

A compartmental modal for type2 diabetes on the effect of plasma glucose -insulin regulatory system by Jacobes model

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Abstract

A compartmental model for diabetes is developed. The model describes the dynamics of the spread of Type 2 diabetes. A theoretical analysis in the non-adherence to drugs is investigated. A system of differential equations is analyzed by stability analysis; the non-trivial critical point obtained is locally asymptotically firm under the given conditions. In consideration of Mathematical model for glucose tolerance test (GTT) is considered, actual glucose data values are fixed using MATLAB least squares curve fitting technique. Two methods are used to numerically work out the distributions of steady states of diabetic sub-populations. The Gauss-Seidel method is more accurate than the Jacobi method. The result show that more than 50% of clinical diagnosis attempt needs to be applied to have more diagnosed population than undiagnosed. The GTT model shows that if severe diet and medication is followed diabetes can be controlled.

Keywords: Type 2 Diabetes; Non-Adherence; Gauss-Seidel Method; Jacobi Method; GTT Model.

1. Introduction

Diabetes is a disease that is caused by the body's breakdown to produce insulin which regulates the amount of blood sugar [1]. Insulin is produced by beta cells that are in the pancreas, when these beta cells die, the amount of insulin produced is low. This is usually caused by lack of physical activity and obesity. Diabetes is also traditional; it develops on people who are genetically vulnerable and is now an epidemic [3]. The failure to manage blood sugar levels leads to more complications. The details on how diabetes is caused is not obviously understood [4].

2. Mathematical formulation

A compartmental model for diabetes is developed, the human being having three blood content, they are Plasma Glucose, Plasma Insulin and Interstitial Insulin Action. Which are given below in the diagram.

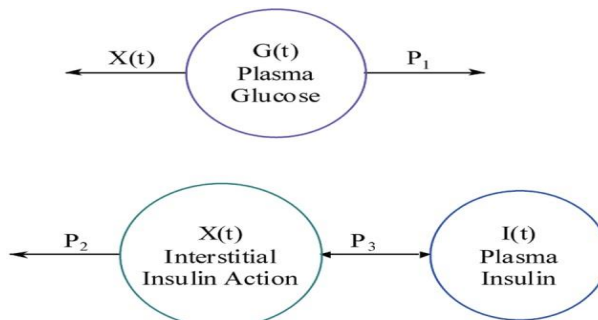


Fig. 1: The Compartmental Flow Chart of the Minimal Model for Glucose Kinetics.

The differential equations describing the dynamics of Figure 1 is given by

$$\dot{G}(t) = -X(t) - p_1 G(t) + p_2 \quad (1)$$

$$\dot{I}(t) = p_3 \quad (2)$$

$$\dot{X}(t) = p_3 - p_2 \quad (3)$$

Substituting (3) in (1), we get

$$\dot{G}(t) = p_2 - p_1 - p_3 \quad (4)$$

With the initial condition that

$$G(t_0) = G_0, X(t_0) = X_0, I(t_0) = I_0 \text{ and } t > 0$$

The total population is given by

$$N(t) = G(t) + I(t) + X(t)$$

From the above figure 1, $I(t)$ is the plasma insulin level, and I_b represents its basal level; $G(t)$ is the plasma glucose level, and its basal level is denoted as G_b . The coupled differential equations corresponding to the glucose minimal model are expressed as

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b \quad (5)$$

$$G(0) = G_0 = G_b + \frac{D}{V}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 [I(t) - I_b]; X(0) = 0 \quad (6)$$

