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MATHEMATICAL ANALYSIS OF INSULIN-GLUCOSE FEEDBACK SYSTEM OF DIABETIES

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Abstract

Mathematical models based on advanced differential equations are utilized to analyze the effect of insulin infusions in human body with the intent of determining better modes of treatment for the metabolism of glucose. We have incorporated the models of several prominent mathematicians in this work, with the particular emphasis on deriving the models, formulas and intent of their works. The purpose of which is to come to a greater understanding of the nature of their models in order to express their works in a more simplified and comprehensive way. This is so that those with little or no conceptual knowledge of these models can come to realize their methodology more easily and with more in-depth understanding. The three Insulin-Feedback models analyze the efficiency of Insulin in regulating glucose dependency upon how the insulin is introduced into the individual. The intent of all the models is to analyze the model of infusion upon the hypoglycemic attributes of glucose in the blood. The first (original) and second models analyses the mechanism of slow ultradian oscillation infusions of insulin into individuals with varying levels of infusion with respect to time. The third model utilizes a time delay over short intervals which create a pulsatile effect in the infusion of glucose.

Keywords: Mathematical Models, Insulin Infusion, three insulin feedback model

1.1 Introduction

Diabetes is a dysfunction of the equilibrium in the regulation of glucose within the body. This is caused by an autoimmune attack on Beta Cells secreted by the Pancreas (Type I) or by the inadequate supply or function of β-cells in counteracting the fluctuations of high and low blood glucose within the body (Type II). This extremely serious medical condition can result in symptoms ranging from nausea, changes in body weight, fatigue to fainting and even death. In order to test whether or not a patient has diabetes, a medical procedure called the Glucose Tolerance Test (GTT) is done in which the patient is administered a high dose of glucose after a full night of fasting. The GTT determines if the individual is a diabetic by the body's response to the high infusion of glucose. The body is supposed to regulate the glucose so that a homeostasis is reached within a few hours. If the individual cannot reach that homeostasis in the typical allotment of a few hours, the individual is deemed to be a diabetic by the physician.

However, the GTT is limited in its accuracy of projecting whether or not the patient has diabetes, sometimes leading to inaccurate diagnosis. Therefore, the aim of this project is to most accurately determine through differential equation models the blood glucose regulatory system (BGRS) during GTT by analytically integrating various parameters that yield accurate projections of diagnosis. The hopes of which are to provide a mathematical solution through differential equations which can provide the medical community with a more accurate rendering of a diagnosis. Because every individual is different, the concentrations of glucose within their bodies vary as well; therefore it is critical to 'individualize' the models and their subsequent parameters to cater to them. This is achieved by the differential equation models through the construction of numerous variables in conjunction with established parameters within each model, thereby taking various factors in account simultaneously. The parameters and variables outlined in the specific models and their respective

equations are attained experimentally in laboratories and are not from my own work.

Before proceeding, it is important to establish a few critical concepts for the casual observer that will help them come to realizing the methodology and logical construction of the models. First of which is that glucose is the main energy bio-chemical which is later broken down to adenosine triphosphate (ATP) that is the main energy source within the body. The blood glucose concentration has an optimal level for each individual, and any excessive departure from this optimal concentration causes severe medical conditions both in excess and in depletion. The lack of homeostatic regulation of glucose is the main determinant of medical experts as to whether or not an individual has diabetes and it is with this knowledge that we tackled these models. Normally, the blood glucose levels tend to be auto-regulatory but they are susceptible to a wide variety of hormones and some hormones e.g. Insulin decreases the blood glucose concentration. Secondly, we make a passing reference to two hormones due to their importance in BGRS. The main regulatory hormone secreted by β-Cells of the pancreas is insulin. The hormone Insulin is responsible for the lowering the concentration of glucose and assists in the combustion of sugar in the tissues and facilitates glucose uptake in muscles and tissues. Without sufficient insulin, the body cannot avail itself of all the energy it needs. The pancreas further secretes α-cells which is stored in the liver in the form of glycogen. This glycogen is converted back into glucose in times of need, for example, low blood sugar. The function of the hormone glycogen is to increase the rate of breakdown of glycogen into glucose.

Further we have come to a few biological conclusions pertaining to the nature of the insulin-glucose feedback system which are relevant to the understanding of these models. They were attained via direct collaboration with the current (2013-2014) VMI Biology Department Head, Colonel Thompson. We determined that there exists a Direct Response to elevated or decreased glucose levels with a critical level of optimal set glucose levels. Pertaining to the utilization of glucose within the body, the brain uses glucose as it's only energy source and because the brain is constantly functioning glucose is always being depleted there, which leads to it being injection independent, meaning that glucose and insulin constantly decay there. Further, we came to the realization of the injection dependent organs and regions of the body that respond when and influx of glucose into the body occurs. They mostly occur in the pancreas which is the main endocrine organ that secretes the hormone insulin from within the blood system. This is directly stimulated by eating a meal in which you will see a quick glucose rise. With this stimulus, a chemical signal is stimulated within the pancreas that causes it to produce β-cells that are the direct producer of the hormone insulin. Finally, the liver is the major storage place of glucose in the body which is why our model needs to take into account the reactions taking place within the liver.

1. **Phase of insulin production:** The remote insulin could be stimulant independent. Glycogen is stored in the liver, muscles and in adipose tissue (fat). In between meals, the pancreas is putting out a subliminal level of insulin with in very minor levels. The pancreas secretes digestive enzymes, produces insulin and glucagon. Glucagon responds when insulin over regulates glucose. It acts as a hormone to metabolically release glucose from the stored cites of the body. There also exists 3 types of amino acids that the pancreas is sensitive to which the pancreas would produce insulin.
2. **Time delaying factors for insulin production:**
    a. Digestion of food products
    b. Absorbed through the blood stream to the pancreas
        i. The pancreas is stimulated
        ii. Time it takes for the insulin to travel through the cells.
        iii. Time to activate receptors to accept glucose into the cell.

APPENDIX C

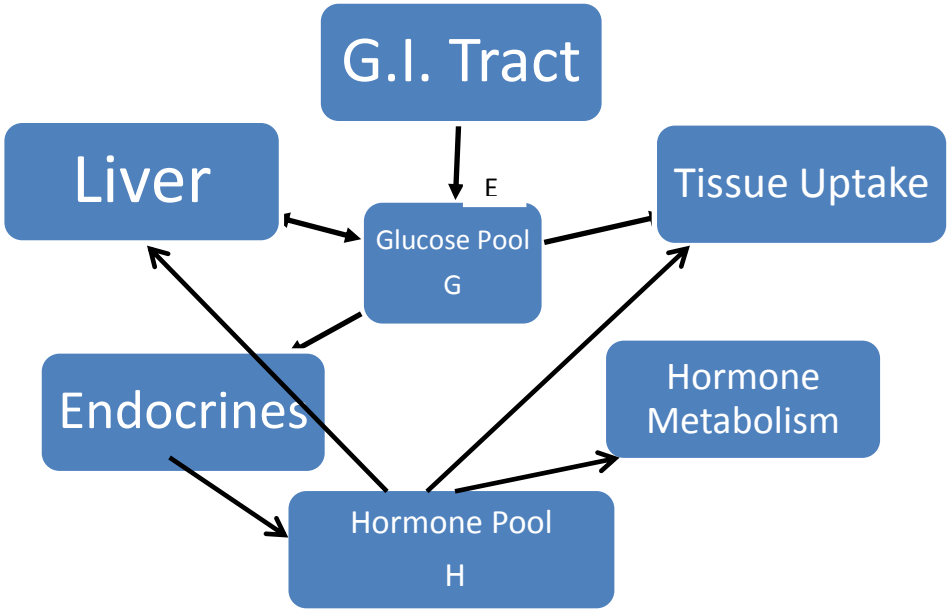


Figure 1-Schematic Diagram of BGRS System

1.2 Formulation of Mathematical Model.

We formulate an appropriate model in two steps indicated below.

Step I Background Information on the Model

Here we state the assumptions, identify suitable variables of study and give the law governing the performance of BGRS.

1) We assume that the following two concentrations adequately describe the performance of BGRS.
   a) Concentration of glucose in the Blood (G)
   b) Net Hormonal Concentration (H)

   By net hormonal concentration, we mean the cumulative effect of all the relevant hormones with the following sign convention: those hormones which describe an overall decrease or increase. In blood glucose concentration (BGC) for example, Insulin, acts to increase H and hence their contribution to H is taken with a positive sign convention. While those hormones which increase BGC for example, cortisol, contribute negatively to H.

