Mathematical Modeling of Insulin Therapy in Patients with Diabetes Mellitus

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***Abstract*—This study presents a Mathematical Model Insulin Therapy in Patients with Diabetes Mellitus which includes external rate at which blood glucose, insulin and epinephrine are being increased in the form, $\dot{Y}=AY+\vec{r}(t)$ and whose solution was analyzed to provide the systems natural frequency, ω_0 , which is the basic descriptor of saturation level of the drug. It was established that the resonance period for the final model, that is, T_0=3.76912 hrs, is in the acceptable therapeutic range and agrees well with the data for the existing insulin therapy. By employing the model, it is shown that, the peak, which is the time period for insulin to be most effective in lowering blood sugar, is shorter than T_0=5.3199 hrs, for the existing model. This model would help the medical practitioners to predict drug therapy in patients with Diabetes Mellitus, in such a way that the concentration of the drug remains in the therapeutic range.**

***Mathematics Subject Classification*: Primary 93A30; Secondary 91B74, 93C05**

***Keywords*— Mathematical Model, Linear System and Resonance Period**

I. INTRODUCTION

Insulin therapy is the treatment of Diabetes Mellitus by administration of exogenous insulin. Insulin is used medically to treat some forms of Diabetes mellitus. Patients with Type 1 Diabetes mellitus usually depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with Type 2 Diabetes mellitus are insulin resistant, have relatively low insulin production, or both. When we eat carbohydrates, they convert into glucose in the digestive system and enter the bloodstream through cells in the wall of the intestinal tract. The pancreas secretes insulin in response, and the insulin then signals to the cells that glucose is available. In insulin resistance, the signaling system is defective, so the cells do not absorb glucose from the bloodstream. This results in accumulation of blood glucose in the bloodstream. People with insulin resistance or pre-diabetes can help their body use insulin normally by being physically active, making wise food choices, and reaching and maintaining a healthy weight. Physical activity helps muscle cells use blood glucose for energy by making the cells more sensitive to insulin. Certain patients with Type 2 Diabetes Mellitus may eventually require insulin if other medications fail to control blood glucose levels adequately, Bergman *et al* [3].

One international unit of insulin (1 IU) is defined as the "biological equivalent" of $34.7\,g$ pure crystalline insulin. This corresponds to the old USP insulin unit, where one unit (U) of insulin was set equal to the amount required to reduce the concentration of blood glucose in a fasting rabbit to 45 mg/dl (2.5 mmol/L). The unit of measurement used in insulin therapy is not part of the International System of Units (abbreviated SI) which is the modern form of the metric system. Instead the pharmacological international unit (IU) is defined by the WHO Expert Committee on Biological Standardization, (Gene G. Marcial AUGUST 13, 2007)

The central problem for those requiring external insulin is picking the right dose of insulin and the right timing. Physiological regulation of blood glucose, as in the non-diabetic, would be best. Increased blood glucose levels after a meal is a stimulus for prompt release of insulin from the pancreas. The increased insulin level causes glucose absorption and storage in cells, reduces glycogen to glucose conversion, reducing blood glucose levels, and so reducing insulin release. The result is that the blood glucose level rises somewhat after eating, and within an hour or so, returns to the normal 'fasting' level. Even the best diabetic treatment with synthetic human insulin or even insulin analogs, however administered, falls far short of normal glucose control in the non-diabetic.

Complicating matters is that the composition of the food eaten affects intestinal absorption rates. Glucose from some foods is absorbed more (or less) rapidly than the same amount of glucose in other foods. In addition, fats and proteins cause delays in absorption of glucose from carbohydrates eaten at the same time. As well, exercise reduces the need for insulin even when all other factors remain the same, since working muscle has some ability to take up glucose without the help of insulin.

Because of the complex and interacting factors, it is, in principle, impossible to know for certain how much insulin (and which type) is needed to 'cover' a particular meal to achieve a reasonable blood glucose level within an hour or two after eating. Non-diabetics' $\beta-$ beta cells on routine basis and automatically manage this by continual glucose level monitoring and insulin release. All such decisions by a diabetic must be based on experience and training (i.e., at the direction of a physician, PA, or in some places a specialist diabetic educator) and, further, specifically based on the individual experience of the patient. But it is not straightforward and should never be done by habit or routine. With some care however, it can be done reasonably well in clinical practice, American Society of Health-System Pharmacists [].

