 = \frac{b_1a_3 - a_1b_2}{b_1}$, $c_2 = \frac{a_1a_5 - a_1b_3}{b_1}$, $c_3 = \frac{b_1a_7}{b_1} = a_7$

$d_1 = \frac{c_1b_2 - b_1c_2}{c_1}$, $d_2 = \frac{c_1b_3 - b_1c_3}{c_1}$

$e_1 = \frac{d_1c_2 - c_1d_2}{d_1}$, $e_2 = \frac{d_1c_3}{d_1} = c_3 = a_7$, (4.38)

$f_1 = \frac{e_1d_2 - e_2d_1}{e_1}$, $g_1 = \frac{f_1e_2}{f_1} = e_2 = c_3 = a_7$

For the sub-system (4.23) to be stable all elements of the first column of equation (4.37) must be of the same sign.

$1 > 0,\ a_1 > 0$ (from property1)

Consequently, all the remaining elements of the first column must be positive

$b_1 > 0 \Leftrightarrow \frac{a_1 a_2 - a_3}{a_1} > 0,$ since $a_1 > 0,\ a_1 a_2 - a_3 > 0$

Therefore, $b_1 > 0 \Leftrightarrow a_1 a_2 - a_3 > 0$

$c_1 > 0 \Leftrightarrow \frac{b_1 a_3 - a_1 b_2}{b_1} > 0$

Plugging the values of b_1 and b_2 in the above expression and making simplification:

$\frac{a_1 a_3 a_3 - a_3^2 - a_1^2 a_4 + a_1 a_5}{a_1 a_2 - a_3} > 0$, Since $a_1 a_2 - a_3 > 0$

$a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 + a_1 a_5 > 0 \Rightarrow a_3(a_1 a_2 - a_3) - a_1(a_1 a_4 - a_5) > 0$

$\Rightarrow a_3(a_1 a_2 - a_3) - a_1(a_1 a_4 - a_5) > 0$

Therefore, $c_1 > 0 \Leftrightarrow a_3(a_1 a_2 - a_3) > a_1(a_1 a_4 - a_5)$

In the same manner, if $d_1, e_1, f_1 > 0$, then the system is stable.

As a result the stability conditions for the model are given below.

(i) $a_1 a_2 - a_3 > 0,$ (ii) $a_1 a_2 - a_3 > \frac{a_1}{a_3}(a_1 a_4 - a_5)$,

(iii) $d_1 > 0,$ (iv) $e_1 > 0,$ (v) $f_1 > 0$,

where d_1, e_1 and f_1 are given in equation (4.38).

4.3 Bifurcation Analysis

4.3.1 Backward Bifurcations

Let us take the relative strength of beta cell functionality as a bifurcation parameter.

From equation (4.31)

$$G = \frac{r_a \pm \sqrt{r_a^2 - 4r_b(1-\omega)}}{2r_b}$$

$$G = \frac{r_a - \sqrt{r_a^2 - 4r_b(1-\omega)}}{2r_b} \rightarrow \text{ lower branch of bifurcation diagram.}$$

$$\frac{\partial G}{\partial \omega} = \frac{\frac{-1}{2}(r_a^2 - 4r_b(1-\omega))^{-\frac{1}{2}} \frac{\partial}{\partial \omega}\left(r_a^2 - 4r_b(1-\omega)\right)}{2r_b}$$

$$= \frac{-4r_b(r_a^2 - 4_b^r(1-\omega))^{-\frac{1}{2}}}{4r_b}$$

$$= -[r_a^2 - 4_b^r(1-\omega))^{-\frac{1}{2}} < 0$$

The negative partial derivative indicates that that the lower branch represents backward bifurcation. This result can be interpreted as “the higher beta cell functionality the lower equilibrium glucose level.