Comparing equation (4) and (5), we get

$$p_2 - p_1 - p_3 = -[p_1 - X(t)]G(t) + p_1 G_b$$

$$[X(t) - p_1]G(t) = p_2 - p_3 - p_1 [1 - G_b]$$

$$G(t) = \frac{p_2 - p_3 - p_1 (1 - G_b)}{(X(t) - p_1)} \quad (7)$$

Comparing equation (3) and (5), we get

$$p_3 - p_2 = -p_2 X(t) + p_3 I(t) - p_3 I_b$$

$$p_3 I(t) = p_3 - p_2 + p_2 X(t) + p_3 I_b$$

$$I(t) = \frac{(1 + I_b)p_3 - (1 - X(t))p_2}{p_3} \quad (8)$$

With $G(0) = G_0$ and $X(0) = 0$. In these equations, $X(t)$ is the interstitial insulin at time t . There are a total of four unknown parameters in this model are $X(t)$, p_1 , p_2 and p_3 which are also defined with the units and brief descriptions are provided below:

p_1	$[\text{min}^{-1}]$	Glucose effectiveness, $p_1 = S_G$, the rate of net glucose utilization without dynamic insulin response (i.e., insulin-independent).
p_2	$[\text{min}^{-1}]$	rate constant expressing the spontaneous decrease of tissue glucose uptake ability
p_3	$[\text{min}^{-2} (\mu\text{U} / \text{mL})^{-1}]$	Insulin-dependent increase in tissue glucose uptake ability.
G_0	$[\text{mg} / \text{dL}]$	Theoretical glycemia at time 0 after the instantaneous glucose bolus.
$G(t)$	mg/dl	Plasma glucose at time t
$I(t)$	U/ml	Plasma insulin concentration at time t
$X(t)$	$[\text{min}^{-1}]$	is the interstitial insulin at time t

Table: 1: Four Measurements (Deviations from Base Lines) of Blood Glucose, and Plasma Insulin Concentration in Two Subjects

Time In min	p_1 (1/min)	p_2 (1/min)	p_3 (1/min)	$X(t)$ (1/min)	I_b [$\mu U/ml$]	G_b [$mg \cdot dl^{-1}$]	$I(t)$ U/ml	$G(t)$ mg/dl
1	0.013	0.07	0.009	13.39	40	80	137.3666	-0.0741
2	0.018	0.02	0.002	11.25	41	169	144.5000	-0.2708
3	0.020	0.04	0.009	13.02	39	75	93.4222	-0.1145
4	0.011	0.05	0.012	18.29	44	165	117.0416	-0.0978
5	0.015	0.04	0.008	15.38	42	78	114.9000	-0.0750
6	0.017	0.03	0.002	8.39	55	65	166.8500	-0.1306
7	0.013	0.03	0.006	12.20	44	77	101.0000	-0.0812
8	0.025	0.05	0.017	18.30	42	125	93.8823	-0.1705
9	0.011	0.05	0.016	17.30	47	75	98.9375	-0.0463
10	0.012	0.03	0.005	20.30	49	190	165.8000	-0.1117
11	0.015	0.05	0.008	16.59	46	79	144.4375	-0.0698
12	0.014	0.03	0.009	17.45	45	130	100.8333	-0.1039

Profiles of subject 8 in [7] produced by equations (7) and (8) with parameters p_1 , p_2 , p_3 , $X(t)$, I_b , and G_b representation equations and parameters for the minimal model of glucose metabolism. Differential equations describing glucose dynamics $[G(t)]$ in a mono compartmental “glucose space” and insulin dynamics in a “remote compartment” $[X(t)]$ are shown at the top. Glucose leaves or enters its space at a rate proportional to the difference between plasma glucose level, $G(t)$, and the basal fasting level, G_b . In addition, glucose also disappears from its compartment at a rate proportional to insulin levels in the “remote” compartment $[X(t)]$. In this model, t = time; $G(t)$ = plasma glucose at time t ; $I(t)$ = plasma insulin concentration at time t ; $X(t)$ = insulin concentration in “remote” compartment at time t ; G_b = basal plasma glucose concentration; I_b = basal plasma insulin concentration; $G(0) = G_b$ (assuming instantaneous mixing of the iv glucose load); p_1, p_2, p_3 and G_b = unknown parameters in the model that are uniquely identifiable from frequently sampled intravenous glucose tolerance test; glucose effectiveness = p_1 ; and insulin sensitivity = p_3 .