2) Since, the variables G and H change with time, we consider G and H as dependent variables while t (time) as the independent variable.

3) From the elementary concentration of the biological facts, stated above, the logistic law governing the performance of BGRS may be written as

$$\frac{dG}{dt} = F_1\,(G,H) + E(t) \qquad (1.1)$$

$$\frac{dH}{dt} = F_2\,(G,H) \qquad (1.2)$$

Where f_1 and f_2 are the same functions of G and H, while E (t) is the external rate at which the BGC is being increased.

Step II (Construction of the Model)

Here, we will formulate a second order differential equation model to describe the performance of BGRS during a GTT.

Let G_o and H_o be the optimal values of G and H respectively. Since we are interested in studying the deviations of G and H from their optimal values, we therefore set,

$G= G-G_o$ and $h=H-H_o$

On substituting these values of G and H in equations (1) and (2), and using Taylor's Expansion, we get:

$$\frac{dg}{dt} = \left[F_2(G_o, H_o) + g\left(\frac{\partial F_1}{\partial G}\right)_o + h\left(\frac{\partial F1}{\partial G}\right)_o + C_1\right] + E(t) \quad (1.3)$$

$$\frac{dh}{dt} = \left[F_2(G_o, H_o) + g\left(\frac{\partial F_2}{\partial G}\right)_o + h\left(\frac{\partial F2}{\partial G}\right)_o + C_2\right] \quad (1.4)$$

Where $\left(\frac{\partial F_1}{\partial F_2}\right)_o$ denotes $\left(\frac{\partial F1}{\partial G}\right)$ $G=G_o$ and $H=H_o$ etc. and C_1 and C_2 contains terms of second and higher powers in g and h. At this stage, we note that:

1. F_1 (G_o, H_o) =0, F_2 (G_o, H_o) =0, because it is assumed that G and H have assumed their optimal values G_o and H_o respectively by the time the fasting patient arrives at the hospital.
2. F_1 and F_2, being small quantities, may be neglected; for the case of mild diabetes, g and h are small.

With these conditions, equation (4) and (5) yields

$$\frac{dg}{dt} = \left[g\left(\frac{\partial F_1}{\partial G_1}\right)_o + h\left(\frac{\partial F_1}{\partial H}\right)_o\right] + E(t) \quad (1.5)$$

$$\frac{dh}{dt} = [g\left(\frac{\partial F_2}{\partial G}\right)_o + h\left(\frac{\partial F_2}{\partial H}\right)_o \quad (1.6)$$

There are a priori no methods to find the values of the numbers $\left(\frac{\partial F_1}{\partial G}\right)_o, \left(\frac{\partial F_1}{\partial H}\right)_o, \left(\frac{\partial F_2}{\partial G}\right)_o, and\ \left(\frac{\partial F_2}{\partial H}\right)_o$ but it is possible to; ascertain their signs in the following way:

a. Sign of $\left(\frac{\partial F_1}{\partial G}\right)_o$

For this purpose, we consider g > 0, h=0 (excessive glucose). It follows from the figure that the BGC will be decreasing on account of the tissue uptake of glucose and the storing of excess glucose in the liver in the form of glycogen, that is $\frac{dg}{dt} < 0$. In turn, equation (6) implies that $\left(\frac{\partial F_1}{\partial H}\right)_o$ must be negative.

b. Sign of $\left(\frac{\partial F_1}{\partial H}\right)_o$

For this purpose, we consider h>0, g=0 (excessive insulin). In this case, $\frac{dh}{dt} < 0$ because excessive insulin will decrease BGC by facilitating tissue uptake of glucose and by increasing the rate of which glucose is converted to glycogen. In turn, equation (6) implies that $\left(\frac{\partial F1}{\partial H}\right)_o$ must be negative.

c. Sign of $\left(\frac{\partial F_2}{\partial H}\right)_o$

Here, we consider h > 0, g=0 (excessive insulin). In this case, the hormone concentration decreases due to hormone metabolism. In turn, equation (7) implies that $\left(\frac{\partial F2}{\partial H}\right)_o$ must be negative.

With the consideration of signs above, we re-write equations (6) and (7) as

$$\frac{dg}{dt} = -a_1 g - a_2 h + E(t) \quad (1.7)$$

$$\frac{dh}{dt} = a_3 g - a_4 h \quad (1.8)$$

where a1, a2, a3, and a4 are all positive constants with obvious meanings.

Since it is the BGS that can be measured easily therefore we attempt to eliminate H if possible, between equations (8) and (9). For this purpose, we proceed as follows.

Differentiation of equation (8) with respect to time gives,

$$\frac{d^2g}{dt^2} = -a_1\frac{dg}{dt} - a_2\frac{dh}{dt} + \frac{dE}{dt} \quad (1.9)$$

Substituting the values of $\frac{dh}{dt}$ from equation (9), we get

$$\frac{d^2g}{dt^2} = -a_1\frac{dg}{dt} - a_2a_3g + a_2a_4h + \frac{dE}{dt} \quad (1.10)$$

Finally, substituting the value of a2h from equation (8) in equation (11) and rearranging, we get

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + {w_o}^2g = M(t) \quad (1.11)$$

Where $2\alpha = (a_1+a_4)$, ${w_o}^2 = (a_1a_4+a_2a_4)$, $M(t) = a_4E(t) + \frac{dE}{dt}$

Equation (12) is a second order D.E. with constant coefficient which governs the BGRS after a heavy load of glucose is ingested.

We note that M (t) is identically zero except for a very short interval in which the glucose load is being ingested and therefore it can be very effectively dealt by introducing Dirac-Delta function. However, for the present we are interested in studying the basic system and therefore if t=0 is defined to be the instant when the glucose load is completely ingested, equation (12) becomes:

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + {w_o}^2g = 0 \quad (1.12)$$

Equation (13) may be identified as the standard equation governing damped free vibrations.

1.3 Analysis of the model.

As in earlier cases, we analyze this model in two steps.

Step 1 (Mathematical Solution)

The auxiliary equation of (13) is:

$m^2 + 2\alpha m + {w_o}^2 = 0$; Whose roots are given by $m = \alpha \pm \sqrt{\alpha^2 - {w_o}^2}$

There are three cases according to $\alpha^2 - wo^2 \gtrless 0$. Referring to the discussion of the LCR model, Case III, we know that every solution g (t) of equation (13) approaches to 0 as $t \to \infty$ and thus our model confirms to reality in predicting that the BGC tends to return ultimately to its optimal concentration. It therefore, passes the test of consistency.

In particular, we consider here the case $\alpha^2 - wo^2 < 0$; the other two cases can be similarly discussed. For $\alpha^2 - wo^2 < 0$, we have;

$$g(t) = Ae^{-\infty t}\cos(Wt - \delta) \quad (1.13)$$

Where $w^2 = {w_o}^2 - \alpha^2$. Rewriting equation (14) in terms of original variable, we have;

$$G(t) = G_o + Ae^{-\alpha t}\cos(wt - \delta) \quad (1.14)$$

Equation (15) contains 5 unknowns (including two constants of integration) vis. G_o, α, w_o, A and δ; the last two being constant of integration. These unknowns can be determined as: G_o, being the BGC before the glucose load is ingested, is determined by measuring the patients' blood glucose concentration immediately upon his arrival at the hospital. The remaining 4 unknowns vis, α, w_o, A and δ can be determined from the four equations.

$$G_j = G_o + Ae^{-\alpha t}\cos(wt_j - \delta), j = 1,2,3,4 \quad (1.15)$$

By taking four additional measurements G_1, G_2, G_3 and G_4 of the patients BGC at time t_1, t_2, t_3 and t_4 respectively. Alternatively, we can determine the five unknowns by the following more effective procedure.

Take n measurements G_1, G_2,…,G_2 of the patients BGC at time t_1,t_2,…t_n respectively (In actual practice, we take n=7 or 8). Next, we find optimal values of Go, α, w_o, A and δ such that the least square error given by:

$$e = \sum_{j=1}^{n} G_j - G_o - Ae^{-\alpha t}\cos\left(Wt_j - \delta\right)^2 \qquad (1.16)$$

is minimized. The problem of minimizing e can be easily solved on a digital computer. Ackerman et al. [1]* has provided a complete Fortran Program for determining optimal values for G_o, α , w_o, A and δ. Obviously, the second method offers a better fit to the data on the entire time interval sine it involves more measurements.