A long-acting insulin is used to approximate the basal secretion of insulin by the pancreas. NPH/isophane, lente, ultralente, glargine and detemir may be used for this purpose. The advantage of NPH is its low cost and the fact that you can mix it with short-acting forms of insulin, thereby minimizing the number of injections that must be administered. The disadvantage is that the activity of NPH is less steady and will peak 4-6 hours after administration, and this peak has the potential of causing hypoglycemia. NPH and regular insulin in combination are available as premixed solutions, which can sometimes simplify administration. The theoretical advantage of glargine and detemir is that they only need to be administered once a day, and they also have steady activity, generally without peaks, although in practice, many patients find that neither lasts a full 24 hours. Glargine and detemir are significantly more expensive, and they cannot be mixed with other forms of insulin, Brunilda Nazario, MD [].

A short-acting insulin is used to simulate the endogenous insulin surge produced in anticipation of eating. Regular insulin, lispro, aspart and glulisine can be used for this purpose. Regular insulin should be given with about a 30 minute lead-time prior to the meal to be maximally effective and to minimize the possibility of hypoglycemia. Lispro, aspart and glulisine are approved for dosage with the first bite of the meal, and may even be effective if given after completing the meal. The short-acting insulin is also used to correct hyperglycemia.

The usual schedule for checking finger stick blood glucose and administering insulin is before all meals and sometimes also at bedtime. More recent guidelines also call for a check 2 hours after a meal to ensure the meal has been "covered" effectively. When insulin glargine or insulin detemir is used, it can be administered at any time during the day, provided that it is given at the same time every day, Dixit *et al* [6].

All the previous models were based on two variables only; glucose and insulin. None of the existing models considered external rates at which glucose, insulin and epinephrine are being increased.

II. PRELIMINARIES

Provided there is no recent digestion, glucose and insulin concentration will be in equilibrium, Ackerman *et al* [1]. If g is taken to be excess glucose concentration and h is excess insulin concentration at time t, then at equilibrium,

$g=h=0$; positive value of g or h corresponds to concentrations greater than the equilibrium values while negative values corresponds to concentrations less than equilibrium values.

If either h or g is a non-zero value then the body tries to restore the equilibrium. It is assumed that the rate of change of these quantities depend only on the values of g and h so that:

$$\frac{dg}{dt}=-ag-bh$$
$$\frac{dh}{dt}=cg-dh \qquad (1)$$

It is assumed that these differential equations are linear with constant coefficients. Assuming $g=h=0$ are equilibrium solutions, it follows that these linear differential equations must be homogenous.

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;

$$\frac{dg}{dt}= F_1(g,h)+J(t)$$
$$\frac{dh}{dt}= F_2(g,h) \qquad (2)$$

Food input source term, $J(t)$, is the source for food input to the plasma glucose level, the contents of which are reduced in a simple exponential manner. This process of meal absorption needs a description. A simple description of this was suggested by Fisher [8] and looks like this:

$$J(t)=Se^{-d_{rate}t}$$

where, S is the quantity constant of meal and d_{rate} is the delay parameter. He suggested that the meal absorption description should be a function which rapidly increases after the meal, and then decays to 0 in 2 to 3 hours.

Let $G(t)$ and $H(t)$ be the concentrations of blood glucose and insulin at time t, respectively. Then G and H satisfy;

$$\frac{dg}{dt} = F_1(G,H)+J(t)$$
$$\frac{dh}{dt} = F_2(G,H) \qquad (3)$$

It is known that after an overnight fast, the concentrations of glucose and insulin in the patient's blood stabilize at their optimal values, that is, G(t)≡constantG_0, H(t)≡ constant H_0. Using this fact, we can show that

$$F_1(g_0,h_0)=0=F_2(g_0,h_0).$$

Let $g=G-G_0$, $h=H-H_0$, then by (3), we have;

$$\frac{dg}{dt} = F_1(g+G_0, h+H_0)+J(t)$$

$$\frac{dh}{dt}=F_2(g+G_0, h+H_0) \qquad (4)$$

In case that g and h are small, (4) can be approximated by a linear system by the "tangent plane approximation"; Thus,

$$F_1(g+G_0, h+H_0) \approx F_1(G_0, H_0)+\frac{\partial F_1}{\partial G}(G_0, H_0)g+\frac{\partial F_1}{\partial H}(G_0, H_0)h$$

$$F_2(g+G_0, h+H_0) \approx F_2(G_0, H_0)+\frac{\partial F_2}{\partial G}(G_0, H_0)g+\frac{\partial F_2}{\partial H}(G_0, H_0)h$$

Thus (4) can be approximated by;

$$\frac{dg}{dt}=\frac{\partial F_1}{\partial G}(G_0, H_0)g+\frac{\partial F_1}{\partial H}(G_0, H_0)h+F(t)$$

$$\frac{dh}{dt}=\frac{\partial F_2}{\partial G}(G_0, H_0)g+\frac{\partial F_2}{\partial H}(G_0, H_0)h \qquad (5)$$