Table: 1 Four measurements (deviations from base lines) of blood glucose, and plasma insulin concentration in two subjects. The differential equation system governing this GTT model is expressed as follows:

$$\frac{dg}{dt} = -p_1 \cdot g - p_2 \cdot i + J \quad (9)$$

$$\frac{di}{dt} = p_3 \cdot g - p_4 \cdot i \quad (10)$$

Where p_i ($i = 1, 2, 3, 4$) are positive constants, J is the rate of glucose infusion from the intestines, $g(t)$ is the difference between blood glucose concentration, $G(t)$ and its baseline value G_b , and $i(t)$ is the difference between plasma insulin concentration, $I(t)$ and its baseline value I_b , as shown in the following equations.

$$g = G - G_b \quad (11)$$

$$i = I - I_b \quad (12)$$

Where $G = G(t)$ represents blood glucose concentration, $I = I(t)$ represents plasma insulin and p_1, p_2, p_3 and p_4 are parameters. Use equations (9) and (10) in equations (7) and (8), we get

$$\frac{d(G - G_b)}{dt} = -p_1(G - G_b) - p_2(I - I_b) + J \quad (13)$$

$$\frac{d(I - I_b)}{dt} = p_3(G - G_b) - p_4(I - I_b) \quad (14)$$

Using Picard's Method of Iteration for the above equations (11) and (12), we get

$$dG(t) - dG(t_0) = [-p_1(G - G_b) - p_2(I - I_b) + J]dt \quad (15)$$

Integrating on both sides we get

$$G(t) = G_b + \int_{t_0}^t [-p_1(G - G_b) - p_2(I - I_b) + J]dt \quad (16)$$

Similarly we get

$$I(t) = I_b + \int_{t_0}^t [-p_3(G - G_b) - p_4(I - I_b)]dt \quad (17)$$

From equations (9) and (10) we create a perturbation variable,

$$g(t) = G(t) - G_0 \text{ and } i(t) = I(t) - I_0$$

Where G_0 and I_0 are the equilibrium values for blood glucose and insulin concentration, respectively. Thus

$$f_1(G_0, I_0) = f_2(G_0, I_0) = 0 \quad (18)$$

We expand the general model to linear terms with these definitions, yielding the linearized perturbation model given by:

$$\frac{dg}{dt} = \frac{\partial f_1(G_0, I_0)}{\partial g} g + \frac{\partial f_1(G_0, I_0)}{\partial i} i \quad (19)$$

$$\frac{di}{dt} = \frac{\partial f_2(G_0, I_0)}{\partial g} g + \frac{\partial f_2(G_0, I_0)}{\partial i} i \quad (20)$$

Where $g(t)$ and $i(t)$ now represent the linearized perturbed variables.

The partial derivatives of the functions f_1 and f_2 are understood the physiology of glucose and insulin. An increase in glucose in the blood will stimulate the tissue uptake of glucose and glycogen storage in the liver. Also, increases in insulin facilitate the uptake of glucose in tissues and the liver. Hence it is clear that

$$\frac{\partial f_1(G_0, I_0)}{\partial g} = -m_1 < 0 \text{ and } \frac{\partial f_1(G_0, I_0)}{\partial i} = -m_2 < 0 \quad (21)$$

However, increase in blood glucose result in the release of insulin, while increases in insulin only result increased metabolism of excess insulin. These facts implies that

$$\frac{\partial f_2(G_0, I_0)}{\partial g} = m_4 > 0 \text{ and } \frac{\partial f_2(G_0, I_0)}{\partial i} = -m_3 < 0 \quad (22)$$

From the above results we can write the linearized system as follows

$$\begin{pmatrix} \dot{g} \\ \dot{i} \end{pmatrix} = \begin{pmatrix} -m_1 & -m_2 \\ m_4 & -m_3 \end{pmatrix} \begin{pmatrix} g \\ i \end{pmatrix}$$

Where $\dot{g} = dg/dt$ and similarly for $i(t)$.

