Mathematical Study of Glucose-Insulin Model with a reference to Diabetes Mellitus

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Abstract

The system for maintaining blood sugar concentration at the proper level is mathematically modeled for diabetes mellitus. Concentration of glucose (C_g) and concentration of Insulin (C_n) at steady state and varying state have been estimated. The rise and fall of blood sugar levels depend on specific mechanisms (use of mean flow concentration) using system of ordinary differential equations. The minimal model and dynamical models give the analytical approach of the glucose levels whereas the present model using embedded Runge-Kutta method measures the physiological values of G and I in terms of rate constants of growth and decay values using numerical approximations. Sixth order formulation is proposed to compute normal blood glucose levels at steady state and at varying state of concentration of glucose and insulin. The metabolism of protein, fat and carbohydrate is analysed for maintaining the newly computed calorie limits ranging from 1346 cal to 2190 cal for average body frames. Results obtained for the justification matche with Gatehood [1].

Keywords: diabetes, glucose, insulin, blood.

Introduction

Diabetes mellitus is a disease caused due to metabolic disorder. The loss of pancreatic insulin secretion develops and leads to impairment of the blood glucose levels and insulin levels. Also the metabolic disorder is an amalgamation of plasma cellular,intracellular and molecular defects centered on the presence of insulin resistance and β-cell failure. The disease development occur specifically within skeletal muscle and pancreatic β-cells. The dysfunction of β-cells leads to over nutrition (glucose overload)in turn, this leads to oxidative stress and mitochondrial abnormalities.These interact with each other to facilitate insulin signaling defects in the cell leading to insulin resistance. Such resistance increases the metabolic demand for insulin and consequently, the β-cell workload prolonged, elevated β-cell loads activate the unfolded protein response, which can promote or limit the amount of insulin secreted by β-cell as well as trigger apoptosis(arthritis)(joints pain). Therefore constitutive activation of the unfolded protein response can lead to a failure in β-cells to properly regulate glucose. In order to maintain the normal blood glucose level within the normoglycemic range (70-120 mg/dl). The major long term effects are caused by hyperglycemia where the plasma glucose concentration exceeds 120 mg/dl. The prolonged hyperglycemia can cause complications which may lead to kidney disease, blindness, loss of limb, diabetic retina, coronary artery disease and other complications related to increase of glucose in the blood stream. Of more immediate concern of hypoglycemia defined by plasma glucose concentration below 70 mg/dl. Such a condition can leads to dizziness, coma and other complications related to decrease in blood glucose from the normal lower level. Intensive insulin therapy involves three to four daily blood glucose measurements by finger pricking followed by subcutaneous injection. These correspond usually to meal times and bed time. Although the process is adequate to maintain the blood glucose level within an acceptable range. Wide fluctuations persuit throughout the day as a consequence of personal daily life activities (such as food intake and excercise) occurring between glucose measurements.

A general approach of Gatewood et al. [1] explains the effect of hormone glucose and insulin secreted by the pituitary and thyroxin produced by thyroid as simplest mathematical form. Kapur [3] presented a compartment model for diabetic mellitus taking the interaction of blood glucose with insulin at different time intervals. Katiyar et al. [8] discussed the regulation of blood glucose level in diabetes mellitus using palatable diet composition. Meena Verma et al. [10] presented the effect of increasing duration of diabetes mellitus type-II on glycated hemoglobin and insulin sensitivity. Daoyan Wel et al. [14] identified a splice variant of KLF4 that is up-regulated in aggressive pancreatic cancer cells and humanpancreatic tumor tissues and increased expression promotes growth of pancreatic tumors in mice and is associated with reduced survival times of patients.

Andrea De Gaetano et al. [17] discussed the Mathematical Modelling of the intravenous glucose tolerance test. Sojung Lee et al. [18] studied the relationship between insulin sensitivity and the biomarkers of endothelial dysfunction. Adrianne C Feldstein et al. [19] explained that the weight loss in diabetes improves glycemic control, reduces blood pressure. R S Falk et al. [20] investigated the relationship between glucose tolerance and cancer risk in a 40 year follow up study of initially healthy middle-aged men.