4.3.2 Hopf Bifurcation Analysis

Lemma 1 (Existence of Hopf bifurcation)

Suppose that C^5 −system (4.23) with $Y \in \mathbb{R}^7$ and $\mu \in \mathbb{R}$ has critical point Y_0 for some parameter $\mu = \mu_0$ and that $J = DF(Y_0, \mu_0)$ has a simple pair of pure imaginary eigenvalues and no other eigenvalues with zero real part. Furthermore, Suppose $\frac{d}{d\mu}\left[Rel\,\lambda(\mu)\right]_{\mu=\mu_0} \neq 0$, then the Hopf bifurcation occurs at $\mu = \mu_0$.

By the characteristic equation (4.36), if it has a simple pair of pure imaginary eigenvalues

$\lambda = \pm$wi(w $> o$) at $\mu = \mu_0$, then

$$\lambda^7 + a_1\lambda^6 + a_2\lambda^5 + a_3\lambda^4 + a_4\lambda^3 + a_3\lambda^2 + a_6\lambda + a_7 = 0$$

$$(wi)^7 + a_1(wi)^6 + a_2(wi)^5 + a_3(wi)^4 + a_4(wi)^3 + a_5(wi)^2 + a_6(wi) + a_7 = 0$$

$$-iw^7 - a_1w^6 + a_2w^5i + a_3w^4 - a_4w^3i - a_5w^2 + a_6wi + a_7 = 0$$

$$(-w^7 + a_2w^6 - a_4w^3 + a_6w)i + (-a_1w^6 + a_3w^4 - a_5w^2 + a_7) = 0$$

$$-w^7 + a_2w^5 - a_4w^3 + a_6w = 0 \tag{4.39}$$

$$-a_1w^6 + a_3w^4 - a_5w^2 + a_7 = 0 \tag{4.40}$$

From equation (4.39)

$$w[-w^6 + a_2w^4 - a_4w^2 + a_6] = 0$$

Since $w > 0$, $-w^6 + a_2w^4 - a_4w^2 + a_6 = 0$ (4.41)

Solving equation (4.40) and (4.41) simultaneously,

$$(a_1a_2 - a_3)w^4 - (a_1a_4 - a_5)w^2 + (a_1a_6 - a_7) = 0$$

Let $b_1 = a_1a_2 - a_3$, $b_2 = a_1a_4 - a_5$, $b_3 = a_1a_6 - a_7$

$$b_1w^4 - b_2w^2 + b_3 = 0$$

Therefore, the pair of pure imaginary eigenvalues can be found as

$$w^2 = \frac{b_2 \pm \sqrt{b_2^2 - 4b_1b_3}}{2b_1} \tag{4.42}$$

Substituting (4.42) into (4.41),

$$-\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1b_3}}{2b_1}\right)^3 + a_2\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1b_3}}{2b_1}\right)^2 - a_4\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1b_3}}{2b_1}\right) + a_6 = 0$$

Next we compute $\frac{d\lambda}{d\mu}$ for some parameter μ based on characteristic equation (4.36) as follows.

$$(7\lambda^6 + 6a_1\lambda^5 + 5a_2\lambda^4 + 4a_3\lambda^3 + 3a_4\lambda^2 + 2a_5\lambda + a_6)\frac{d\lambda}{d\mu}$$

$$+\left(\frac{da_1}{d\mu}\lambda^6 + \frac{da_2}{d\mu}\lambda^5 + \frac{da_3}{d\mu}\lambda^4 \quad \frac{da_4}{d\mu}\lambda^3 + \frac{da_5}{d\mu}\lambda^2 + \frac{da_6}{d\mu}\lambda + \frac{da_7}{d\mu}\right) = 0$$

Notice $\lambda = \pm wi$ at $\mu = \mu_0$.

$$[7(wi)^6 + 6a_1(wi)^5 + 5a_2(wi)^4 + 4a_3(wi)^3 + 3a_4(wi)^2 + 2a_5(wi) + a_6]\frac{d\lambda}{d\mu}$$

$$+[\frac{da_1}{d\mu}(wi)^6 + \frac{da_2}{d\mu}(wi)^5 + \frac{da_3}{d\mu}(wi)^4 + \frac{da_4}{d\mu}(wi)^3 + \frac{da_5}{d\mu}(wi)^2 + \frac{da_6}{d\mu}(wi) + \frac{da_7}{d\mu}] = 0$$

