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Stability Analysis of Detecting Diabetics on Blood Glucose Regulatory Systems

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ABSTRACT

In this paper, we investigate the stability of blood glucose regulatory system. This fact is used to diagnose diabetes in the context of glucose tolerance test. The second order differential equation, which result in the formulation to describe the glucose tolerance test during the performance of blood glucose regulatory system (BGRS) and its stability analyzed here. The model has been used to analyze two cases of the glucose level to find whether the glucose level is stable and where the glucose level is unstable.

Keywords : Mathematical Modeling, Diabetes, Glucose Tolerance Test, Stability

I. INTRODUCTION

The study of stability analysis of blood glucose regulatory system is important in diagnose diabetes in the context of glucose tolerance test. The paper has been discussed about the model to analyze two cases of the glucose level.

Several authors have studied the stability of blood glucose regulatory system. To mention just a few, RA, Cobelli [1] investigated the meal simulation model of the glucose insulin system. In a related system wilinska, ME, chassin,LJ, allen, JM, dunger , DB, hovorka [2] investigated the simulation environment to evaluate closed-loop insulin delivery system in type 1 diabetes. In the same way Kanderiaet.al [3] investigated about the identification of intraday metabolic profiles during closed-loop glucose control in individuals with type 1 diabetes. Steil, and Reifman [4] discussed about mathematical modeling research to support the development of automated insulin-delivery systems. Alan Osborne [5] studied about the mathematical model for the detection of diabetes. Braun, martin [6] studied about the Differential equation and their applications. E.Ackerman et.al [7] investigated about the blood glucose regulation and diabetes in the concepts and models of biomathematics. Ingrid and Edelman [8] studied about the evaluation and treatment of diabetic foot ulcers. Moller [9] discussed about the stochastic state space modeling of nonlinear systems-with application to marine ecosystems. Kanderian, Weinzimer, and Steil [10] studied about the identifiable virtual patient model: comparison of simulation and clinical closed-loop. Kristensen, NR, Madsen, H, Ingwersen, SH [11] investigated using stochastic differential equations for PK model development. Tornoe, Overgaard, Agerso, Nielsen, Madsen and Jonsson, [12] investigated about the stochastic differential equations in NONMEM : implementation, application and comparison with ordinary differential equations. Martin Brau, [13] studied about a model for the detection of diabetes. Dr. Dimplekumar chalishajar, Caret Andrew C.Stanford, [14] discussed mathematical analysis of insulin-gulcose feedback system of diabete. Tolic, Iva M, Eri Mosekilde and Jeppe sturis. [15] Investigated about the Modeling the insulin-glucose feedback system: the significance of pulsatile insulin secretion.

This Paper is organized as follows. In section 2 preliminaries and basic definitions are given. Mathematical modeling and analysis have been given in section3. Section 4 includes some examples to illustrate the proposed theory and finally conclusion isdrawn.

Preliminary:

1. This section describes the basic definition of stability and prevailing research work.

Definition 1: Stability of a linear system.

Consider the following linear differential equation

$$X'\langle t\rangle = A\,X\langle t\rangle \quad (1)$$

With initial condition

$X(0) = x_0 = (x_{10}, x_{20}, \dots\dots.., x_{n0})^T$

Where $X = (x_1, x_2, \dots\dots\dots., x_n)^T$ and $A \in R^{n\times n}$

The autonomous system (1) is said to be stable

I. Stable iff for any x_0, there exist, $\varepsilon > 0 \ni \|X\langle t\rangle\| \le t$ for $t \ge 0$

II. Asymptotically stable iff $\lim_{t\to\alpha}\|X\langle t\rangle\| = 0$.

Solution representation of a given system can be found by using Laplace Transform Techniques.

Solution representation of a liner homogeneous system

Let us consider the system of the form

$$X'\langle t\rangle = AX\langle t\rangle$$

where $X\langle 0\rangle = x_0$

Taking Laplace transform on both sides

$$S\,X\langle S\rangle - X\langle 0\rangle = A\,(X)$$

$$X\langle S\rangle = \frac{x_0}{S-A}$$

By using inverse Laplace transform

$$X\langle t\rangle = e^{AT}.x_0$$

Solution representation of a liner non homogeneous and nonlinear system

Let us consider the system of the form

$$X'\langle t\rangle = AX\langle t\rangle + f\langle x\rangle$$

Taking Laplace Transform on both the sides

$$SX\langle S\rangle - X\langle 0\rangle = AX\langle S\rangle + f\langle x\rangle$$