Step II Interpretation of Results

1. From equation (13), we find that there are two system parameters viz α and w_o; out of these we have to select the one which is a more suitable and dependable descriptor of the response of BGRS to a GTT. Based on a number of experiments, Ackerman et al [1] concluded that a slight error in the measurement of G causes a very significant error in the value of α while the parameter wo was relatively insensitive to the error in G. Thus wo may be rearranged as a more faithful parameter for developing criteria for the diagnosis of diabetes.
   Since wo is the natural frequency of the system therefore we define the corresponding period by $To = \frac{2\pi}{w_o}$. Due to the convenience To be considered as a suitable parameter to provide a criterion for the diagnosis of diabetes.
2. From a wide range of data, collected from different sources, it is contended that "a value of less than 4 hours for To indicated normalcy while appreciably more than 4 hours implied mild diabetes." This may be considered as an analytical basis to interpret the result of a GTT.
3. Since the usual period between meals is about 4 hours, therefore the above criteria suggest the interesting possibility that the sociological factors may also play a role in the BGRS.

II. Analysis of the First Slow Ultradian Oscillation Model

Introduction

The intention of this chapter is to mathematically derive the equations to the simplified system of equations model and come to a greater understanding of the methodology and significance of both models. Much research has been done on the most appropriate way to treat and model the feedback system of glucose and insulin and the body. The mathematics below display something called a "feedback loop" in which the stimulation of one system (i.e. eating, insulin infusion etc.) directly results in the stimulation of all the other systems, thus yielding the system equations as seen below. What was found was that the best way to treat the system in cases of hormonal dysfunction (Type 1 Diabetes) is via oscillatory methods of insulin injection as opposed to a constant rate of infusion or chaotic and sporadically high dose injections. The reason we came to this conclusion is the way the mathematics of the feedback systems work, and how the relationship between glucose and insulin has a slight time delay, with oscillations in the concentrations of both within the blood stream. Although the exact biological origin of the mechanisms which affect the ultradian oscillations of insulin secretion is unknown, we believe it to be from either activity of an intrapancreatic pacemaker, or the instability in the insulin-glucose feedback system. In this chapter, you will see the simplification of several models presented within the main text analyzed.[1]

Note: All of the original equations modeling the original insulin-glucose feedback system developed by Sturis et al. and its subsequent parameters are outlined in Appendix A:

The derivations of the original functions (equations 1-12) above are shown below and how it relates to the simplified model below (13-17):

$$\frac{dI_p}{dt} = aI_p + bI_i + cG + d \qquad (2.13)$$

The coefficients a and b are simply attained by expanding equation 1 and collecting like terms.

$$\frac{dI_p}{dt} = f_1(G) - E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_p}{t_p} \quad (2.13.1)$$

$$= f_1(G) - \left(-\frac{E}{V_p} - \frac{1}{t_p}\right) I_p + \left(\frac{E}{V_i}\right) I_i =$$

$$\text{Where } a = \left(-\frac{E}{V_p} - \frac{1}{t_p}\right) I_p \;\; b = \left(\frac{E}{V_i}\right) \quad (2.13.2)$$

The coefficients c and d are attained by a Taylor polynomial expansion of equation 7. In order to simplify the derivatives that are the components of the coefficients for the simplified model, we will assume that $\gamma = \frac{C_1 - \frac{G}{V_g}}{a_1}$. The coefficient d is identical to f_1 (G) while c is the first order expansion of f_1(G). The derivation of equation 7 and how it relates to c and d are outlined below:

$$f_1(G) = \frac{R_m}{1 + e^{\left((C_1 - \frac{G}{V_g})/a_1\right)}} \quad (2.7)$$

$$f_1(G) = \frac{R_m}{1 + e^{\gamma}} = d \quad (2.13.3)$$

$$f_1'(G) = c = \frac{\left[0 * (1 + e^{\gamma}) - \left((R_m) * \left(0 + -\frac{1}{V_g a_1} * e^{\gamma}\right)\right)\right]}{[1 + e^{\gamma}]^2}$$

$$c = \frac{\frac{R_m}{V_g a_1} * e^{\gamma}}{[1 + e^{\gamma}]^2} \quad (2.13.4)$$

The coefficients e and f are again simply attained by expanding equation 2 and collecting like terms.

$$\frac{dI_i}{dt} = eI_p + fI_i \quad (2.14)$$

$$\frac{dI_i}{d_t} = E\left(\frac{I_p}{V_p} - \frac{I_p}{V_i}\right) - \frac{I_i}{t_i} \quad (2.14.1)$$

$$= -E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_i}{t_i} = \left(-\frac{E}{V_i} - \frac{1}{t_i}\right) I_i + \left(\frac{E}{V_p}\right) I_p$$

$$f = \left(-\frac{E}{V_p} - \frac{1}{t_p}\right) I_p \;\; e = \left(\frac{E}{V_i}\right) \quad (2.14.2)$$

The coefficient's g and h are derived the first order Taylor polynomial expansions of f_3*f_4, k, l, and n are derived from the first, second and third order Taylor polynomial expansions of f_5 respectively. While the coefficients a and p come from the combination of constants from the Taylor expansions of the of f_2 and the parameter G_{in}. The simplified equation above is attained from the equations 8-11 and the respective relationship of those equations is outlined below:

$$\frac{dG}{dt} = gI_iG + hG + kx_3 + lx_3^2 + nx_3^3 + p \quad (2.15)$$

$$\frac{dG}{dt} = G_{in} - f_2(G) - f_3(G) * f_4(I_i) + f_5(x_3) \quad (2.3)$$

$$g, h = f_4(I_i) \approx f_4(\hat{x}) + f_4'(\hat{x})(I_i - \hat{x})$$

$$f_3'(G) = \frac{G}{C_3V_g} * [f_4(\hat{x}) + f_4'(\hat{x})(I_i - \hat{x})] \quad (2.15.1)$$

$$\left(\frac{G}{C_3V_g} * f_4(\hat{x})\right) + \left(\frac{G}{C_3V_g} * f_4'(\hat{x}) * I_i\right) + \left(\frac{G}{C_3V_g} * f_4'(\hat{x}) * (\hat{x})\right)$$

$$g = f_3'(G) = \frac{GI_i}{C_3V_g} * \frac{(U_m - U_o) * (\beta c(\hat{x})^{-\beta-1}}{(1 + (c\hat{x})^{-\beta})^2}$$

$$g = \frac{(U_m - U_o) * (\beta c(\hat{x})^{-\beta-1}}{(C_3V_g)(1+(c\hat{x})^{-\beta})^2} * GI_i \quad (2.15.2)$$

$$h = \frac{G}{C_3V_g}\left[\left[\frac{U_m - U_o}{(1 + e^{\left(-\beta Ln\left(\frac{I_i}{C_4} * \left(\left(\frac{1}{V_1} + \frac{1}{Et_i}\right)\right)\right)\right)}}\right] - \left[\frac{(U_m - U_o) * (\beta c(C\hat{x})^{(-\beta-1)}}{((1 + (C\hat{x})^{(-\beta)})^2}\right] * \hat{x}\right]$$

$$h = \left[\left[\frac{U_m - U_o}{(1+e^{\left(-\beta Ln\left(\frac{I_i}{C_4} * \left(\left(\frac{1}{V_1} + \frac{1}{Et_i}\right)\right)\right)\right)}(C_3V_g)}\right] - \left[\frac{(U_m - U_o) * (\beta c(C\hat{x})^{(-\beta-1)}}{((1+(C\hat{x})^{(-\beta)})^2 (C_3V_g)}\right] * \hat{x}\right] * G \quad (2.15.3)$$