We recall $F_1(G_0, H_0)=0=F_2(G_0, H_0)$. This approximation is good if g and h are small. This procedure is called the linearization of (3) at point

$$(G_0, H_0)$$

From (5),

$$\frac{\partial F_1}{\partial G}(G_0, H_0), \frac{\partial F_1}{\partial H}(G_0, H_0), \frac{\partial F_2}{\partial G}(G_0, H_0), \frac{\partial F_2}{\partial H}(G_0, H_0)$$

are unknown because functions F_1 and F_2 are unknown.

$$\frac{\partial F_1}{\partial G}(G_0, H_0), \frac{\partial F_1}{\partial H}(G_0, H_0), \frac{\partial F_2}{\partial G}(G_0, H_0), \frac{\partial F_2}{\partial H}(G_0, H_0)$$

By using the Basic Biological Facts,

$\frac{\partial F_1}{\partial G}(G_0,H_0)$, $\frac{\partial F_1}{\partial H}(G_0,H_0)$, $\frac{\partial F_2}{\partial H}(G_0,H_0)$ are negative and $\frac{\partial F_2}{\partial G}(G_0,H_0)$ is positive.

Assuming that g=0, $\dot{h}$ will also be negative for h greater than 0. The liver will immediately start to degrade the insulin, since the insulin has exceeded its equilibrium value. Thus the constant d, must also be positive.

Similarly, b must be positive since a positive value of g causes the endocrine glands to secret those hormones which tend to increase h. Likewise, c must be positive since the concentration of hormones in the blood changes accordingly through hormone metabolism.

It is therefore in the form;

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

$$\frac{dh}{dt}= cg-dh \qquad (6)$$

where a , b , c and d are positive constants.

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

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

$$\frac{dh}{dt}= cg-dh+P(t) \qquad (7)$$

The insulin input P(t) will be given through injection at subcutaneous level at periodic intervals, which leaks its contents into the system over a period of time. Therefore, P(t) may be defined as;

$$P(t)=\frac{\rho t}{\bar{t}-t_0}+b$$

At $t=t_0$, $P(t)=0$

$$\Rightarrow b=-\frac{\rho t}{\bar{t}-t_0}$$

$$\therefore P(t)=\frac{\rho \bar{t}-t}{\bar{t}-t_0}=\lambda+\mu t$$

where,

$$\lambda=\frac{\rho t_0}{\bar{t}-t_0}, \mu=-\frac{\rho}{\bar{t}-t_0}$$

and ρ is quantity of injection, t_0 is time of injection, $\bar{t}$ is time lag to maximum, Nilam Nilam [9].

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.

Thus, if it is assumed that there is no recent digestion, the following systems of differential equations results;

$$\frac{dg}{dt} = F_1(g,h,e)$$

$$\frac{dh}{dt} = F_2(g,h,e) \qquad (8)$$

$$\frac{de}{dt} = F_3(g,h,e)$$

for some functions F_1, F_2 and F_3, where e represents epinephrine.

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 $g=h=e=0$ are equilibrium solutions, it follows therefore that these linear differential equations must be homogeneous.

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

$$\begin{aligned}\frac{dg}{dt} &= -ag-bh+fe+J(t)\\ \frac{dh}{dt} &= cg-dh+ke+P(t)\\ \frac{de}{dt} &= -lg-mh+ne+Z(t)\end{aligned} \tag{9}$$

with a, b, c, d, f, k, l, m and n as constants, Kwach, Ongati and Simwa [7]. This is in the form;

$$\begin{bmatrix}\dot{g}\\ \dot{h}\\ \dot{e}\end{bmatrix}=\begin{bmatrix}-a & -b & f\\ c & -d & k\\ -l & -mn & \end{bmatrix}\begin{bmatrix}g\\ h\\ e\end{bmatrix}+\vec{r}(t) \tag{10}$$

or more compactly as $\dot{Y}=AY+\vec{r}(t)$. This system can be solved explicitly once the constants are known.

III. THE TIME PERIOD FOR INSULIN TO BE MOST EFFECTIVE IN LOWERING BLOOD SUGAR

From the Mathematical Model in equation (9) for Drug Therapy in Patients with Diabetes Mellitus which includes external rate at which blood glucose, insulin and epinephrine are being increased in the form, $\dot{Y}=AY+\vec{r}(t)$, it was established that the resonance period for the final model, T_0=3.76912 hrs, is in the acceptable therapeutic range and agrees well with the data for the existing insulin therapy, Kwach *et al* [4].