Several attempts at building a satisfactory model of the glucose-insulin system are recorded in the literature. Minimal method plays a role on the metabolism of glucose in the early eighties. In the study carried out by various researchers the glucose concentration and insulin concentration were considered at equilibrium of change in glucose and insulin with respect to time. The process of administering the concentration was a quite lengthy execution. But by introducing two forcing functions and mean flow as differential equations. We can close form solution for better understanding with reduced number of measurements.

In order to achieve the tighter glucose control there is a need to focus on the computations of mean flow concentration against the mean flow of glucose and insulin through glucose tolerance test under the various physiological conditions. We can notice from the present mathematical model the enhancement of accuracy in the conclusion of the blood glucose level at 70-120 mg/dl for the average body frame at PFC = [1346 cal to 2190 cal].

Formulation and Analysis:

The model assumes two forcing functions in glucose tolerance in the study with parametric analysis. The first forcing function as two differential equations describing the glucose concentration (C_g) and the plasma-glucose concentration (C_p) and the second forcing function as single differential equation as insulin concentration in the blood (C_h) as

$$\frac{dC_g}{dt} = -[m_1 + C_p]C_g + m_1 C_{g-b} \quad (1)$$

$$\frac{dC_p}{dt} = -m_2 C_p + m_3[C_h - C_{h-b}] \quad (2)$$

$$\frac{dC_h}{dt} = m_4[C_g - m_5]t - m_6[C_h - C_{h-b}] \quad (3)$$

$$C_g(0) = m_0\ ,\ C_p(0) = 0\ ,\ C_h(0) = m_7 + C_{h-b}$$

Defining

C_g =G, the blood glucose concentration at time (t)

C_p =P, the plasma glucose concentration

$C_h - I$, the blood insulin concentration

$C_{g-b} = \alpha -$ the subjects baseline glycemia

$C_{h-b} = \beta -$ the subjects baseline insulinemia

$m_0 -$ the theoretical glycemia at time t=0 after the instantaneous glucose bolus

m_1 - the glucose "mass action " rate constant (glucose effectiveness)

m_2 - the rate constant denotes the decrease of tissue glucose uptake ability.

$m_3 -$ the insulin dependent increase in tissue glucose uptake ability.

$m_4 -$ rate of pancrease release of insulin after the bolus per minute.

$m_5 -$ the pancreatic target glycemia.

$m_6 -$ the first order decay rate constant

$m_7 -$ the theoretical plasma insulin concentration at time t =0 above basal value.

Then the equations (1), (2) and (3) become

$$\frac{dG}{dt} = -[m_1 + p]G + m_1 \propto \quad (4)$$

$$\frac{dp}{dt} = -m_2\, p + m_3[I - \beta] \quad (5)$$

$$\frac{dI}{dt} = m_4[G - m_5]t - m_6[I - \beta] \quad (6)$$

with

$$C_g(0) = G(t = 0) = m_0 \quad (7)$$

$$C_p(0) = p(t = 0) = 0 \quad (8)$$

$$C_h(0) = I(t = 0) = m_7 + \beta \quad (9)$$

Equation (1) reflects that, the G is positive and exceeds the steady state value. This means that glucose appears in blood and is transported into the cells where it is metabolized. The term $m_1 \propto$ gives the input of glucose through absorption from the intestinal circulation subsequent to feeding. It could also represent direct intravenous infusion. The linearity of equations (1),(2) and(3) will be assumed so as to change from existing coupled form to the non coupled form. On the basis of specific mechanism, we consider in our model that the effectiveness of each hormone in stimulating a glucose response at steady state level as

$$I = \sum a_i I_i = H \quad (10)$$

Where H denotes the specific hormone to stimulate the uptake of glucose for the growth hormone and I_i- the concentration of specific hormone insulin infusion and a_i- the measure of effectiveness of each hormone which could be negative.

