A Mathematical Model For The Study Of Diabetes Mellitus

R Yadav¹ and Maya²
¹Associate professor, Lovely Professional University, Punjab, India
²Student M.Sc. Mathematics(Hons), Lovely Professional University, Punjab, India

Email: rakesh.21798@lpu.co.in, ralhmaya3@gmail.com

Abstract. This paper focuses on a latest approach to study the diabetes mellitus. A new mathematical model of all glucose-insulin interactions is proposed by the incorporation of time delay. Then the mathematical model is formulated, and after that the analysis of the model is discussed. In order to confirm the theoretical results, we carried out the numerical simulations. Computer simulations are used to evaluate the effectiveness of the proposed work. Also, the behaviour of proposed mathematical model for different values of time delay will be shown.

1. Introduction

Diabetes Mellitus, usually called as diabetes is a cluster of several symptoms indicating disordered metabolism, thought to be caused by variety of factors based upon inheritance and surroundings or environment, that finally result in irregular sugar levels in bloodstream, also known as hyperglycaemia [1].

In all the living beings, body cells need energy in order to function properly and that energy is provided by glucose. During food intake, the carbohydrates thus obtained split up to form glucose. Therefore, after every meal intake, the glucose level rises in our bodies. At that point of time, the role of insulin comes in picture. Insulin is basically a hormone secreted by the pancreas to control the levels of glucose in the bloodstream. The unbounded glucose in our body is mainly absorbed by this produced insulin. If this whole procedure of regulating levels of glucose in bloodstream fails then diabetes occurs [4].

Diabetes Mellitus occurs as result of two types of failures in controlling the glucose levels in our bodies and the two types are named as type I and type II. Type I diabetes takes place when the pancreas is not capable of secreting required amount of insulin in order to absorb free blood glucose [7]. This type of diabetes cannot be cured. Due to which, in order to survive, patients suffering from type I diabetes mellitus are required to take insulin multiple times a day by artificial methods such as injections or pills[9]. On the other hand, type II diabetes turns out when secreted insulin is not capable of attaching with body cells to take in and hold the additional sugar from the bloodstream [3].

For a normal healthy person, the concentration of glucose in blood is managed within a secure range of 70-150mg/dl as insulin is secreted by the pancreas. When almost negligible or no such secretion occurs in a human body, results in a chronic disorder called type I diabetes mellitus. Type I diabetic patients have prolonged hyperglycaemia with blood glucose concentration regulated within the range greater than 150mg/dl [8]. As this open loop, the insulin therapy of taking insulin injections is all based upon measuring irregular glucose levels, therefore, in few situations, when a patient takes improper dosages of insulin, blood glucose concentration can severely fall less than 50mg/dl, causing an instant condition called as hypoglycaemia. This kind of sudden situation in type I diabetic patients can even be the reason of death and coma, while on the other hand hyperglycaemia can cause many long-term complexities such as heart failures, retinal vascular disease, leg or foot amputations [2].
Clearly, to control glucose levels, simple and effective interventional measures like regular exercise, eating healthy, eating on time can turn out to be a large contribution in preventing this chronic disorder diabetes mellitus.

Mathematical modelling deals with abundance of literature. These models have provided a simpler way to get proper knowledge of Diabetes dynamics. Several exciting mathematical models including glucose-insulin interaction and epidemiology of diabetes are based upon totally unique aspects of diabetes during the last decades in general [7]. There are many other models based on glucose and insulin distributions and those models can be used to explain the interaction between glucose and insulin. All these models are valid under certain conditions and assumptions.

2. Formulation of mathematical model

One of the most intriguing topics is mathematical modelling of glucose-insulin interaction. Various mathematical models were built to predict and to get proper understanding of the glucose-insulin dynamics. In this paper, we are proposing following general mathematical model for glucose-insulin interaction under the consideration of time delay.

\[
\frac{dx}{dt} = -p_1 x(t) - px(t - s)y(t - s) + p_3, t \in [0, T] \ldots (1)
\]

\[
\frac{dy}{dt} = r_1 x(t) - r_2 y(t), t \in [0, T] \ldots (2)
\]

with initial conditions given as:

\[
x(\varphi) = \mu(\varphi), \varphi < 0, \ldots (3)
\]

\[
y(\varphi) = \psi(\varphi), \varphi < 0, \ldots (4)
\]

Here \(x, y\) are both positive. \(x\) and \(y\) are appointed as blood glucose concentration and insulin concentration respectively, rate constant \(p_1\) is representing disappearance of glucose that is insulin independent, rate constant \(p_2\) is representing disappearance of glucose that is insulin dependent, \(p_3\) is rate of glucose infusion, rate constant \(r_1\) is representing insulin produced by glucose stimulation, rate constant \(r_2\) is appointed degeneration of insulin and \(s\) here represents the time delay which explains time taken to show some response by the pancreas to the feedback of level of glucose.