$$\Rightarrow [-7w^6 + 6a_1w^5i + 5a_2w^4 - 4a_3w^3i - 3a_4w^2 + 2a_5wi + a_6]\frac{d\lambda}{d\mu}$$

$$+[-\frac{da_1}{d\mu}w^6 + \frac{da_2}{d\mu}w^5i + \frac{da_3}{d\mu}w^4 - \frac{da_4}{d\mu}w^3i - \frac{da_5}{d\mu}w^2 + \frac{da_6}{d\mu}wi + \frac{da_7}{d\mu}] = 0$$

$$\Rightarrow [(-7w^6 + 5a_2w^4 - 3a_4w^2 + a_6) + (6a_1w^5 - 4a_3w^3 + 2a_5w)i]\frac{d\lambda}{d\mu}$$

$$+\left[\left(-\frac{da_1}{d\mu}w^6 + \frac{da_3}{d\mu}w^4 - \frac{da_5}{d\mu}w^2 + \frac{da_7}{d\mu}\right) + \left(\frac{da_2}{d\mu}w^5 - \frac{da_4}{d\mu}w^3 + \frac{da_6}{d\mu}w\right)i\right] = 0$$

$$\Rightarrow [(-7w^6 + 5a_2w^4 - 3a_4w^2 + a_6) + (6a_1w^5 - 4a_3w^2 + 2a_5w)i]\frac{d\lambda}{d\mu} =$$

$$-\left[\left(-\frac{da_1}{d\mu}w^6 + \frac{da_3}{d\mu}w^4 - \frac{da_5}{d\mu}w^2 + \frac{da_7}{d\mu}\right) + \left(\frac{da_2}{d\mu}w^5 - \frac{da_4}{d\mu}w^3 + \frac{da_6}{d\mu}w\right)i\right]$$

$$\Rightarrow \frac{d\lambda}{d\mu} = \frac{\left[\left(-\frac{da_1}{d\mu}w^6 + \frac{da_3}{d\mu}w^4 - \frac{da_5}{d\mu}w^2 + \frac{da_7}{d\mu}\right) + \left(\frac{da_2}{d\mu}w^5 - \frac{da_4}{d\mu}w^3 + \frac{da_6}{d\mu}w\right)i\right]}{(-7w^6 + 5a_2w^4 - 3a_4w^2 + a_6) + (6a_1w^5 - 4a_3w^2 + 2a_5w)i}$$

We have, $sign\left\{\frac{d}{d\mu}(Re\lambda(\mu)\right\} = \text{sign}\left\{Re(\frac{d\lambda}{d\mu})\right\}$ (Wang, 2015)

$$sign\left\{\frac{d}{d\mu}(Re\lambda(\mu)\right\} = sign[\frac{\left(-\frac{da_1}{d\mu}w^6 + \frac{da_3}{d\mu}w^4 - \frac{da_5}{d\mu}w^2 + \frac{da_7}{d\mu}\right)(-7w^6 + sa_2w^4 - 3a_4w^2 + a_6) + \left(\frac{da_2}{d\mu}w^5 + \frac{da_4}{d\mu}w^3 - \frac{da_6}{d\mu}\omega\right)(6a_1w^5 - 4a_3w^3 - 2a_5\omega)}{(-7w^6 + 5a_2w^4 - 3a_4w^2 + a_6)^2 + (6a_1w^5 - 4a_3w^2 + 2a_5w)^2}]$$

$$= -sign[(-\frac{da_1}{d\mu}\ w^6 + \frac{da_3}{d\mu} w^4 - \frac{da_5}{d\mu} w^2 + \frac{da_7}{d\mu})\ (-7w^6 + 5a_2 w^4 -$$

$$3a_4\ w^2 + a_6)\ \ + \left(\frac{da_2}{d\mu}\ w^5 - \frac{da_4}{d\mu} w^3 + \frac{da_6}{d\mu} w\right) (6a_1 w^5 -$$