$$X\langle S\rangle = \frac{x_0}{S-A} + \frac{f\langle x\rangle}{S-A}$$

$$= \frac{x_0}{S-A} + L[e^{At}].L[f\langle x\rangle]$$

$$= \frac{x_0}{S-A} + L[e^{At} * f\langle x\rangle]$$

By using the definition of convolution and applying Inverse Laplace transform, we get

$$x\langle t\rangle = e^{At}x_0 + e^{At} * f\langle x\rangle$$

$$x\langle t\rangle = e^{At}x_0 + \int_0^t e^{A\langle t-S\rangle}.f\langle x\langle S\rangle\rangle\, dS$$

2. **Stability analysis:**

Consider the liner system of the form

$$x\langle t\rangle = A.X\langle t\rangle \quad (a)$$

with the initial condition x(0)=x₀. Where A is a $n \times n$ matrix

Theorem 1: Let e^{At} be a fundamental matrix of (a). Then (a) is stable iff ∃ a constant K>0 with

$$\|\mathbf{e^{At}}\| \le \mathbf{K} \quad (b)$$

Proof:

Assume (b) holds and let $X\langle t\rangle$ be the solution of (a) with $x\langle 0\rangle = x_0$

Then, since $x\langle t\rangle = e^{At}x_{0,}$ if for a given $\in > 0$

Choose $\delta = \frac{\epsilon}{K}$,

We have, $\|x\langle t\rangle\| = \|e^{At}x_0\| < \in$ for $\|x_0\| < \delta$

=>Thus (a) is stable

Conversely, suppose (a) is stable and fix $\in > 0, \delta > 0$ with

$$\|e^{At}x_0\| < \epsilon\ \forall\, x_0 \in R^n \text{ With } \|x_0\| < \delta$$

$$\frac{\|e^{At}x_0\|}{\delta} = \left\|\frac{e^{At}x_0}{\delta}\right\| < \frac{\in}{\delta}$$

Since $\frac{x_0}{\delta}$ range over the interior of the unit ball, we obtain

$$\|e^{At}\| = \sup\{\|e^{At}x_0\|: \|y\| < 1\} < \frac{\epsilon}{d}$$

This completes the proof

Theorem 2: The system (a) is asymptotic stable iff

$\|e^{At}\| \to 0$ **as** $t \to \infty$ **(c)**

Proof:

Assume (c) holds

i.e. $\|e^{At}\| \to 0$ as $t \to \infty$

Then (b) holds $\|e^{At}\| \leq K$ holds for some $t > 0$ and

$\lim_{t\to\infty} x\langle t\rangle = \lim_{t\to\infty} x\langle t\rangle x_0 = 0$ for any t. $\langle 0\rangle = x_0$

Thus (a) is asymptotically stable.

Conversely, assume system (a) is asymptotically stable, by using the definition, Equation (c) holds explicitly. This completes the proof.

II. MAIN WORK

Formulation of Mathematical Model

Diabetic blood glucose level has been formulated in two steps.

Step 1

In the first step, assumptions have been stated, have to identify suitable variables and give the law governing the performance of BGRS.

(i) The following two concentration describe the performance of blood glucose regulatory system

1. Concentration of glucose in the blood(X).
2. Concentration of Net Hormonal (Y).

With the following sign convection, by net hormonal concentration, it means the cumulative effect of all the relevant hormones. When the contribution is negatively to Y the hormones which increases BGC for example Cortisol. The hormones which decrease blood glucose concentration For example insulin are regarded to increase Y and their contribution to Y is taken with positive sign.

(ii) Since, we are considering X and Y as dependent variables with t as the independent variable X and Y changes with time.

(iii) From the elementary consideration of the biological facts, In above, the logistic law which is governing the performance of BGRS may be written as

$$\frac{dX}{dt} = F_1\langle X, Y\rangle + E(t) \qquad (1)$$

$$\frac{dY}{dt} = F_2\langle X, Y\rangle \qquad (2)$$

Where f_1 and f_2 are some functions of X and Y, While E(t) is the external rate at which the BGC is being increased.

Step 2(construction of mathematical model)

Second order differential equation has been formulated to describe the performance of BGRS during GTT.