In order to simplify the derivatives that are the components of the coefficients for the simplified model, we will assume that $\Delta = \frac{\propto}{V_p - C_5}$

$$f_5(x_3) = \frac{R_g}{1+e^{\alpha\left(\frac{x_3}{V_p} - C_5\right)}} \quad (2.11)$$

$$k = f_5'(x_3) = \frac{[0 * (1+e^{\Delta x_3}) - (R_g) * (0 + \Delta e^{\Delta x_3})]}{(1+e^{\Delta x_3})^2}$$

$$k = f_5'(x_3) = \frac{-R_g \Delta e^{\Delta x_3}}{(1+e^{\Delta x_3})^2} \quad (2.15.4)$$

$$l = f_5''(x_3) = \frac{(1 + e^{\Delta x_3})^2 * \left(-R_g \Delta e^{\Delta x_3} \Delta\right) - \left(-R_g \Delta e^{\Delta x_3}\right) 2(1 + e^{\Delta x_3}) e^{\Delta x_3} \Delta}{(1 + e^{\Delta x_3})^4}$$

$$l = f_5''(x_3) = \frac{-\Delta^2 e^{\Delta x_3} R_g (1+e^{\Delta x_3})}{(1+e^{\Delta x_3})^3} \quad (2.15.5)$$

$$\text{n} = f_5'''(x_3) = -\Delta^2 R_g \left[\frac{(1 + e^{\Delta x_3})(\Delta e^{\Delta x_3} - 2\Delta e^{2\Delta x_3}) - (e^{\Delta x_3} - e^{2\Delta x_3}) 3(1 + e^{\Delta x_3})^2 e^{\Delta x_3} \Delta}{(1 + e^{\Delta x_3})^4}\right]$$

$$\text{n} = f_5'''(x_3) = -\Delta^3 R_g \left[\frac{(1 + e^{\Delta x_3})(e^{\Delta x_3} - 2e^{2\Delta x_3}) - 3e^{\Delta x_3}(e^{\Delta x_3} - e^{2\Delta x_3})}{(1 + e^{\Delta x_3})^4}\right]$$

$$n = f_5'''(x_3) = -\Delta^3 R_g \left[\frac{e^{\Delta x_3} - 4e^{2\Delta x_3} + e^{3\Delta x_3}}{(1+e^{\Delta x_3})^4}\right] \quad (2.15.6)$$

$$p = G_{in} - f_2(G) \quad (2.15.7)$$

For the equations 16-18, the coefficient r is attainted by simple algebra whereby the coefficient of the original model equations is directly translated to the simplified model. The derivation of which is seen below:

$$\frac{dx_1}{dt} = \frac{3}{t_d}(I_p - x_1); \ (2.4) \qquad \frac{dx_2}{dt} = \frac{3}{t_d}(x_1 - x_2); \ (2.5) \qquad \frac{dx_3}{dt} = \frac{3}{t_d}(x_2 - x_3); \ (2.6)$$

$$\frac{dx_1}{dt} = (rI_p - rx_1); \qquad \frac{dx_2}{dt} = (rx_1 - rx_2); \qquad \frac{dx_3}{dt} = (rx_2 - rx_3)$$

$$r = \frac{3}{t_d} \ (2(4, 5, 6).1)$$

III. Analysis of the Second Slow Ultradian Oscillation Model

Introduction

The purpose of further manipulating the first simplified oscillatory model is to come to greater conclusions and understanding of specific attributes of the model with specific regards to the relevant range of the stated variables. What was done to the simplified system of equations was to linearize the functions using Taylor polynomial expansions on the original system of equations. This applied to all of the simplified model equations except for equation 21, which needed to be expressed in the form of 21-29 because equation 15 contained terms that were not linear. What was discovered by this system of equations was that the hepatic glucose production is the main contributing factor in the mean rate of plasma glucose. Further, it was determined by the derivations and graphical representation of the system of equations that there exits an upper bound and lower bound to the hepatic glucose production which is directly dependent upon the mean rate of insulin infusion. When the infusion is low, the hepatic glucose production reaches a "saturation" state in which the "oscillatory component of the insulin infusion acts to reduce the average plasma glucose concentration." Conversely, when the insulin infusion is high, the hepatic glucose production is "near total suppression." Mathematically speaking, this means that whether or not equation 15's second derivative has a positive or negative sign dictates whether or not the mean plasma glucose concentration increases or decreases.

Equation 19 represents the exogenous insulin infusion, whereby this equation is directly attained from equation 13. As you can see from comparing the two equations, the variables attached to the coefficient of 'a' and 'b' are directly translated from equation 13 to equation 19. However, in equation 19, the parts of the equation factored with 'm' are attained via a derivation of equation 7. This derivation is outlined below:

$$m\left(1 + Asin\left(\frac{2\pi t}{T}\right)\right) \approx \frac{R_m}{1+e^{\left((C_1 - \frac{G}{V_g})/a_1\right)}} \quad (3.1)$$

$$y_j = Y_j + A_j \sin\left(\left(\frac{2\pi t}{T}\right) + \phi_j\right), \quad j = 1,2,3,4,5 \quad (3.2)$$

In order to come to a greater understanding of equation 21 we have utilized the equations 21-25. The calculations below reflect the relationship between these equations. First we solved for G(t) in relation to equation 22 and 23 respectively.

$$\frac{dG(t)}{dt} + P(t)G(t) = Q(t) \quad (3.3)$$

$$P(t) = -gI_i(t) - h \quad (3.4)$$

$$Q(t) = kx_3(t) + lx_3^2(t) + nx_3^3(t) + p \quad (3.5)$$

$$P(t)G(t) = Q(t) - \frac{dG(t)}{dt}$$

$$G(t) = \frac{Q(t)}{P(t)} - \frac{dG(t)}{dt}\frac{1}{P(t)} \quad (3.3.1)$$

$$G(t) = \frac{kx_3(t)+lx_3^2(t)+nx_3^3(t)+p}{-gI_i(t)-h} - \frac{dG(t)}{dt}\frac{1}{-gI_i(t)-h} \quad (3.3.2)$$

Next, we went on to solve for the analytical solution to equation 24.

$$G(t) = \frac{1}{\mu(t)}(\mu(t_o)G_0 + \int_{t_0}^{t} \mu(\xi)Q(\xi)d\xi \quad (3.6)$$

$$G(t)\mu(t) = \int_{t_o}^{t} Q(\xi)\mu(\xi)d\xi + C \quad (3.6.1)$$

$$G(t)\mu(t) = \int_{t_o}^{t} Q(\xi)\mu(\xi)d\xi + G_0\mu_{to} \quad (3.6.2)$$

Knowing the information above, we went on to solve the analytical solution for equation 25 utilizing equations 26 and 27. This was the most critical evolution of the simplified model because it is in direct relationship to equation 21 as it's more general solution.

$$\mu(t) = e^{H\left(\cos\left(\frac{2\pi t}{T}+\phi_i\right)-\cos(\phi_i)\right)}e^{-Jt} \quad (3.7)$$

$$J = g\langle I_i\rangle + h \quad (3.8)$$

$$H = \frac{gA_iT}{2\pi} \quad (3.9)$$

$$Integration\ Factor\ (I.F.) = e^{\int_{t_o}^{t} p(\xi)d\xi + C}$$

$$e^{\int_{t_o}^{t}(-gI_i(\xi)-h)d\xi} = e^{H\left(\cos\left(\frac{2\pi t}{T}+\phi_i\right)-\cos(\phi_i)\right)}e^{-Jt} \quad (3.4.1)$$

$e^{\int_{t_o}^{t}(-gI_i(t)-h)dt} = e^{\int_{t_o}^{t} -g\left(\left(Y_i+A_i sin\left(\frac{2\pi t}{T}+\phi_i\right)\right)-h\right)dt}$ When in equation 20, y_j, j = 2 = I_i

$$= e^{-gY_i\int_{t_o}^{t}dt} + gA_i\int_{t_o}^{t} sin\left(\frac{2\pi t}{T}+\phi_i\right)dt - \int_{t_o}^{t} hdt \quad (3.4.2)$$

$$= e^{-gY_i(t-t_o)} - gA_i\left[\frac{-cos\left(\frac{2\pi t}{T}+\phi_i\right)}{\frac{2\pi}{T}}\right]_{t_o}^{t} - h(t-t_o) \quad (3.4.3)$$

$$= e^{-gY_i(t-t_o)} + gA_i\frac{T}{2\pi}\left[cos\left(\frac{2\pi t}{T}+\phi_i\right) - cos\left(\frac{2\pi t_o}{T}+\phi_i\right)\right] - h(t-t_o)$$

$$= e^{-gY_i(t-t_o)} + H\left[cos\left(\frac{2\pi t}{T}+\phi_i\right) - cos(\phi_i)\right] - h(t-t_o) \quad (3.4.4)$$

$$= e^{-gY_i(t-t_o)} + H\left[cos\left(\frac{2\pi t}{T} + \phi_i\right) - cos(\phi_i)\right] - (h + g\langle I_i\rangle)(t) + g\langle I_i\rangle(t) + h(t_o)$$