The characteristic equation for this linear system is given by

$$\det \begin{vmatrix} -m_1 - \lambda & -m_2 \\ m_4 & -m_3 - \lambda \end{vmatrix} = \lambda^2 + (m_1 + m_2)\lambda + m_1 m_3 + m_2 m_4 = 0 \quad (23)$$

That is $p(\lambda) = \lambda^2 + d_1 \lambda + d_2$ where $d_1 = m_1 + m_2$, $d_2 = m_1 m_3 + m_2 m_4$. Note that the d_i 's are positive.

By our definitions above, this characteristic equation only has positive coefficients. From basic differential equations, this implies that the solutions λ are either complex with negative real part or both Eigen values are negative reals. Both situations give a stable equilibrium as we would expect from this self-regulatory system.

We are only measuring the blood glucose level in the GTT, so we only need the linearized solution for $g(t)$. We expect the under damped situation with complex Eigen values. Physiologically, you can think of the your body's response to a "sugar high" (maximum of blood glucose), which is followed after an hour or two by a "sugar low" (minimum of blood glucose below equilibrium) that encourages more eating. It follows that the general solution is given by

$$g(t) = e^{-\alpha t} (c_1 \cos(\omega t) + c_2 \sin(\omega t)) \quad (24)$$

Where

$$\alpha = \frac{m_1 + m_3}{2} \text{ and } \omega = \frac{1}{2} \sqrt{4(m_1 m_3 + m_2 m_4) - (m_1 + m_3)^2}$$

If we take $c_1 = A \cos(\omega \delta)$ and $c_2 = A \sin(\omega \delta)$. Then we can approximate the blood glucose level by

$$G(t) = G_0 + A e^{-\alpha t} \cos(\omega(t - \delta)) \quad (25)$$

Note that there are 5 parameters to be determined in this equation (One can actually reduce it to 4 by requiring that $g(0)=0$.) We compute the values of these parameters by a nonlinear least square method. If $G_1, G_2, G_3, \dots, G_n$ are measurements of the patient's blood glucose concentration at times $t_1, t_2, t_3, \dots, t_n$, then we find the values of $G_0, A, \alpha, c_1, c_2, \omega, \delta$ that minimize the mean square error function:

$$E = \sum_{k=1}^n G_k - G_0 - A e^{-\alpha t} \cos(\omega(t - \delta)) \quad (26)$$

Note that the requirement $c_1, c_2, c > 0$ implies that condition (24) is satisfied.

We examine the theory described above with a normal and a diabetic subject given the GTT. The table below gives the data collected on two subjects.

Example:-

Table 2: Data From the Glucose Tolerance Test. Subject A Is A Normal Subject. While Subject B Is A Diabetic

t (hr)	Subject A	Subject B
0	70	100
0.5	150	185
0.75	165	210
1	145	220
1.5	90	195
2	75	175
2.5	65	105
3	75	100
4	80	85
6	75	100

3. conclusion

The problem of diabetes control caused by non-adherence to drugs is considered. A system of differential equations is analyzed by considering the stability at steady states. The results show that the stability point is asymptotically stable. The resulting system of linear equations is solved numerically to obtain the population distribution of different diabetic groups. The two methods were used. The compartmental model and perturbation model were discussed. To effectively control diabetes, more than 90% clinical diagnosis effort is required. The clinical efforts need to be stepped up much more than non-adherence. From the GTT model analysis, taking low GI foods and medication effectively control diabetes. The glucose concentration data can be used to determine if a patient is diabetic or not. This method considers data over a long period of time. This compartmental model can be used to effectively control blood sugar levels.

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