Equations (4),(5) and (6) will be taken for differentiation with respect to time t to change from coupled form to non coupled form. We have

$$\frac{d^2G}{dt^2} = -m_1 \frac{dG}{dt} - G\frac{dP}{dt} - P\frac{dG}{dt} = -[m_1 + P]\frac{dG}{dt} - G\frac{dP}{dt} \quad (11)$$

$$\frac{d^2P}{dt^2} = -m_2 \frac{dP}{dt} + m_3 \frac{dI}{dt} \quad (12)$$

$$\frac{d^2I}{dt^2} = m_4 + \frac{dG}{dt} - m_4 m_5 - m_6 \frac{dI}{dt} \quad (13)$$

Then, the conditions become

$$\left(\frac{dG}{dt}\right)_{t=0} = m_0 + m_1, \left(\frac{dp}{dt}\right)_{t=0} = m_0, \left(\frac{dI}{dt}\right)_{t=0} = m_0 + m_7 \quad (14)$$

Introducing (4), (5), and (6) in (11), (12) and (13) we obtain

$$\frac{d^2G}{dt^2} = -[(m_1 + p)^2 + m_2\, p - m_3(I - \beta)]G - (m_1 + p)(m_1\alpha) \quad (15)$$

$$\frac{d^2P}{dt^2} = -m_2{}^2(-P) - m_2\, m_3(I - \beta) + m_3[m_4(G - m_5) + m_6(I - \beta)] \quad (16)$$

$$\frac{d^2I}{dt^2} = m_4 - (m_1 + p)G + m_1\alpha - m_4 m_5 - m_6[m_4(G - m_5) - m_6(I - \beta)] \quad (17)$$

At various interval of time for three to four food intake depending on PFC (1346cal to 2190cal), the glucose through absorption from the intestinal circulation subsequent to the input of the insulin, we can define the uptake glucose for sensitive inputs (symmetrical sinusoidal) followed by positive coefficients $m_0, m_1, m_2, m_3, m_4, m_5, m_6$ and m_7 as

$$G(t) = Je^{-st}\sin\omega t \text{ at P and I} \quad (18)$$

Where $J = \frac{k}{\omega}$

k =k(t) ,the input of insulin

$S = K\delta(t)$ (this becomes two parameter classification of blood-glucose control system)

$\delta(t)$- the dirac delta function (rapid infusion over a short time period)

$\omega^2 = {\omega_0}^2 - \alpha^2$

$\alpha = 0.014\text{min}^{-1}, 0.0048\text{min}^{-1}$

${\omega_0}^2 = 0.0019\text{min}^{-2}, 0.0003\text{min}^{-2}$

$\omega = \frac{2\pi}{T}, \omega^2 = |-0.00195639| = 0.00195639$

T=T(t):4,8,12,16 hrs

Then $S = K\delta(t) = k\int_{-\infty}^{\infty}\delta_1(t)dt = k$ with $\int_{-\infty}^{\infty}\delta_1(t)dt = 1$ (19)

This does not happen in any case of glucose insulin model. Since the first meal supplied starts chemically interacted by insulin concentration to enhance the required glucose level.

Then (18) becomes

$G(t) = \frac{k}{(0.00195639)^{1/2}} e^{-K\delta(t)t} \sin\omega t$ at P and I (20)

Where $\delta(t)$ is the Dirac delta function defined for the chemical action between blood-glucose concentration and the insulin concentration following by stimulation action for giving the normal blood-glucose level. The function is expressed for segregating the assigned meals for three to four time intervals as,

$$\delta(t) = \begin{cases} 0, & t < 4hrs \ \ t \neq 0 \\ \frac{1}{8}g_1(t), & 4\text{hrs} < t < 8hrs \\ \frac{1}{12}g_2, & 8\text{hrs} < t < 12hrs \\ \infty, & 12\text{hrs} < t < 16hrs. (t = 0) \ \ t \geq 16\text{hrs} \end{cases} \quad (21)$$

Also at $\omega = (0.00195639)^{1/2}$, the values of G(t) starts decreasing from t=4hrs to t=16hrs.

The numerical method using R-K-F scheme is employed with sixth order to obtain series of approximations using $\Delta t = 4\text{hrs} = h$ in finding k_1, k_2, k_3, k_4, k_5 and k_6 in the following equations.