$$4a_3 w^3 + 2a_5\ \omega)]$$

$$= -sign[\Big(-\frac{da_1}{d\mu}\ w^6 + \frac{da_3}{d\mu} w^4 - \frac{da_5}{d\mu} w^2 + \frac{da_7}{d\mu})\ (-6w^6 + 4a_2 w^4 - 2a_4\ w^2)$$

$$+ \left(\frac{da_2}{d\mu}\ w^4 - \frac{da_4}{d\mu} w^2 + \frac{da_6}{d\mu}\right) (6a_1 w^4 - 4a_3 w^2 + 2a_5) w^2\Big)]$$

$$= -sign[(-\frac{da_1}{d\mu}\ w^6 + \frac{da_3}{d\mu} w^4 - \frac{da_5}{d\mu} w^2 + \frac{da_7}{d\mu})\ (-6w^4 + 4a_2 w^2 - 2a_4\ )$$

$$+ \left(\frac{da_2}{d\mu}\ w^4 - \frac{da_4}{d\mu} w^2 + \frac{da_6}{d\mu}\right) (6a_1 w^4 - 4a_3 w^2 + 2a_5)]$$

$$= -sign[(-\frac{da_1}{d\mu}\ w^6 + \frac{da_3}{d\mu} w^4 - \frac{da_5}{d\mu} w^2 + \frac{da_7}{d\mu})\ (-3w^4 + 2a_2 w^2 - a_4\ )$$

$$+ \left(\frac{da_2}{d\mu}\ w^4 - \frac{da_4}{d\mu} w^2 + \frac{da_6}{d\mu}\right) (3a_1 w^4 - 2a_3 w^2 + a_5)]$$

By equation (4.42) it follows that

$$sign\left\{\left[\frac{d}{d\mu}(Re\lambda(\mu)\right]_{\mu=\mu_0}\right\} =$$

$$sign[(\frac{-da_1}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^3 + \frac{da_3}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 - \frac{da_5}{d\mu}\ (\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1})$$

$$+ \frac{da_6}{d\mu})(-3\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 + 2a_2\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right) - a_4)$$

$$+(\frac{da_2}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 - \frac{da_4}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)$$

$$+ \frac{da_6}{d\mu})\left(3a_1\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 - 2a_3\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right) + a_5\right)]$$

By the above analysis we can now state the following result.

Suppose that parameter β varies while other parameters fix and system (4.23) with $Y \in \mathbb{R}^7$ and $\beta \epsilon \mathbb{R}$ has critical point Y_0 for parameter $\beta = \beta^*$, if the parameter of the system satisfy

$$-\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^3 + a_2\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 - a_4\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right) + a_6 = 0$$

Then system (4.23) has a simple pair of pure imaginary eigenvalues given by

$$\lambda = \pm wi = \pm i\left(\frac{b_2 + \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^{1/2} \text{ or } \lambda = \pm wi = \pm i\left(\frac{b_2 - \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^{1/2}$$

Furthermore, if

$$\left\{\left[\frac{d}{d\beta}(Re\lambda(\beta)\right]_{\beta=\beta^*}\right\} = [(\frac{-da_1}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^3 + \frac{da_3}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 - \frac{da_5}{d\mu}\ (\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}) +$$

$$\frac{da_6}{d\mu})(-3\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 + 2a_2\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right) - a_4) + (\frac{da_2}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 -$$

$$\frac{da_4}{d\mu}\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right) + \frac{da_6}{d\mu})\left(3a_1\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right)^2 - 2a_3\left(\frac{b_2 \pm \sqrt{b_2^2 - 4b_1 b_3}}{2b_1}\right) + a_5\right)] \neq 0$$

Then system (4.23) undergoes Hopf bifurcation at $\beta = \beta^*$ for some $\beta^* > 0$

Property 2: $b_1 |_{\beta=0} > 0$, $b_2 |_{\beta=0} > 0$, $b_1 |_{\beta=0} > 0$

Proof: at $\beta = 0$, $q_{21} = 0$

First we prove for $b_1 |_{\beta=0} > 0$, and the others follows.