$$= e^{H\left[\cos\left(\frac{2\pi t}{T}+\phi_i\right)-\cos(\phi_i)\right]-Jt} * e^{g\langle I_i\rangle t+h(t_o)-gY_i(t-t_o)} \quad (3.4.5)$$

$$\mu(t) \approx (1 + H\left(\cos\left(\frac{2\pi t}{T} + \phi_i\right) - \cos(\phi_i)\right)e^{-Jt} \quad (3.10)$$

$$G(t) = C_0 + C_1\cos\left(\frac{2\pi t}{T}\right) + C_2\sin\left(\frac{2\pi t}{T}\right) + C_3\cos\left(\frac{2\pi t}{T}\right) + C_4\sin\left(\frac{2\pi t}{T}\right) + C_5\cos\left(\frac{2\pi t}{T}\right) + C_6\sin\left(\frac{2\pi t}{T}\right) + C_7\cos(\frac{2\pi t}{T}) + C_8\sin(\frac{2\pi t}{T})) \quad (3.11)$$

$$\text{Set } \tau = \left[H\left(\cos\left(\frac{2\pi t}{T} + \phi_i\right) - \cos(\phi_i)\right)\right]$$

$$G(t) = \left\{\frac{1}{1 + H\tau e^{-Jt}}\right\} * \{1 + [\tau]e^{-Jt}\}G_o + \int_{t_o}^{t}\{1 + \tau e^{-Jt}\}Q(\xi)d\xi$$

$$C_o = \frac{[1 + \tau]G_o}{[1 + \tau]} + \left\{\frac{1}{1 + H\tau e^{-Jt}}\right\}\left\{t + H\frac{sin\left(\frac{2\pi\varepsilon}{T} + \phi_i\right)}{\frac{2\pi}{T}} - \frac{1}{tcos(\phi_i)}\right\}Q(\xi)d\xi$$

$$C_o = -\frac{2K_0+K_2}{2J} + \varepsilon \quad (3.12)$$

$$K_0 = k\langle x_3\rangle + l\langle x_3\rangle^2 + n\langle x_3\rangle^3 + p \quad (3.13)$$

$$K_2 = A_3^2(l + 3n\langle x_3\rangle) \quad (3.14)$$

$$\frac{\langle G\rangle - G_{SS}}{G_{SS}} = \frac{K_2}{2K_0} - \frac{\varepsilon J}{K_0} \quad (3.15)$$

$$C_oJ = \frac{K_2}{2} - \frac{2\varepsilon J}{2} - \frac{2k_o}{2} \quad (3.12.1)$$

$$\frac{\langle G\rangle + \frac{k_o}{J}}{G_{SS} - \frac{k_o}{J}} = \frac{k_2 - 2\varepsilon J}{2k_o} \quad (3.12.2)$$

$$C_o \approx \frac{-k_o}{J} + \frac{K_2}{2J} + \varepsilon \quad (3.12.3)$$

$$\left.\frac{\partial^2 f_5(x_3)}{\partial x_3^2}\right|_{\langle x_3\rangle} < 0 \quad (3.16)$$

$$\langle x_3\rangle < -\frac{l}{3n} = 70.9 \text{ mU} \quad (3.17)$$

$$m < 13.5 \text{ mU min}^{-1} \quad (3.18)$$

$$\langle x_3\rangle < V_pC_5 = 78.0 \text{ mU} \quad (3.19)$$

IV. Analysis of Pulsatile Delivery of Insulin and the Effect of Frequency

As related in the previous glucose-feedback systems models, the exogenous insulin infusion was done via ultradian oscillations which left a fluctuation, yet continuous supply of insulin to the patient. This model is different in that the infusion of insulin is being done rhythmically with intervals of time in which no insulin is being exogenously infused. The period of time in-between pulsatile infusions was made to be 15 minutes with the amount infused at each pulse remaining constant throughout the experiment.

$$I_{pulse}(\xi) = \frac{I_{constant}}{\xi} \tag{4.1}$$

$$(1-\xi)f_r(I_{basal}) + \xi f_r\left(I_{pulse}(\xi)\right) = f_r(I_{constant}) \tag{4.2}$$

$$(1-\xi)f_5(I_{basal}) + \xi f_5\left(I_{pulse}(\xi)\right) < f_5(I_{constant}) \tag{4.3}$$

V. Conclusion

The aim of this project was to analyze the work of several prominent mathematicians in this area of study, and explore the mathematics behind their systems of equations, models and relationships thereof. As an undergraduate student, much of these topics and derivations of models would be far too complicated and laborious for a student of my caliber to decipher by themselves and in a reasonable amount of time. Therefore, the work seen up to this point was the simplification and derivation of the models to create a succinct and logical progression and relationship between them. What was required to complete this work utilized everything from Taylor polynomial expansions, highly complex multi-derivative and integral transformations, Mat lab solvers and the amalgamation of multiple systems of equations to create systems that were intrinsically connected and revealed information about the nature of the glucose and insulin feedback systems in the body. All of which was done so with the intent of helping make a less advanced mathematics student be able to come to the realization of many of the key attributes of higher level doctoral mathematics. While this project was not intended to discover new unfounded connections between the glucose insulin feedback systems, it did provide much clarity that we believe can be beneficial to many mathematicians.

The critical relationship between the glucose and insulin concentrations within the human body is the main determinant whether or not an individual suffers from type I or type II diabetes. The use of advanced differential equations was required to come to an analytical solution to the glucose insulin feedback as it pertains to the human body's concentration of both glucose and insulin. This is because multitudes of variables, parameters and systems of equations within systems of equations required this method of approach. While the original system of equations above was the foundation of all three chapters, it was further expanded upon to determine how different parameters and concentrations of glucose or insulin would affect the models. While all three models were looking at different aspects of the glucose insulin feedback system, the most impressive feature of all three models is how glucose impacts insulin concentrations and vice versa within the body. All three models showed a bounded region of concentrations of glucose and insulin within the body, the stimuli of one system created the stimuli of another proportionally in both increasing and deceasing values, and the eventual homeostasis of both system with respect to time.

In the scientific field, mathematics has long been an integral part of analyzing bodily functions and reactions to determine cures for illnesses. Differential equations are often necessary to model reactions occurring in the body due to the complex nature of our systems, hormones and much more. Ordinary differential equations can easily be expanded to include the more contemporary time delayed differential equations as explored by more modern mathematicians. This special kind of differential equations models the same systems in the body but often times has a greater degree of accuracy because they can 'time' the equations to be expressed at different intervals within a given time span.

Appendix A and with Definitions of Parameters and Variables

Analysis of the First Slow Ultradian Oscillation Model

$$\frac{dI_p}{dt} = f_1(G) - E\left(\frac{I_p}{V_p} - \frac{I_p}{V_i}\right) - \frac{I_p}{t_p} \quad (2.1)$$

$$\frac{dI_i}{d_t} = E\left(\frac{I_p}{V_p} - \frac{I_p}{V_i}\right) - \frac{I_i}{t_i} \quad (2.2)$$

$\frac{dI_p}{dt}$: The amount of insulin in the plasma with respect to time.
$f_1(G)$: "The pancreatic insulin production controlled by the glucose concentration." This is directly responsive to an influx of insulin either exogenously or injected into the body.
-E: "A constant transfer rate for exchange of insulin between plasma and remote compartments"
I_p: "The amount of insulin in the plasma"
I_i: "The amount of insulin in the intracellular space"
v_p: "The distribution volume for insulin in the plasma"
v_i: "The effective volume of the intracellular space"
t_p: "The insulin in the plasma as a time constant" represented in

$$\frac{dG}{dt} = G_{in} - f_2(G) - f_3(G) * f_4(I_i) + f_5(x_3) \quad (2.3)$$

$\frac{dG}{dt}$: "The amount of glucose in the body with respect to time"
G_{in} : "The influx of glucose in the plasma and intracellular space at an exogenously controlled rate."
$f_2(G)$: "The insulin-glucose independent utilization (uptake by the brain and nerve cells)"
$f_3(G)$: "The glucose utilization by the muscle and fat cells"
$f_4(I_i)$: "The relationship between the plasma insulin concentration and the cellular glucose uptake"
$f_5(x_3)$: "The influence of insulin on the hepatic glucose production"

$$\frac{dx_1}{dt} = \frac{3}{t_d}(I_p - x_1) \quad (2.4)$$

$$\frac{dx_2}{dt} = \frac{3}{t_d}(x_1 - x_2) \quad (2.5)$$

$$\frac{dx_3}{dt} = \frac{3}{t_d}(x_2 - x_3) \quad (2.6)$$

$\frac{dx_1}{dt}$: "the inhibition of hepatic glucose production via the insulin stimulating pancreatic insulin production.
$\frac{dx_2}{dt}$: "Physiological action of insulin on the utilization of glucose in correlation with concentration of insulin in a slowly equilibrating intercellular compartment rather than with the concentration of insulin in the plasma."
$\frac{dx_3}{dt}$: "Time lag between the appearance of insulin in the plasma and its inhibitory effect on the hepatic glucose production.
t_d : "The response of the hepatic glucose production to changes in the plasma insulin concentration involves a time delay. This delay is assumed to be of third order.
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.