X_0 and Y_0 are the optimal values of X and Y respectively. Here main interest is in studying the derivatives of G and H from their optimal value therefore we have

$$x = X - X_0 \text{ and } y = Y - Y_0 \qquad (3)$$

Substituting these values in equation (1) and (2), and Taylor's expansion,

We get,

Where, $F_{10} = f_{(G_0,H_0)}$

$$\frac{dx}{dt} = \left[f_{10} + x\langle\frac{\partial f_1}{\partial X}\rangle^\circ + y\langle\frac{\partial f_1}{\partial Y}\rangle^\circ + C_1\right] + E(t)$$

$$\frac{dx}{dt} = \left[f_{10} + x\langle\frac{\partial f_{10}}{\partial X}\rangle + y\langle\frac{\partial f_{10}}{\partial Y}\rangle + C_1\right] + E(t) \qquad (4)$$

Where, $F_{20} = f_{(G_0,H_0)}$

$$\frac{dy}{dt} = \left[f_{2o} + x\langle\frac{\partial f_2}{\partial X}\rangle^\circ + y\langle\frac{\partial f_2}{\partial Y}\rangle^\circ + C_2\right]$$

$$\frac{dy}{dt} = \left[f_{2o} + x\langle\frac{\partial f_{20}}{\partial X}\rangle + y\langle\frac{\partial f_{20}}{\partial Y}\rangle + C_2\right] \qquad (5)$$

Where $\langle\frac{\partial f_{10}}{\partial x}\rangle$ denotes $\langle\frac{\partial f_{10}}{\partial x}\rangle X = X_0$ etc., and C_1 and C_2 contains terms of second and higher powers in g and h.

I. Here we can note that $f_{10} = 0, F_{20} = 0$ because it is assumed that G and H have assumed their optimal values X_0 and Y_0 respectively by the time the fasting patient arrives at the hospital,and

II. E_1 and E_2 , being small quantities, may be nrglected;for the case of mild diabetes, x and y are small. With these conditions, equation (4) and (5) becomes

$$\frac{dx}{dt} = \left[x\langle\frac{\partial f_{10}}{\partial X}\rangle + h\langle\frac{\partial f_{10}}{\partial Y}\rangle\right] + E(t)$$
(6)

$$\frac{dy}{dt} = \left[x\langle\frac{\partial f_{20}}{\partial X}\rangle + y\langle\frac{\partial f_{20}}{\partial Y}\rangle\right]$$
(7)

There are a priori no methods to find the values of the numbers $\langle\frac{\partial f_{10}}{\partial X}\rangle, \langle\frac{\partial f_{10}}{\partial Y}\rangle, \langle\frac{\partial f_{20}}{\partial X}\rangle$ and $\langle\frac{\partial f_{20}}{\partial Y}\rangle$, but we may ascertain their signs in the following way:

A. Sign of $\langle\frac{\partial f_{10}}{\partial X}\rangle$

It is considering x>0, y=0 that is excessive glucose leads to account of the tissue uptake of glucose that BGC will be decreasing and the excess of glucose stored in the form of glucose, that is, $\frac{dx}{dt} < 0$, implies that $\langle\frac{\partial f_{10}}{\partial X}\rangle$ must be negative.

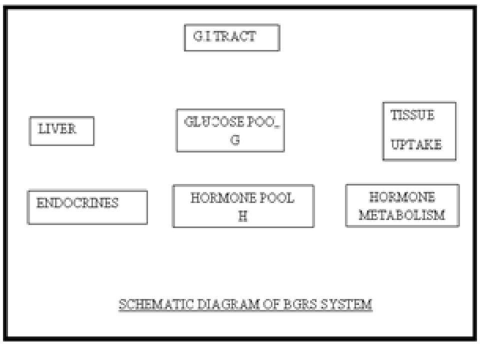


Figure A

B. Sign of $\langle\frac{\partial f_{10}}{\partial Y}\rangle$

It is considering y>0, x=0 that is excessive insulin leads to facilitating tissue uptake of glucose that is $\frac{dy}{dt} < 0$ because excessive insulin will decrease BGC and by increasing the rate at which is converted to glycogen, implies that $\langle\frac{\partial f_{10}}{\partial Y}\rangle$ must be negative.

C. Sign of $\langle\frac{\partial f_{20}}{\partial X}\rangle$

It is considered that x>0,y=0 that is excessive insulin). In this case $\frac{dx}{dt} > 0$, it is well known that after we eat any carbohydrates, the processes G.I tract sends a signal to the pancreas to decrease more insulin. Then $\langle\frac{\partial f_{20}}{\partial X}\rangle$ must be positive.