Let $T_d = \frac{3}{t_d}$, $e_1 = q_{11} + q_{22} + q_{33} + q_{44}$,

$$e_2 = q_{11}q_{22} + q_{11}q_{33} + q_{11}q_{44} + q_{22}q_{33} + q_{22}q_{44} - R^2$$

$$e_3 = q_{11}q_{22}q_{33} - R^2\, q_{11} + q_{11}q_{22}q_{44} + q_{11}q_{33}q_{44} + q_{22}q_{33}q_{44} - R^2 q_{44}$$

Thus we have,

$$a_1 = e_1 + 3T_d\,,\ a_2 = e_2 + 3T_d\, e_1 + 3T_d^2,\ a_3 = e_3 + 3T_d\, e_2 + 3T_d^2 + T_d^3$$

Then it follows that,

$$b_1 = a_1a_2 - a_3 = (e_1 + 3T_d\,)\,(e_2 + 3T_d^2 + T_d^3) - (e_3 + 3T_d^2e_2 + T_d^3 + T_d^3)$$

$$= e_1e_2 - 3T_de_1^2 + 3T_d^2e_1 + 3T_d\, e_2 + 3T_d^2e_1 + 9T_d^3 - e_3 - 3T_d\, e_2 - 3T_d^2 - T_d^3$$

$$= e_1e_2 + 3T_de_1^2 + 3T_d^2e_1 + 8T_d^3 - e_3$$

$$= 3T_d\ \ e_1^2 + 3T_d^2e_1 + 8T_d^2 + (e_1\, e_2 - e_3)$$

but, $e_1\, e_2 - e_3 > 0$.

Therefore, $\mathrm{b}_1 > 0$, the prove is done. Similarly $\mathrm{b}_2 > 0$, $\mathrm{b}_3 > 0$ at $\beta = 0$

Lemma 2: If (i) $a_4\ |_{\beta=0} < \frac{b_2^2-4b_1b_3}{b_1^2}\ |_{\beta=0} < (a_2^2 - 4a_4)\ |_{\beta=0}$ and

$(ii)\ \frac{b_2}{b_1} < a_2$, then $h(0) > 0$

Condition (i) can be rewrite as, $\sqrt{a_4} < \frac{\sqrt{b_2^2-4b_1b_3}}{b_1} < \sqrt{a_2^2 - 4a_4}$

Proof: Denote,

$$h(\beta) =: \left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^3 + a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^2 - a_4\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right) + a_6$$

Claim, $h(0) = -\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^3 + a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^2$

$$- a_4\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right) + a_6 > 0$$

$$h(0) = -\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^3 + a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^2 - a_4\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right) + a_6$$

$$h(0) > -\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^3 + a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^2 - a_4\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)$$

$$= -\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)[\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^2 - a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right) + a_4]$$

Thus it suffices to show that

$$h(0) = -\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)[\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^2 - a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right) + a_4] > 0$$

or equivalently,

$$\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right)^3 - a_2\left(\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}\right) + a_4 < 0 \qquad (4.43)$$

The left hand side of (4.43) is quadratic form. To prove the above inequality it is equivalent to prove $\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}$ lies between the roots of $x^2 - a_2x + a_4 = 0, i.e$

$$\frac{a_2-\sqrt{a_2^2-4a_4}}{2} < \frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1} < \frac{a_2+\sqrt{a_2^2-4a_4}}{2} \qquad (4.44)$$

First we consider the right hand side of inequality (4.44) using condition (ii) together with

$$\frac{\sqrt{b_2^2-4b_1b_3}}{b_1} < \sqrt{a_2^2-4a_4}$$

$$\frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1} = \frac{b_2}{2b_1}\frac{+\sqrt{b_2^2-4b_1b_3}}{2b_1} < \frac{a_2}{2} + \frac{\sqrt{a_2^2-4a_4}}{2} = \frac{a_2+\sqrt{a_2^2-4a_4}}{2}$$

$$\therefore \frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1} < \frac{a_2+\sqrt{a_2^2-4a_4}}{2} \qquad (4.45)$$