$$f_1(G) = \frac{R_m}{1 + e^{\left((C_1 - \frac{G}{V_g})/a_1\right)}} \quad (2.7)$$

R_m: "The rate of glucose metabolism within the cell"
C_1 : A given parametric value attained by experimental tests that pertains to the process within the function.
G: "Glucose"
V_g: "The Volume of Glucose"
a_1: A given parametric value attained by experimental tests that pertains to the process within the function.

$$f_2(G) = U_b(1 - e\text{^}(-G/(C_2 * V_g) \quad (2.8)$$

U_b, C_2: Are given parametric values attained by experimental tests that pertains to the process within the function.
V_g: "The Volume of Glucose."

$$f_3(G) = \frac{G}{C_3 * V_g} \quad (2.9)$$

C_3: A given parametric value attained by experimental tests that pertains to the process within the function.

$$f_4(I_i) = U_0 + \frac{U_m - U_0}{1 + e\text{^}\left(-\beta \ln\left(\frac{I_i}{C_4\left(\frac{1}{V_i} + \frac{1}{Et_i}\right)}\right)\right)} \quad (2.10)$$

$U_0, U_m, \beta, C_4, t_i, V_i$: Are all given parametric values attained by experimental tests that pertain to the process within the function.

$$f_5(x_3) = \frac{R_g}{1 + e^{\alpha\left(\frac{x_3}{V_p} - C_5\right)}} \quad (2.11)$$

R_g: A given parametric value which denotes rate of glucose
α: A given constant transfer rate
C_5: A given parametric value attained by experimental tests that pertains to the process within the function.

$$\frac{dI_p}{dt} = m\left(1 + Asin\left(\frac{2\pi t}{T}\right)\right) - E\left(\frac{I_p}{V_p} - \frac{I_p}{V_i}\right) - \frac{I_p}{t_p} \quad (2.12)$$

m: Represents the mean rate of the insulin infusion (21mU min^{-1}).
A: Represents the amplitude of the insulin infusion.
t: Represents time.
T: Represents the total period of time set at (120 minutes)

$$\frac{dI_p}{dt} = aI_p + bI_i + cG + d \quad (2.13)$$

a: Constant value attained via algebraic methods of equation 1.
b: Constant value attained via algebraic methods of equation 1.
c: Constant attained by taking the first derivative of equation 7.
d: Equivalent to equation 7.

$$\frac{dI_i}{dt} = eI_p + fI_i \quad (2.14)$$

e: Constant value attained via algebraic methods of equation 2.
f: Constant value attained via algebraic methods of equation 2.

$$\frac{dG}{dt} = gI_iG + hG + kx_3 + lx_3^2 + nx_3^3 + p \quad (2.15)$$

g: Attained by the product of a constant equation 9 and first degree Taylor polynomial expansion of equation 10.
h: Attained by the product of a constant equation 9 and first degree Taylor polynomial expansion of equation 10.
k: Attained by the first order Taylor polynomial expansion of equation 11.

l: Attained by the second order Taylor polynomial expansion of equation 11.
n: Attained by the third order Taylor polynomial expansion of equation 11.
p: The summation of the remaining constants via the Taylor polynomial expansions of the above equations.

$$\frac{dx_1}{dt} = rI_p - rx_1 \quad (2.16)$$

$$\frac{dx_2}{dt} = rx_1 - rx_2 \quad (2.17)$$

$$\frac{dx_3}{dt} = rx_2 - rx_3 \quad (2.18)$$

r: Attained via algebraic methods of equations 4,5 and 6 respectively.

Analysis of the Second Slow Ultradian Oscillation Model

$$\frac{dI_p}{dt} = m\left(1 + Asin\left(\frac{2\pi t}{T}\right)\right) + aI_p + bI_i \quad (3.1)$$

Note: Equation is the
m: Constant value equivalent to 21mUmin^{-1}
A: Equivalent to 0 when under a constant exogenous insulin infusion and set to 0.3 for oscillatory insulin infusion.
t: Time.
T: Periodization of time equivalent to 120 minutes.

$$y_j = Y_j + A_j \sin\left(\left(\frac{2\pi t}{T}\right) + \phi_j\right), \quad j = 1,2,3,4,5 \quad (3.2)$$

y_j: Equivalent to I_p, I_i , x_1, x_2, x_3 because the "time averages of the quantities are the same in the case of an oscillatory insulin infusion as in the case of a constant infusion.
Y_j: Does not depend on time, therefore the value depends on "a linear manner on the mean rate of insulin infusion and not the amplitude.
A_j: Does not depend on time, therefore the amplitude will be constant (slope=0)
Φ_j: Denotes the phase shifts of I_p, I_i, x_1, x_2, and x_3.

$$\frac{dG(t)}{dt} + P(t)G(t) = Q(t) \quad (3.3)$$

Note: Equation 24 is the general solution of equation 21. Equations 21-28 all have to do with the linearization of equation 15 above. This is because equation 15 is the only equation in the simplified model that has nonlinear terms.

$$P(t) = -gI_i(t) - h \quad (3.4)$$

g: Refer to 2.15.2 above for the coefficients expression.
I_i: Represents the Insulin in the intercellular space.
h: Refer to 2.15.3 above for the coefficients expression.

$$Q(t) = kx_3(t) + lx_3^2(t) + nx_3^3(t) + p \quad (3.5)$$

k: Refer to 2.15.4 above for the coefficients expression.
l: Refer to 2.15.5 above for the coefficients expression.
n: Refer to 2.15.6 above for the coefficients expression.
p: Refer to 2.15.7 above for the coefficients expression.

$$G(t) = \frac{1}{\mu(t)}(\mu(t_o)G_0 + \int_{t_0}^{t} \mu(\xi)Q(\xi)d\xi \quad (3.6)$$

$$\mu(t) = e^{H\left(\cos\left(\frac{2\pi t}{T}+\phi_i\right)-\cos(\phi_i)\right)}e^{-Jt} \quad (3.7)$$

$$J = g\langle I_i\rangle + h \quad (3.8)$$

$$H = \frac{gA_iT}{2\pi} \quad (3.9)$$

A_i: Represents the amplitude of the I_i
g: Refer to 2.15.2 above for the coefficients expression.
T: Periodization of time equivalent to 120 minutes.

$$\mu(t) \approx (1 + H\left(\cos\left(\frac{2\pi t}{T} + \phi_i\right) - \cos(\phi_i)\right)e^{-Jt} \quad (3.10)$$

H: Refer to equation 3.9 above.
ϕ_i: Denotes the phase shift of I_i.
J: Refer to equation 3.8 above.

$$G(t) = C_o + C_1\cos\left(\frac{2\pi t}{T}\right) + C_2\sin\left(\frac{2\pi t}{T}\right) + C_3\cos\left(\frac{2\pi t}{T}\right) + C_4\sin\left(\frac{2\pi t}{T}\right) + C_5\cos\left(\frac{2\pi t}{T}\right) + C_6\sin\left(\frac{2\pi t}{T}\right) + C_7\cos(\frac{2\pi t}{T}) + C_8\sin(\frac{2\pi t}{T})) \quad (3.11)$$

C_o: Equivalent to equation 3.12 below.
$C_{1\text{-}8}$: The expansion of the square and cube terms of equation $x_3(t)$ in equation 3.2 when substituted into equation 3.6

$$C_0 = -\frac{2K_0+K_2}{2J} + \varepsilon \quad (3.12)$$

K_o: Equivalent to equation 3.13 below.
K_2: Equivalent to equation 3.14 below.
J: Refer to equation 3.8 above.
ε: Represents a "small term which is a function of the amplitude and phase of the oscillations of $I_i(t)$ and $x_3(t)$.

