MATHEMATICAL MODEL FOR DRUG THERAPY IN PATIENTS WITH DIABETES MELLITUS

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Abstract

This study presents a new mathematical model for Drug Therapy in Patients with Diabetes Mellitus which includes external rate at which blood glucose, insulin and epinephrine is being increased in the form, $\dot{Y} = f_i(g,h,e) + r_i(t)$. The system has been analyzed and solved to provide the systems natural frequency, ω_0, which is the basic descriptor of saturation level of the drug. We establish that the resonance period for the final model, that is, T_0=3.76912 hrs, agrees well with the data for the existing insulin therapy, showing that the peak, which is the time period for insulin to be most effective in lowering blood sugar, is in the acceptable therapeutic range.

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1 Introduction

Diabetes Mellitus is a chronic condition in which blood glucose (sugar) is above the normal range, that is, 3.5-10.0 mmol/L. When we eat food, the body breaks down all of the sugars and starches into glucose, which is the basic fuel for the cells in the body. The blood always has some glucose in it because the body needs glucose for energy. Insulin takes the sugar from the blood into the cells. When glucose builds up in the blood instead of going into cells, it can lead to diabetes Mellitus [2].

The pancreas produces the hormone insulin that helps glucose get from the blood into body cells where it is converted into energy. In patients with Diabetes Mellitus, the pancreas produces little or no insulin or body cells cannot respond to insulin very well. Glucose therefore cannot get into the cells and builds up in the blood. Type 1 Diabetes Mellitus develops when the pancreas no longer produces insulin. People with Type 1 Diabetes Mellitus need daily injections of insulin in order to control the levels of glucose in their blood. Type 1 Diabetes Mellitus usually occurs in children or young adults and accounts for about 5 to 10 percent of all cases of Diabetes Mellitus. Type 2 Diabetes Mellitus is the most commonly occurring type of Diabetes Mellitus. This form of Diabetes Mellitus usually occurs in adults but is becoming more common in children and adolescents. In Type 2 Diabetes Mellitus, the body is able to produce insulin but the insulin produced is either insufficient or the body is unable to respond to its effects. This leads to a build up of glucose in the blood. People with Type 2 Diabetes Mellitus often need to take tablets or insulin to help the body's supply of insulin work better, American Society of Health-System Pharmacists [3]. Type 2 Diabetes Mellitus is a progressive disease in which β-cell function deteriorates overtime. Findings from the U.K. Prospective Diabetes Study (UKPDS) showed that deterioration in β-cell function occurred in the diet-only treatment group as well as in patients treated with sulfonylureas or metformin, suggesting that neither of these agents slowed the rate of decline, Turner *et al* [12]. The UKPDS also showed that even basal insulin (ultralente) did not slow β-cell deterioration. Another study found that ~ 30 percent of patients initially treated with a sulfonylurea drug have a poor response; the remaining 70 percent experience a failure rate of ~ 45 percent per year, Groop [6]. It is, therefore, reasonable to conclude that most patients with type 2 Diabetes Mellitus will eventually need exogenous insulin, Bergman *et al* [4]. In 1939, Himsworth and Ker introduced the first approach to measure the insulin sensitivity *in vivo*. The real start of modeling the glucose-insulin dynamics is thought to have began with the so-called

minimal model proposed by the team of Bergman and Cobelli in the early eighties, Cobelli *et al* [5].

Gestational Diabetes Mellitus occurs only during pregnancy. Its onset is when a woman is pregnant and normally disappears after birth. The changes and weight gain associated with pregnancy may make it hard for the body to keep up with its need for insulin. As a result glucose builds up in the blood. Excess glucose in the blood can be harmful to the baby. Women with gestational Diabetes Mellitus have to control blood glucose levels to minimize risks to the baby. This can be done through a healthy diet but insulin or oral medication may also be needed. Women who have had gestational Diabetes Mellitus have a higher risk of developing Type 2 Diabetes Mellitus later in life. Babies born to women who had gestational Diabetes Mellitus have a higher risk of obesity and developing Type 2 Diabetes Mellitus as adults. Gestational Diabetes Mellitus is increasing throughout the world. Diabetes Mellitus is a chronic metabolic disease that is increasing in prevalence in the United States.

Diabetes control is measured by both blood glucose and glycated hemoglobin, HbA1c levels. HbA1c levels are measured in percentage points and reflect the level of blood glucose control over the preceding two to three months. The HbA1c normal range is 4 to 6 percent, Larsen *et al* [10]. The American Diabetes Association recommends HbA1c goal for people with Diabetes Mellitus is 7 percent or under, which equals an average blood glucose level of approximately 150mg/dl. A large majority, approximately 90 percent of those with Diabetes Mellitus require oral anti-diabetes medications, insulin injections, or both, to reach desired blood glucose goals.