$G_1(t) = G_0(t) + k$ (22)

Where $k = h[\frac{37}{378}k_1 + \frac{250}{651}k_3 + \frac{125}{594}k_4 + \frac{512}{1771}k_6]$

Here k_2,k_5 values are negligibly small, dropping them in equation (22),we obtain

$$k_1 = f(x_i, y_i)$$

$k_2 = f(x_i + 0.2h, y_i + 0.2k_1h)$ not considered since the numerical value negligible small

$$k_3 = f(x_i + 0.3h, y_i + 0.075k_1h + 0.225k_2h)$$

$$k_4 = f(x_i + 0.6h, y_i + 0.3k_1h - 0.9k_2h + 1.2k_3h)$$

$k_5 = f(x_i + h, y_i - 0.2037k_1h + 2.5k_2h + 2.592k_3h + 1.296k_4h) =$ not considered since the numerical value negligible small

$$k_6 = f(x_i + 0.875h, y_i + 0.0294k_1h + 0.3419k_2h + 0.0415k_3h + 0.4003k_4h + 0.06176k_5h)$$

$y_{i+1} = y_i[0.0978k_1 + 0.6613k_3 + 0.2104k_4 + 0.2891k_6] \times h$

We compute p(t) and I(t) for various time intervals in the form of meals inputs at every four hours using calculated values of $G(t)$ and $I(t)$.but in the case of verification between glucose and insulin,the excess of glucose orally or intravenously given then, the variation of blood glucose is measured with k=0(the insulin input). Diabetes mellitus case the administration of insulin is to monitor the response of blood glucose level by varying S(t), G(t) and $\delta(t)$ at various values of t, then the blood glucose level varies between 96-120mg/dl using (21) without assigned meals but after 8 hours meal interval. After this there appears the rise in $G(t)$ reaching the blood glucose level upto 143mg/dl interval R.K.F results give the blood glucose level upto 143mg/dl. The range of [PFC] with protein: fat: carbohydrate is introduced in the analysis of the model as 15%:30%:55% to extract the calorie levels 1346 to 2190 for a normal body frame.

Results and discussion

Glucose-insulin model has been studied to minimize the observed response of $G(t)$ and $I(t)$ which leads to confidence to the general mathematical form of the model. Parameters used in the numerical approximations are $\alpha = 0.014\text{min}^{-1}$, $\omega^2 = 0.00195639, m_0 = 2.0$, $m_2 = 2.2$, $m_3 = 2.4$, $m_4 = 2.6$, $m_5 = 2.8$, $m_6 = 3.0$ with t=0,t= 4,t= 8,t=12 and t=16 hrs. They give the proper sensitivity of insulin for the inputs of glucose with $\delta(t)$. Findings of G,P and I using R.K.F method give the evidence of normal blood-glucose concentration with normal insulin available from the beta cells of pancreas. For the first approximation with G_1, T_1, I_1 with $\delta_1(t)$, $G(t)$(***) with the chemically balancing constants $m_0, m_1, m_2, m_3, m_4, m_5$ and m_6 chosen, there appears the rapid increase but by introducing the special mechanism terms G(t) and $\delta(t)$. Results showdamped oscillations. But in second approximation it comes near to normal response than it comesto critically damped. In third and fourth approximation results show no oscillatory response. For more specific quantification of blood – glucose response of typical diabetic with high level of blood sugar and to maintain relatively long time period, we consider $\alpha = 0.0048\text{min}^{-1}$ to $0.00947\text{min}^{-1}$and $\omega^2 = 0.0003\text{min}^{-2}$ to 0.000736min^{-2}.

The response of interaction of glucose with insulin concentration levels for diabetes mellitus needs the utilization of PFC at 15% : 30% : 55% to achieve the calorie range for normal body frames. But for small and large body frames it is to be redefined for sensitivity constants$m_0, m_1, m_2, m_3, m_4, m_5, m_6$ and m_7. The response of blood glucose will give according to meals distribution at three to four times per day.