$$K_0 = k\langle x_3\rangle + l\langle x_3\rangle^2 + n\langle x_3\rangle^3 + p \quad (3.13)$$

k: Refer to 2.15.4 above for the coefficients expression.
l: Refer to 2.15.5 above for the coefficients expression.
n: Refer to 2.15.6 above for the coefficients expression.
p: Refer to 2.15.7 above for the coefficients expression.
$\langle x_3\rangle$: Equals approximately 70.9mU for the simplified model and 78.0mU for the original model.

$$K_2 = A_3^2(l + 3n\langle x_3\rangle) \quad (3.14)$$

A_3: The amplitude of the oscillations of $x_3(t)$
l: Refer to 2.15.5 above for the coefficients expression.
n: Refer to 2.15.6 above for the coefficients expression.

$$\frac{\langle G\rangle - G_{ss}}{G_{ss}} = \frac{K_2}{2K_0} - \frac{\varepsilon J}{K_0} \quad (3.15)$$

$\langle G\rangle$: Represents the mean value of
G_{ss}: Represents the "steady state value of G(t)."
K_2: Component of mean value of G(t), which primarily derives from equation 3.2 and 3.5
K_0: Component of mean value of G(t), which primarily derives from equation 3.5
J: Refer to equation 3.8 above.
ε: Represents a "small term which is a function of the amplitude and phase of the oscillations of $I_i(t)$ and $x_3(t)$.

$$\frac{\partial^2 f_5(x_3)}{\partial x_3^2}\Big|_{\langle x_3\rangle} < 0 \quad (3.16)$$

Note:

$\partial^2 f_5(x_3)$: Represents the 2nd order partial derivative of equation 2.11 with respect to $\langle x_3 \rangle$
∂x_3^2: Represents the partial derivative of x_3^2 of equation 3.5 with respect to $\langle x_3 \rangle$

$$\langle x_3 \rangle < -\frac{l}{3n} = 70.9 \text{ mU} \quad (3.17)$$

$\langle x_3 \rangle$: Represented here as the simplified model value.

n: Refer to 2.15.6 above for the coefficients expression.

$$m < 13.5 \text{ mU min}^{-1} \quad (3.18)$$

m: Represents the "mean rate of insulin infusion."

$$\langle x_3 \rangle < V_p C_5 = 78.0 \text{ mU} \quad (3.19)$$

$\langle x_3 \rangle$: Represented here as the original model value.
V_p: Represents the volume of plasma
C_5: A given parametric value attained by experimental tests that pertains to the process within the function.

Analysis of the Pulsatile Infusion of Insulin

$$I_{pulse}(\xi) = \frac{I_{constant}}{\xi} \quad (4.1)$$

$$(1-\xi) f_r(I_{basal}) + \xi f_r\left(I_{pulse}(\xi)\right) = f_r(I_{constant}) \quad (4.2)$$

$$(1-\xi) f_5(I_{basal}) + \xi f_5\left(I_{pulse}(\xi)\right) < f_5(I_{constant}) \quad (4.3)$$

APPENDIX B

Table 1
Parameters of the original system of equations

Parameter	Value	Parameter	Value
V_p (1)	3	U_b (mg min^{-1})	72
V_i (1)	11	C_2 (mg l^{-1})	144
V_g (1)	10	C_3 (mg l^{-1})	1000
E (1 min^{-1})	0.2	U_o (mg min^{-1})	40
t_p (min)	6	U_m (mg min^{-1})	940
t_i (min)	100	α (1 mU^{-1})	0.29
t_d (min)	36	β	1.77
R_m (mU min^{-1})	210	C_4 (mU l^{-1})	80
a_1 (mg l^{-1})	300	C_5 (mU l^{-1})	26
C_1 (mg l^{-1})	2000	R_g (mU l^{-1})	180

Table 2
Parameters of the simplified model

Parameter	Value	Parameter	Value
a (min^{-1})	-0.233	h (min^{-1})	0.00264
b (min^{-1})	0.0182	k (mg mU^{-1} min^{-1})	17.5
c ((mU min) mg^{-1})	0.00479	l (mg mU^{-2} min^{-1})	-0.315
d (mU min^{-1})	-43.9	n (mg mU^{-3} min^{-1})	0.00148
e (min^{-1})	0.0667	p (mg min^{-1})	80.5
f (min^{-1})	-0.0282	r (min^{-1})	0.0833
g (mU^{-1} min^{-1})	-0.0000944		

APPENDIX C – MATLAB CODES AND GRAPHS

```
function SolverMain()
% Define Global parameters
global C1 C2 C3 C4 C5 Vg Vp Vi tp ti td E Rm Rg a1 Ub U0 Um alpha beta Gin

SetParameters;
fprintf('Loading parameters... \n');
%load('parameters.mat');

PlotFiGraphs = 0; % 0 for no; 1 for yes

if PlotFiGraphs
    Glucose = linspace(0,400,80);
    VgScaledGlucose = Glucose*Vg*10;
    InsulinI = linspace(0,1000,200);
    ViScaledInsulin = InsulinI*Vi/3;
    InsulinP = linspace(0,100,200);
    VpScaledInsulin = InsulinP*Vp;
```

```
    figure
     plot(Glucose,f1(VgScaledGlucose),'-o');
    figure
     plot(Glucose,f2(VgScaledGlucose),'-o');
    figure
     plot(Glucose,f3(VgScaledGlucose),'-o');
    figure
     plot(InsulinI,f4(ViScaledInsulin),'-o');
    figure
     plot(InsulinP,f5(VpScaledInsulin),'-o');
end

% Time Interval
tI = 0;
tF = 1000;

% Initial Conditions
ip_I = 21;
ii_I = 21;
g_I  = 216;
x1_I = 0;
x2_I = 0;
x3_I = 0;

options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);
[Time,Solution] = ode45(@ModelEqns,[tI tF],[ip_I ii_I g_I x1_I x2_I
x3_I],options);

% Name solutions for clarity
Ip = Solution(:,1);
Ii = Solution(:,2);
G  = Solution(:,3);
X1 = Solution(:,4);
X2 = Solution(:,5);
X3 = Solution(:,6);

figure
plot(Time,Ip,'-')
figure
plot(Time,Ii,'-')
figure
plot(Time,G,'-')
figure
plot(Time,X1,'-')
figure
plot(Time,X2,'-')
figure
plot(Time,X3,'-')

clear all;
end
```

```
function res = ModelEqns(t,SOL)
global Vp Vi tp ti td E Gin
```

```
Ip = SOL(1); % assign variables from SOL vector
Ii = SOL(2); %
G  = SOL(3); %
x1 = SOL(4); %
x2 = SOL(5); %
x3 = SOL(6); %

dIpdt = f1(G)-E*(Ip/Vp-Ii/Vi)-Ip/tp;
dIidt = E*(Ip/Vp-Ii/Vi) - Ii/ti;
dGdt  = Gin-f2(G)-f3(G)*f4(Ii)+f5(x3);
dx1dt = 3/td*(Ip-x1);
dx2dt = 3/td*(x1-x2);
dx3dt = 3/td*(x2-x3);

res = [dIpdt; dIidt; dGdt ; dx1dt ; dx2dt ; dx3dt]; % return solution vector
end
```

```
function SetParameters()
global C1 C2 C3 C4 C5 Vg Vp Vi tp ti td E Rm Rg a1 Ub U0 Um alpha beta Gin

close all;
clc;

%  Parameters    - UNITS
C1 = 2000;     % - mg/L
C2 = 144;      % - mg/L
C3 = 1000;     % - mg/L
C4 = 80;       % - mU/L
C5 = 26;       % - mU/L
Vg = 10;       % - L
Vp = 3;        % - L
Vi = 11;       % - L
tp = 6;        % - min
ti = 100;      % - min
td = 36;       % - min
E  = 0.2;      % - L/min
Rm = 210;      % - mU/min
Rg = 180;      % - mg/min
a1 = 300;      % - mg/L
Ub = 72;       % - mg/min
U0 = 40;       % - mg/min
Um = 940;      % - mg/min
alpha = 0.29; % - L/mU
beta  = 1.77; % -
Gin = 216;     % - mg/min

%save('parameters.mat');

End
```

```
function Output = f1(x)
    global C1 Vg Rm a1
    Output = Rm./(1+exp(-x./(a1*Vg)+C1/a1));
```