Then we consider the left hand side of inequality (4.44) by using condition

$$\sqrt{a_4} < \frac{\sqrt{b_2^2-4b_1b_3}}{b_1}$$

$$\frac{a_2-\sqrt{a_2^2-4a_4}}{2} = \frac{(a_2-\sqrt{a_2^2-4a_4}\,)(\,a_2+\sqrt{a_2^2-4a_4})}{2(a_2+\sqrt{a_2^2-4a_4})} = \frac{4a_4}{2(a_2+\sqrt{a_2^2-4a_4})}$$

$$= \frac{2a_4}{a_2+\sqrt{a_2^2-4a_4}} < \frac{2a_4}{\frac{b_2+\sqrt{b_2^2-4b_4b_3}}{b_1}} < \frac{2a_4}{\frac{2\sqrt{b_2^2-4b_1b_3}}{b_1}} = \frac{a_4}{\frac{\sqrt{b_2^2-4b_1b_3}}{b_1}}$$

$$\frac{\frac{<b_2^2-4b_1b_3}{{b_1}^2}}{\frac{\sqrt{b_2^2-4b_1b_3}}{b_1}} = \frac{\sqrt{b_2^2-4b_1b_3}}{b_1} < \frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1}$$

$$\therefore \frac{a^2-\sqrt{a_2^2-4a_4}}{2} < \frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1} \tag{4.46}$$

From (4.45) and (4.46),

$$\frac{a_2^2-\sqrt{a_2^2-4a_4}}{2} < \frac{b_2+\sqrt{b_2^2-4b_1b_3}}{2b_1} < \frac{a_2+\sqrt{a_2^2-4a_4}}{2}$$, The proof is done.

Definition (Wang, 2015)

If $r_a^2+4r_b\left(\frac{po}{ao}-1\right)>0$ then it holds $h(\beta_2)>0.$ where β_2 is the $\beta-$coordinate of the equilibrium point E_2 for the complete system (4.20). Consequently, the following result follows:

If (i) $a_4\ |_{\beta=0} < \frac{b_2^2-4b_1b_3}{b1^2}\ |_{\beta=0} < (a_2^2-4a_4)\ |_{\beta=0}$

(ii) $\frac{b_2}{b_1} < a_2$

(iii) $r_a^2+4r_b\left(\frac{po}{ao}-1\right)>0,$ there exist $\beta=\beta^*\in(0,\beta_2)$ at which the Hopf bifurcation occurs. This result is direct result of intermediate value theorem. If conditions (i) and (ii) are satisfied $h(o)>0$. If condition (iii) is satisfied $h(\beta_2)<0$. Therefore, there exists $\beta=\beta^*\in(0,\beta_2)$ such that, $h(\beta^*)=0.$ Hence, the Hopf bifurcation occurs at $\beta=\beta^*$.

CHAPTER FIVE

CONCLUSION AND FUTURE WORK

5.1. Conclusions

In this paper, human glucose insulin regulation system under the influence of pancreatic beta cell was formulated. The model incorporates state variables like glucose, plasma insulin, interstitial insulin, externally ingested glucose in the form of food, beta cell mass and time delay.

Mathematical manipulation such as critical point, local stability conditions and bifurcation analysis was carried out. The bifurcation parameter for the model analysis was the relative strength of beta cell functionality. If this parameter is too low, which indicates poor beta-cell functionality, then the body may develop diabetes in the long run. This parameter is defined as the ratio of beta cell proliferation to apoptosis parameter. The backward bifurcation is interpreted as the higher beta-cell functionality, the lower equilibrium glucose level. In physiological context, if the relative strength of beta-cell functionality is too weak, the body will develop the pathological state, which in our model is the trivial equilibrium point. However, if the relative strength of beta-cell functionality is strong, the body could have healthy states, which in the model are represented by the interior equilibrium points.

5.2 Future Work

This research topic can be enriched more by including other variables like physical exercise and then making stability and bifurcation analysis at steady state points and different bifurcation parameters. Moreover, a sensitivity analysis can be made so as to identify a variable that needs to be controlled for a better treatment of a patient of diabetics. Furthermore, all the results need to be supported by numerical simulations for further understanding of the dynamics using actual data.

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