In 2007 the National Diabetes Information Clearinghouse (NDIC) reported the following statistics;

(a) 190 million diabetics worldwide

(b) 23.6 million diabetic Americans

(c) 57 million adult Americans with pre-diabetic conditions

The estimated Diabetes Mellitus prevalence in Kenya ranges between 2.7 percent (rural) and 10.7 percent (urban). The prevalence of impaired glucose tolerance is 8.8 percent (rural) and 14.4 percent (urban). The real numbers of people living with Diabetes Mellitus is unknown: data for most of the regions is not available. In 2003, non-communicable diseases (diabetes, cardiovascular diseases, chronic lung diseases and cancer) contributed 53 percent of hospital

admissions in Kenya. Diabetes Mellitus accounted for 27 percent of these hospital admissions, Kenya Diabetes Management and Information Centre [8].

2 Preliminaries

In mid 1960's Drs. Rosevear and Molnar of the Mayo Clinic and Ackerman and Gatewood of the University of Minnesota discovered a fairly reliable criterion for interpreting the results of a GTT. The discovery was based on a simple model they developed for the blood glucose regulatory system (BGRS) where g is taken to be excess glucose concentration and h is excess insulin concentration at time t;

$$\begin{aligned} \dot{g} &= -ag - bh \\ \dot{h} &= cg - dh \end{aligned} \qquad (1)$$

with a, b, c and d as constants.

The aim of Ackerman *et al* [1], was to construct a model which would accurately describe the blood glucose regulatory system during a glucose tolerance test, and in which one or two parameters would yield criteria for distinguishing normal individual from Diabetes Mellitus and pre-diabetes. Their model is a simplified one, requiring only a limited number of blood samples during a GTT. It centers attention on the concentrations of glucose and insulin. If there is an external rate $J(t)$ at which the blood glucose is being increased, $J(t)$ is incorporated into the system of differential equation;

$$\begin{aligned} \dot{g} &= -ag - bh + J(t) \\ \dot{h} &= cg - dh \end{aligned} \qquad (2)$$

If there is an external rate $P(t)$ at which insulin is being increased, $P(t)$ is incorporated into the system of differential equation;

$$\begin{aligned} \dot{g} &= -ag - bh + J(t) \\ \dot{h} &= cg - dh + P(t) \end{aligned} \qquad (3)$$

If the blood glucose concentration were to be less than 30mg/100ml, the sympathetic nervous system would begin to play a significant role in increasing the blood sugar by increasing the secretion of epinephrine and glucagon. If there is an internal rate at which the blood glucose concentration is being increased, epinephrine is included as a separate variable in this model of blood glucose regulatory system, kwach *et al* [9] . Thus, if it is assumed that there is no recent digestion, the following systems of differential equations results;

$$\begin{aligned} \dot{g} &= -ag - bh + fe + J(t) \\ \dot{h} &= cg - dh + ke + P(t) \\ \dot{e} &= -lg - mh + ne + Z(t) \end{aligned} \qquad (4)$$

where e represents epinephrine, a, b, c, d, f, k, l, m, n are constants and $Z(t)$ is the external rate at which epinephrine is increased. In this case, where there is an internal rate at which the blood glucose concentration is being increased, it is assumed that these differential equations are linear with constant coefficients. Assuming $g=h=e=r(t)$ are equilibrium solutions, it follows that these linear differential equations must be nonhomogeneous. It is therefore assumed that they are in the form;

$$\begin{aligned} \dot{g} &= F_1(g,h,e) + J(t) \\ \dot{h} &= F_2(g,h,e) + P(t) \\ \dot{e} &= F_3(g,h,e) + Z(t) \end{aligned} \qquad (5)$$

for some functions F_1, F_2 and F_3. This results to a system of equations in the form $\dot{Y} = f_i(g,h,e) + r_i(t)$ where $r_i(t)$ represent the external rates at which glucose, insulin and epinephrine are being increased. This system can be solved explicitly once the constants are known.