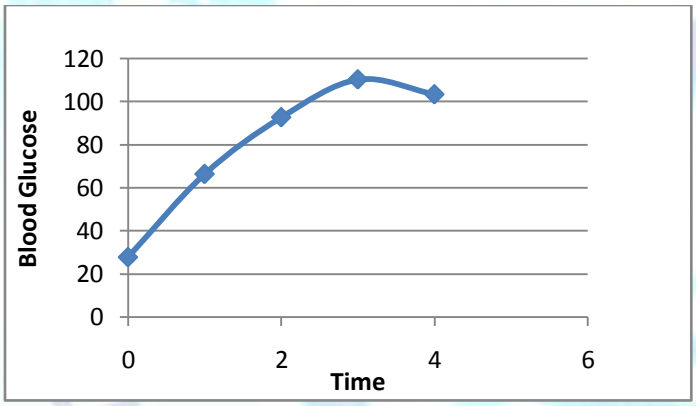

Fig 1: Blood Glucose with time ($\delta = 0, t < 4\ hrs$), PFC:[1217-1827] cal [G and t]

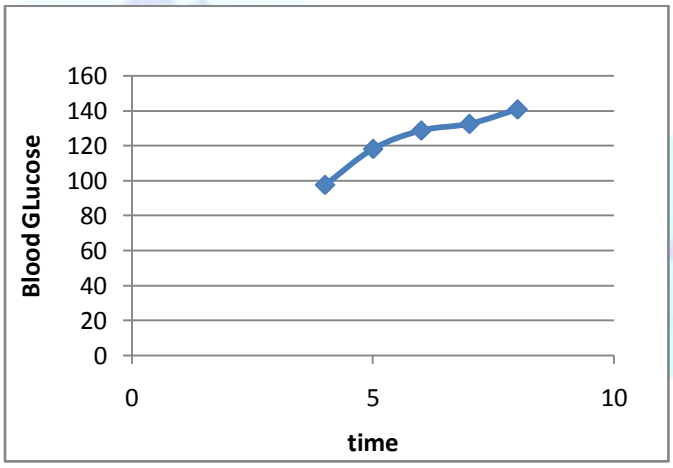

Fig 2: Blood Glucose with time $\left(\delta = \frac{1}{8}, g_1(t)\right)$, PFC: [1346-2190] cal

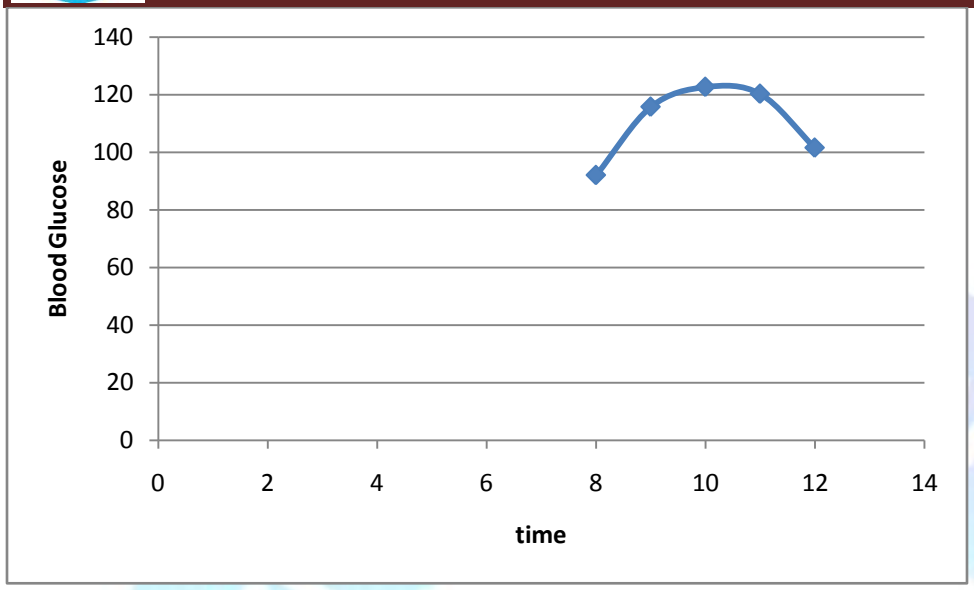

Fig 3: Blood Glucose with time $\left(\delta = \frac{1}{12}, g_2(t)\right)$, PFC: [1482-2300] cal

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