In the remaining part of this paper we will analyse the qualitative behaviour of the model. After that, we will describe the numerical methods used to find the solution of the proposed model. Then, for different values of the time delay, we show the behaviour of the proposed model. In the end, these conclusions are discussed.

3. Mathematical model’s analysis

Now the qualitative analysis of the behaviour of proposed mathematical model shall be discussed. In this, we shall now do the investigation of the delay system of coupled equations (1) & (2) mentioned in formulation. The equilibrium point of the equations (1) & (2) is

\[
x(t) = x(t - s) = x(0) = x^* \forall t,
\]

\[
y(t) = y(t - s) = y(0) = y^* \forall t
\]

as a result, all the derivatives with respect to time vanish identically. Hence, on putting

\[
x(t) = x(t - s) and \dot{x} = 0,
\]

\[
y(t) = y(t - s) and \dot{y} = 0,
\]

in equations (1) & (2), we obtain

\[
0 = -p_1 x^* - p_2 x^* y + p_3 \ldots (4a)
\]

\[
0 = r_1 x^* - r_2 y^* \ldots (4b)
\]

after applying arithmetic operations on both the above equations, we get

\[
p_2 r_1 x^2 + p_1 r_2 x^* - p_3 r_2 = 0
\]

On solving this quadratic equation, the fixed or equilibrium point \((x^*, y^*)\) is as follows:

\[
x^* = \frac{-p_1 r_2 + \sqrt{(p_1 r_2)^2 + 4 p_2 r_2 p_3 r_1}}{2 r_2 p_2}
\]

\[
y^* = \frac{-p_1 r_2 + \sqrt{(p_1 r_2)^2 + 4 p_2 r_2 p_3 r_1}}{2 r_2 p_2}
\]
$x^* \geq 0$ and $y^* \geq 0$ since all the involved parameters are thought to be positive. So, the interior-equilibrium point $B_1 = (x^*, y^*)$ exists unconditionally.

The linearized model can be obtained about this equilibrium point $B_1$ of the model equations (1) & (2), let $u(t) = x(t) - x^*$, $v(t) = y(t) - y^*$, thus,

\[
\begin{align*}
\frac{du}{dt} &= -p_1 u(t) - p_2 y^* u(t - s) - p_2 x^* v(t - s) - p_2 u(t - s) v(t - s) - p_1 x^* - p_2 x^* y^* + p_3, \quad \cdots (5) \\
\frac{dv}{dt} &= r_1 u(t) - r_2 v(t) + r_1 x^* - r_2 y^*. \quad \cdots (6)
\end{align*}
\]

After the removal of nonlinear terms and by using equilibria conditions, we get the linear vibrational system as

\[
\begin{align*}
\frac{du}{dt} &= -p_1 u(t) - p_2 y^* u(t - s) - p_2 x^* v(t - s) \quad \cdots (7) \\
\frac{dv}{dt} &= r_1 u(t) - r_2 v(t) \quad \cdots (8)
\end{align*}
\]

Thus, from the obtained linearized model the characteristic equation is

\[
\Delta(\xi, s) = \xi^2 + p\xi + (r\xi + l)e^{-\xi s} + m = 0 \quad \cdots (9a)
\]

Here,

\[
p = p_1 + r, \quad r = p_2 y^*, \quad l = p_2 r_1 x^* + p_2 r_2 y^* \quad \text{and} \quad m = p_1 r_2.
\]

Putting $s = 0$, we get the equation (9) as follows

\[
\Delta(\xi, 0) = \xi^2 + (p + r)\xi + l + m = 0 \quad \cdots (9b)
\]

Clearly, sum of roots of $= -(p + r)$ and product of roots=$l + m$.