3 Drug Saturation Level

From the model in equation (4);

$$\begin{aligned} \frac{dg}{dt} &= -ag - bh + fe + J(t) \\ \frac{dh}{dt} &= cg - dh + ke + P(t) \end{aligned}$$

$$\frac{de}{dt} = -lg-mh+ne+Z(t)$$

Differentiating

$$\frac{dh}{dt}=cg-dh+ke+P(t)$$

of equation (4) w.r.t t gives;

$$\frac{d^2h}{dt^2}=c\frac{dg}{dt}-d\frac{dh}{dt}+k\frac{de}{dt}+\frac{d}{dt}(P(t)) \qquad (6)$$

Substituting for

$$\frac{dg}{dt}=-ag-bh+fe+J(t)$$

and

$$\frac{de}{dt}=-lg-mh+ne+Z(t)$$

of equation (4) in equation (5) gives;

$$\frac{d^2h}{dt^2}+cag+cbh-cfe-cJ(t)+d\frac{dh}{dt}+klg+kmh-kne-kZ(t)-\frac{d}{dt}(P(t))=0$$

From equation (4), assuming $e=0$ and $Z(t)=0$

$$\frac{d^2h}{dt^2}+d\frac{dh}{dt}+(cb+km)h+(ca+kl)g=cJ(t)+\frac{d}{dt}(P(t))$$

From equation (4),

$$cg=\frac{dh}{dt}+dh-P(t)$$

$$\Rightarrow g=\frac{1}{c}\left(\frac{dh}{dt}+dh-P(t)\right)$$

$$\Rightarrow \frac{d^2h}{dt^2}+\left(a-d+\frac{k}{c}l\right)\frac{dh}{dt}+\left(cb+km+ad+\frac{k}{c}d\right)h=cJ(t)+\frac{d}{dt}(P(t))$$

This is in the form of;

$$\frac{d^2h}{dt^2}+2\alpha\frac{dh}{dt}+\omega_0^2 h=r(t) \qquad (7)$$

$\Rightarrow\alpha=\frac{1}{2}(\frac{kl}{c}+a+d)$ and $\omega_0^2=(\frac{1}{c}kld+ad+bc+km)$

The resonance period is given by; $T_0=\frac{2\pi}{\omega_0}$

The value of ω_0 which is the systems natural frequency is the basic descriptor of saturation level of the drug.

Using secondary data, kwach *et al* [6];

$a=-2.92, b=-4.34, c=0.208, d=-0.78, f=1.24, k=0.14,$

l=-2.94, m=-0.98, n=0.54

$\Rightarrow\omega_0^2=2.2776-0.90272-0.1372+1.5735$

$\Rightarrow\omega_0^2=2.78118$

$\Rightarrow\omega_0=1.667687$

$\Rightarrow T_0=\frac{2\pi}{\omega_0}=\frac{2\pi}{1.667687}=3.76912$ hrs.

The following chart lists the types of injectable insulin with details about onset (the length of time before insulin reaches the bloodstream and begins to lower blood sugar), peak (the time period when the insulin is most effective in lowering blood sugar) and duration (how long insulin continues to lower blood sugar). These three factors may vary, depending on your body's response. The final column provides some insight into the "coverage" provided by the different insulin types in relation to mealtime. Classifications of insulin are,

3.1 Rapid Acting Insulin

Brand Name	Generic Name	Onset	Peak	Duration
Apidra	insulin glulisine	10 - 20 mins	55 mins	3 hours
Humalog	insulin lispro	15 mins	1 - 1.5 hours	2 - 5 hours

NovoLog	insulin aspart	10 - 20 mins	1 - 3 hours	3 - 5 hours

3.2 Short Acting

Brand Name	Generic Name	Onset	Peak	Duration
Regular (R)	Humulin , Novolin	30-60 mins	2 - 5 hours	5 - 8 hours
Velosulin		30 mins- 1 hour	2-3 hours	2-3 hours

3.3 Intermediate Acting

Brand Name	Onset	Peak	Duration
NPH(N)	1 - 2 hours	4-12 hours	18-24 hours
Lente(L)	1-2 $\frac{1}{2}$ hours	3-10 hours	18-24 hours

3.4 Long Acting

Brand Name	Generic Name	Onset	Peak	Duration
Apidra	insulin glulisine	10 - 20 mins	55 mins	3 hours
Humalog	insulin lispro	15 mins	1 - 1.5 hours	2 - 5 hours
NovoLog	insulin aspart	10 - 20 mins	1 - 3 hours	3 - 5 hours

3.5 Pre-Mixed

Brand Name	Onset	Peak	Duration
Humulin 70/30	30 mins	2-4 hours	14-24 hours
Novolin 70/30	30 mins	2-12 hours	Up to 24 hours
NovoLog 70/30	10 - 20 mins	1 - 4 hours	Up to 24 hours
Humulin 50/50	30 mins	2-5 hours	18- 24 hours
HumuLog 75/25	15 mins	30 mins-2 $\frac{1}{2}$ hours	16-20 hours

Premixed insulin is a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen, Jacobon *et al* [7], with the numbers following the brand name indicating the percentage of each type of insulin). It is worth noting that the resonance period given by T_0=3.76912 hrs agrees well with the data given above for the existing insulin therapy.