D. Sign of $\langle\frac{\partial f_{20}}{\partial Y}\rangle$

It is considering y>0, x=0(excessive insulin). Equation (7) implies that $\langle\frac{\partial f_{20}}{\partial Y}\rangle$ must be negative. while the hormone concentration decreases due to hormone metabolism

With the considering of above signs equations (6) and (7) can rewrite as

$$\frac{dx}{dt} = -\theta_1 x - \theta_2 y + E(t) \qquad (8)$$

$$\frac{dy}{dt} = \theta_3 x - \theta_4 x \qquad (9)$$

Where $\theta_1, \theta_2, \theta_3$ and θ_4 are all positive constants

Differentiating equation (8) w.r.t time gives,

$$\frac{d^2x}{dt^2} = -\theta_1 \frac{dx}{dt} - \theta_2 \frac{dy}{dt} + \frac{dE}{dt} \qquad (10)$$

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

$$\frac{d^2x}{dt^2} = -\theta_1 \frac{dx}{dt} - \theta_2\theta_3 x + \theta_2\theta_4 y + \frac{dE}{dt} \qquad (11)$$

Now substituting the value of $\theta_2 y$ from equation(8) in equation(11), and rearranging the term

We get,

$$\frac{d^2x}{dt^2} + 2\alpha\frac{dx}{dt} + \omega^2 x = M(t) \qquad (12)$$

Where $2\alpha = (\theta_1 + \theta_4), \omega^2 = \langle\theta_1\theta_4 + \theta_2\theta_3\rangle$ and $M(t) = \theta_4 E(T) + \frac{dE}{dt}$

Equation (12) is a second order differential equation with constant co-efficient which governs the BGRS after a heavy load of glucose is ingested.

If $M(t) \neq 0, M\langle t\rangle = e^{-at}$ where a is constant adoption rate then equation (12) becomes

$$\frac{d^2x}{dt^2} + 2\alpha\frac{dx}{dt} + \omega^2 x = e^{-at}$$

Here first main in studying the basic system and if t=0 is defined to be the instant when the glucose load is completely ingested, then equation (12) will be

$$\frac{d^2x}{dt^2} + 2\alpha\frac{dx}{dt} + \omega^2 x = 0 \qquad (13)$$

Equation (13) may be identified as the standard equation governing damped vibration [1]. Now analyzing the model in two steps. In first step solution is obtained and in second step interpretation of the result has been discussed.

Analysis of the model:

The auxiliary equation of (13) is

$x'' + 2 \propto x' + \omega_0^2 x = 0$, where

$\propto = \frac{\theta_1+\theta_4}{2}$, $\omega_0^2 = \langle\theta_1\theta_4 + \theta_2\theta_3\rangle$

Let $x_1 = x, x_2 = x'$

On Differentiating x_1 and x_2

We get,

$x' = x_2, x_2' = -2\alpha x_{2-}\omega^2 x_1$

$$\begin{bmatrix} x_1' \\ x_2' \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\omega_0^2 & -2\alpha \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

This can be written in the matrix form $X' = AX$

Where A = $\begin{bmatrix} 0 & 1 \\ -\omega^2 & -2\alpha \end{bmatrix}$ and X=$\langle x_1, x_2\rangle$

Eigen value of A can be found by putting

$Det\langle A - \lambda I\rangle = o\ is \begin{bmatrix} 0-\lambda & 1 \\ -\omega^2 & -2\propto \end{bmatrix} = 0$

Characteristic equation is given by $\lambda^2 + 2 \propto \lambda + \omega^2 = 0$ and

Corresponding eigenvalues are given by

$$\lambda = \alpha \pm \sqrt{\propto^2 - \omega^2}$$

Three cases have been considered to analyze the model.

Case 1:

$\propto^2 - \omega_0^2 < 0$, then the eigen values are real and distinct.

Solution of (1) is given by

X(t) = $e^{\alpha t}\left[Ae^{\sqrt{\alpha^2-\omega^2}}\ t + Be^{-\sqrt{\alpha^2-\omega^2}}\ t\right]$by using

If the eigenvalues have the negative real part, then the given system is stable by using theorem 1.

Case 2:

$\propto^2 - \omega_0^2 = 0$, then the given system will have repeated eigen value.

The Solution is in the form of x(t) = (A+B)$e^{\alpha t}$

In this case, stability not only depend on the negative sign of the eigenvalues but also the geometric multiplicity.