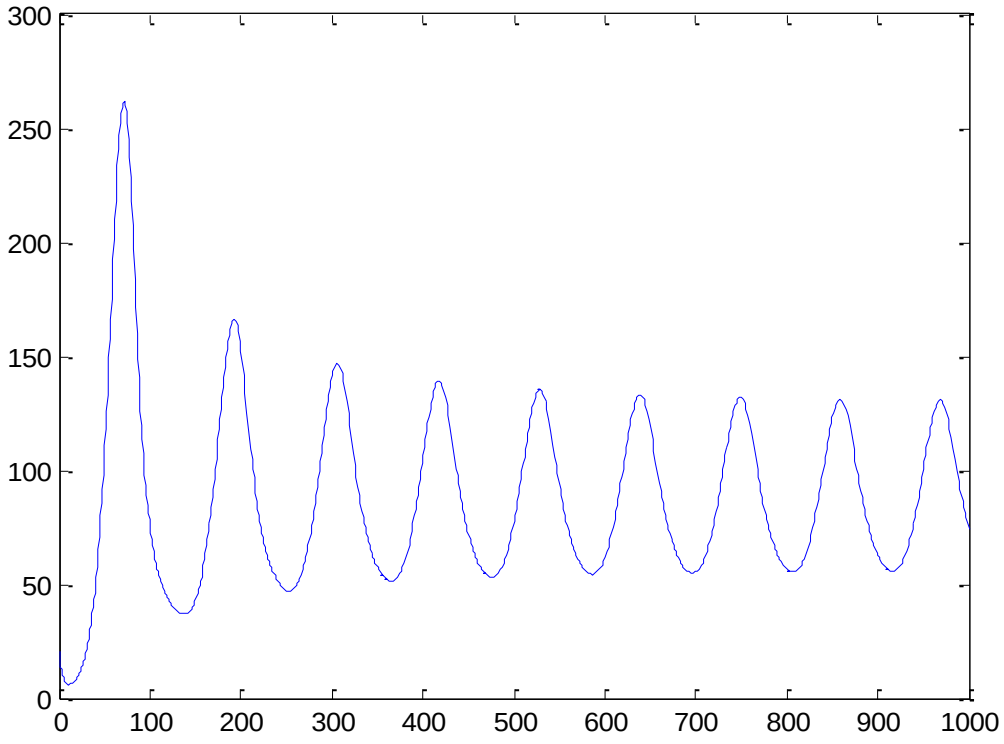
```
End
```

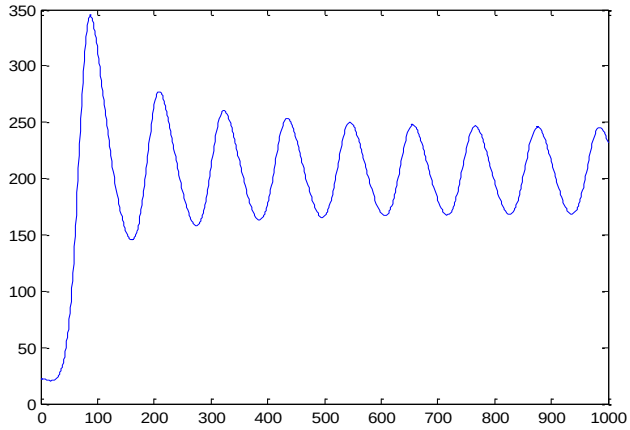
```
function Output = f2(x)
    global C2 Vg Ub
    Output = Ub.*(1-exp(-x./(C2*Vg)));
end
```

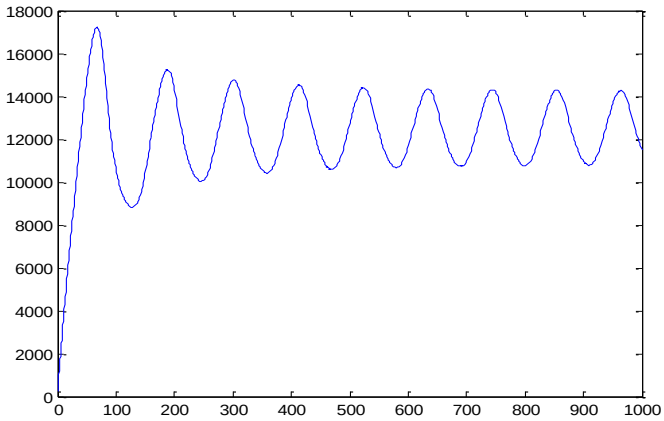
```
function Output = f3(x)
    global C3 Vg

    Output = x./(C3*Vg);
end
```

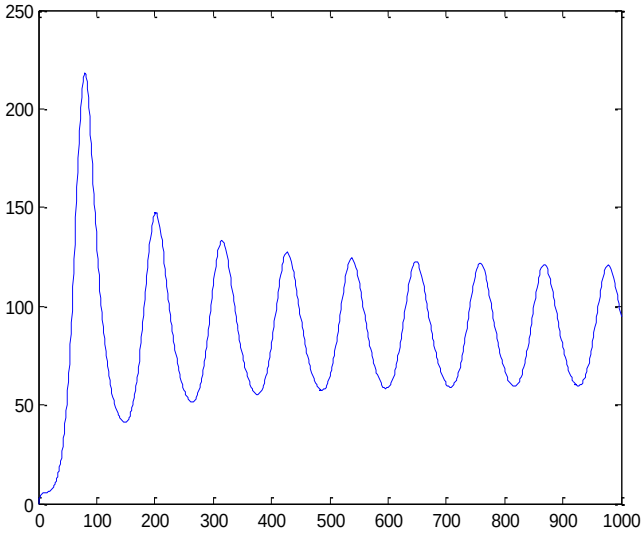
```
function Output = f4(y)
    global C4 Vi ti E U0 Um beta

    Output = U0+(Um-U0)./(1+exp(-beta*log(y.*(1/(C4*Vi)+1/(C4*E*ti)))));
end
```

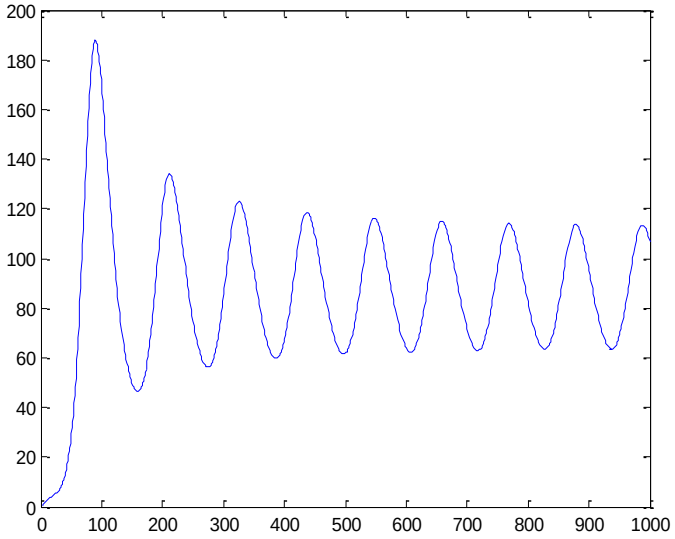
```
function Output = f5(x3)
    global C5 Vp Rg alpha

    Output = Rg./(1+exp(alpha*(x3./Vp-C5)));
end
```

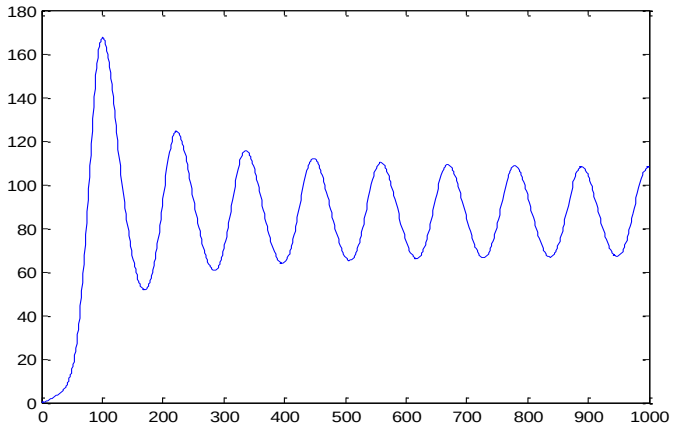












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