4 Verification of the model

From the model proposed by Li, Kuang and Mason, Li *et al* [11] for normal glucoseinsulin regulatory system, H. Wang *et al* [13] proposed the following generic model to simulate the dynamics of the insulin therapies for type 1 diabetic patients:

$$\dot{G}=G_{in}(t)-f_2(G(t)-f_3(G(t))f_4(I(t-\tau_3))+f_5(I(t-\tau_2))$$

$$\dot{I}=I_{in}(t)-d_i(t) \quad (8)$$

and the homogeneous form of the equation is given by

$$I^{'}(t)=-d_iI(t)$$

Separating the variables;

$$\frac{I^{'}(t)}{I(t)}=-d_i$$

Integrating;

$$\int dI(t)I(t)=\int -d_idt$$

$$ln|I(t)|=-d_it+c$$

$$|I(t)|=e^{-d_it}e^c$$

$$I_h(t)=C_0e^{-d_it}$$

h:homogeneous and *nh*:non-homogeneous.

Trying trial solution;

$$I_{nh}(t)=C_0e^{-d_it}$$

Differentiating;

$$I^{'}(t)=C_0^{'}(t)e^{-d_it}+C_0(t)e^{-d_it}(-d_i)$$

$$C_0^{'}(t)e^{-d_it}+C_0(t)e^{-d_it}(-di)=I_{in}(t)-d_iC_0(t)e^{-d_it}$$

$$C_0^{'}(t)=I_{in}(t)e^{d_it}$$

$$C_0(t)-C_0(0)=\int_0^t I_{in}(s)e^{d_is}ds$$

$$C_0(t)=C_0(0)+\int_0^t I_{in}(s)e^{d_is}ds$$

$$C_0(t)=I(0)+\int_0^t I_{in}(s)e^{d_is}ds$$

$I(t)=I_{in}(t)+I_{in}(t)$

$=C_0e^{-d_it}+[I(0)+\int_0^t I_{in}(s)e^{d_is}ds]e^{-d_it}$

$=C_0e^{-d_it}+I(0)e^{-d_it}+e^{-d_it}\int_0^t I_{in}(s)e^{d_is}ds$

$=C_1e^{-d_it}+e^{-d_it}\int_0^t I_{in}(s)e^{d_is}ds$

But $I(0)=C_1$

$\Rightarrow I(t)=I(0)e^{-d_it}+e^{-d_it}\int_0^t I_{in}(s)e^{d_is}ds$

In order to find a ω-periodic solution, we set $I(t+\omega)=I(t)\ \forall t$,

$I(t+\omega)=e^{-d_i(t+\omega)}(I_0+\int_0^{t+\omega} I_{in}(s)e^{d_is}ds)=e^{-d_it}e^{-d_i\omega}(I_0+\int_0^t I_{in}(s)e^{d_is}ds)+\int_t^{t+\omega} I_{in}(s)e^{d_is}ds)$

$=I(t)e^{-d_i\omega}+e^{-d_it}e^{-d_i\omega}\int_t^{t+\omega} I_{in}(s)e^{d_is}ds$

$I(t+\omega)=I(t)$

$(I-e^{-d_i\omega})I(t)=e^{-d_it}e^{-d_i\omega}\int_t^{t+\omega} I_{in}(s)e^{d_is}ds$

and thus, if we denote by $I^\star(t)$, the positive ω-periodic solution, we have

$I^\star(t)=\frac{e^{-d_it-d_i\omega}}{1-e^{-d_i\omega}}\int_t^{t+\omega} I_{in}(s)e^{d_is}ds$

5 Conclusion and recommendation

This paper presents a model for drug therapy in diabetics. The component of glucose, insulin and epinephrine has been added as an external rate to come up with the final model. The importance of these components lies in their ability in predicting the time interval for the drug to remain in the therapeutic range for a longer period of time. This leads to a system of equations, which are expressed in the form $\dot{Y} = f_i(g,h,e) + r_i(t)$ and whose solution has been analyzed to provide the systems natural frequency, ω_0, which is the basic descriptor of saturation level of the drug. We establish that the resonance period for the final model, that is, T_0=3.76912 hrs, agrees well with the data for the existing insulin therapy, showing that the peak, which is the time period for insulin to be most effective in lowering blood sugar, is in the acceptable therapeutic range. Future research may take into consideration oral therapy in the treatment of Diabetes Mellitus.

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