From the model in equation (1);

$$\frac{dg}{dt}=-ag-bh$$

$$\frac{dh}{dt}=cg-dh$$

differentiating

$$\frac{dh}{dt}=cg-dh$$

of equation (1) w.r.t t gives,

$$\frac{d^2h}{dt^2}=c\frac{dg}{dt}-d\frac{dh}{dt} \tag{11}$$

Substituting $\frac{dg}{dt}=-ag-bh$ from equation (1) in equation (11) gives;

$$\frac{d^2h}{dt^2}+d\frac{dh}{dt}+acg+bch=0 \tag{12}$$

Also from equation (1),

$$\frac{dh}{dt}=cg-dh$$

which leads to

$$\Rightarrow g=\frac{1}{c}\left(\frac{dh}{dt}+dh\right) \tag{13}$$

Substituting equation (13) in equation (12) gives;

$$\frac{d^2h}{dt^2}+(a+d)\frac{dh}{dt}+(ad+bc)h=0 \tag{14}$$

which can be expressed in the form;

$$\frac{d^2h}{dt^2}+2\alpha\frac{dh}{dt}+\omega_0^2 g=0$$

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

$$\begin{aligned}\Rightarrow \omega_0^{\,2} &= (-2.92\times -0.78)+(-4.43\times 0.208)\\ &= 2.2976-0.90272\\ &= 1.39488\end{aligned}$$

$\Rightarrow\omega_0$=1.181050

$\Rightarrow T_0=\frac{2\pi}{\omega_0}=\frac{2\pi}{1.181050}$=5.3199 hours.

Table (3.1): Insulin and Glucose Plasma levels during an FSIGT test.

Time t(min)	Glucose g(mg/dl)	Insulin h(μU/ml)	Time t(min)	Glucose g(mg/dl)	Insulin h(μU/ml)	Time t(min)	Glucose g(mg/dl)	Insulin h(μU/ml)
0	92	11	16	196	35	72	84	11
2	350	26	19	192	30	82	77	10
4	287	136	22	172	30	92	82	8
6	251	85	27	163	27	102	81	11
8	240	51	32	142	30	122	82	7
10	216	49	42	124	22	142	82	8
12	211	45	52	105	15	162	85	8
14	205	41	62	92	15	182	90	7

For purely illustrative purposes, secondary values and raw data of insulin and glucose plasma levels during Frequently Sampled Intravenous Glucose Tolerance (FSIGT) test as shown in table (3.1) was used to show that, the peak, which is the time period for insulin to be most effective in lowering blood sugar, is in the acceptable therapeutic range, Pacini and Bergman [10].

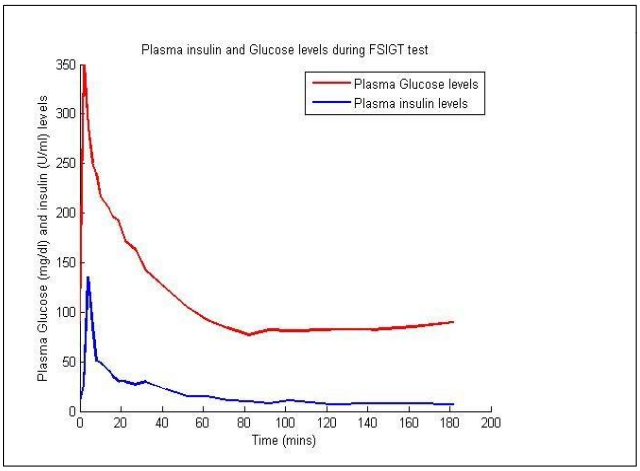

Figure 3.1 Insulin and Glucose Plasma levels during an FSIGT test.

IV. CONCLUTION AND RECOMMENDATION

This paper presents a Mathematical modeling of insulin therapies in Patients with Diabetes Mellitus described by equation (9). External rates at which blood glucose, insulin and epinephrine have been successfully incorporated in the existing model of blood glucose regulatory system (BGRS). The importance of these external rates lies in their ability to administer Insulin in such a way that the concentration remains in the therapeutic range. The model is expressed as a system of linear non-homogenous equations in the form $\dot{Y}=AY+\vec{r}(t)$ and whose solution is analyzed to provide the systems natural frequency, ω_0, which is the basic descriptor of saturation level of Insulin. It has been established that the resonance period for this 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, within a shorter time, is in the acceptable therapeutic range.

Patient factors, including individual variations in insulin absorption, levels of exercise, local massage, and, especially, local subcutaneous blood flow can influence the effectiveness of an insulin regimen. Short intense physical exercise can also accelerate the absorption of subcutaneously injected insulin. Future research may investigate these factors and take into consideration oral therapy in the treatment of Diabetes Mellitus.

V. ACKNOWLEDGEMENT

Special thanks to Dr. Amos Otedo of Kisumu East District Hospital, Kisumu, Kenya, for his valuable comments and allowing us to access the secondary data; Norrine Kawour, a Medical student at Boston University of Medicine, USA for her useful comments on one of our discussions and anonymous reviewers for their input.

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