Case 3:

$\propto^2 - \omega_0^2 < 0$, then the eigen value are imaginary

The solution is in the form of

X(t) = $e^{\alpha t}\left[A\cos\sqrt{\alpha^2-\omega^2}\ t + B\sin\sqrt{\alpha^2-\omega^2}\ t\right]$

In this case, stability depends upon the negativity of the eigenvalue.

III. EXAMPLES

Some examples are illustrated to show applicability of the proposed theory. The proposed method helps in finding the stability by analyzing the eigenvalue of the corresponding system. It can be noted that one may find the stability of the system actually without solving the system explicitly

Example1:

Consider $\theta_1 = 3 , \theta_2 = 0 , \theta_3 = 5 , \theta_4 = 1$

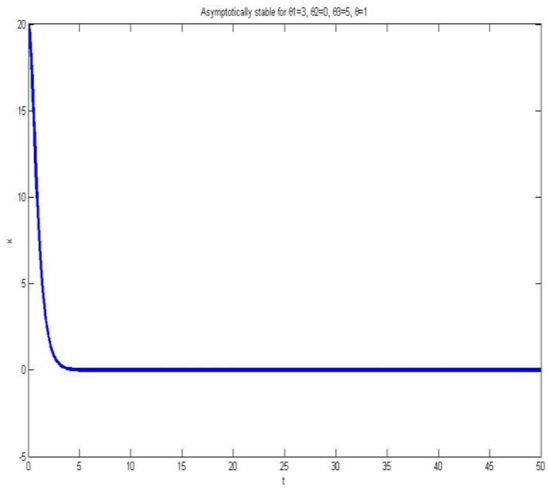
Then $\alpha = 2$ *and* $\omega = 2$.

Then the characteristic equation is $\lambda^2 + 4\lambda + 4$=0

Eigen values are λ = -2,-2

Eigen values are negative. Hence the given system is stable.

This can be seen in the following figure.



Example 2:

Consider $\theta_1 = 1/2 , \theta_2 = 3/2 , \theta_3 = 1/2 , \theta_4 = 1/2$

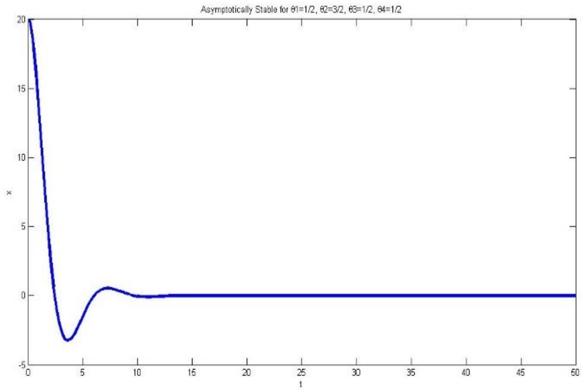
Then $\alpha = 2$ *and* $\omega = 2$

Then the characteristic equation is $\lambda^2 + \lambda + 1$=0

Eigen values are $\frac{-1\pm\sqrt{3i}}{2}$, whose real parts are negative.

Hence the given system is stable.

This can be seen in the following figure.



Example 3:

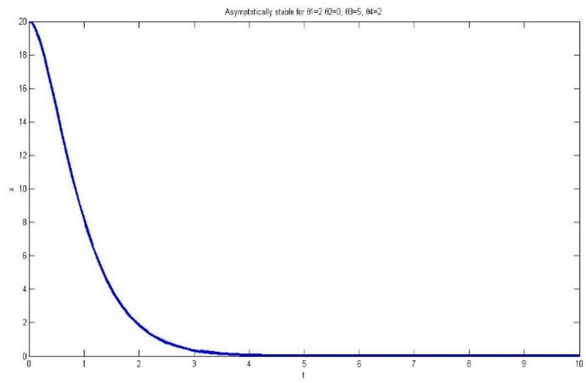
Consider $\theta_1 = 2 , \theta_2 = 0 , \theta_3 = 5 , \theta_4 = 2$

Then $\alpha = 1$ *and* $\omega = 2$

Then the characteristic equation is $\lambda^2 + 2\lambda + 4$=0

Roots are $-1 \pm 1.7321i$, The given system has negative real parts

Hence the system is stable. This can be seen in the following figure.



IV. CONCLUSION

In this paper, the stability of blood glucose regulatory system is studied. This fact is used to diagnose diabetes in the context of glucose tolerance test. From the result, the model has been used to analyze two cases of the glucose level. Where the glucose level is stable and where the glucose level is unstable.

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