Thus, it can be seen that both the roots of equation (9b) are negatively real or complex conjugate with real parts(<0) if and only if

\[
p + r > 0 \quad \text{and} \quad l + m > 0 \quad \cdots (10)
\]

Hence, for $s = 0$, the equilibrium point $B_1$ is locally asymptotically stable in the absence of time delay if and only if both conditions $p + r > 0$ and $l + m > 0$ hold simultaneously.

The interior-fixed point $B_2$ is locally asymptotically stable when $s = 0$ if

\[
(r_1 - p_2 x^*)^2 < 4r_2(p_1 + p_2 y^*) \quad \cdots (11)
\]

Now for $s \neq 0$, if $\xi = i\omega$ is a root of characteristic equation (9a), then $\omega$ ($\omega > 0$) satisfy the equations given as

\[
\begin{align*}
\omega r \sin\omega + l \cos\omega &= \omega^2 - m \quad \cdots (12) \\
\omega r \cos\omega - l \sin\omega &= -p\omega \quad \cdots (13)
\end{align*}
\]

Adding the squares of both the above equations, we get

\[
\begin{align*}
\omega^2 r^2 \sin^2\omega + l^2 \cos^2\omega + 2\omega r \sin\omega \cos\omega + \omega^2 r^2 \cos^2\omega + l^2 \sin^2\omega \\
-2\omega r \sin\omega \cos\omega \omega^2 = \omega^4 + m^2 - 2\omega^2 m + p^2 \omega^2
\end{align*}
\]

\[
\Rightarrow \omega^2 r^2 (\sin^2\omega + \cos^2\omega) + l^2 (\sin^2\omega + \cos^2\omega) = \omega^4 + m^2 - 2\omega^2 m + p^2 \omega^2
\]

\[
\Rightarrow -\omega^2 r^2 - l^2 + \omega^4 + m^2 - 2\omega^2 m + p^2 \omega^2 = 0
\]

\[
\Rightarrow \omega^4 + (p^2 - r^2 - 2m)\omega^2 + m^2 - l^2 = 0 \quad \cdots (14)
\]

On solving, we obtain

\[
\omega^2 = \left[\left(-(p^2 - r^2 - 2m)\right) \pm \sqrt{(p^2 - r^2 - 2m)^2 - 4(m^2 - l^2)}\right] / 2
\]

From equation (14), it follows that if

\[
p^2 - r^2 - 2m > 0 \quad \text{and} \quad m^2 - l^2 > 0 \quad \cdots (15)
\]

then equations (12) & (13) do not have any real solutions. From equation (14), we observe that there exists a unique positive solution $\omega_+^2$ if

\[
l^2 - m^2 < 0 \quad \cdots (16)
\]

If $m^2 - l^2 > 0$, $r^2 - p^2 - 2m > 0$, and $(r^2 - p^2 - 2m)^2 > 4(m^2 - l^2) \quad \cdots (17)$

hold, then there exists two positive solutions $\omega_+^2$.

The necessary and sufficient conditions for nonexistence of instability induced due to time delay can be found by using following theorem:

3.1. Theorem 1a

A set of necessary and sufficient conditions for $B_1$ to be locally asymptotically stable for all $s \geq 0$ is the following:

All the roots of $\Delta(\xi, 0) = 0$ have real parts which are also negative.
For all real roots and $s \geq 0$, $\Delta(i\omega, s) \neq 0$, $i = \sqrt{-1}$.

3.1.1. Theorem 2a. If conditions given in equation (10) and equation (15) and theorem 1a are satisfied, then equilibrium $B_1$ is asymptotically stable for all $s < s_0$ and unstable for $s > s_0$. Moreover, as $s$ increases through $s_0$, $B_1$ bifurcates into small amplitude periodic solutions, where $s_0 = s_{0j}$ as $j = 0$.

Proof: For $s = 0$, $B_1$ is asymptotically stable if condition equation (10) holds. Hence, by Butler’s lemma, $B_1$ remains stable for $s < s_0$. We need to show that

$$\frac{d(\text{Re} \xi)}{ds} \bigg|_{s=s_0, z=z_0} > 0.$$ 

This will imply that there exists at least one eigen value with positive real part for $s > s_0$. Furthermore, the conditions of Hopf bifurcation[2] are then satisfied yielding the required periodic solution.

Substituting $z_0^2$ into equation (11) and solving for $s$, we get

$$s_{0j} = \frac{1}{z_0} \arctan\left( \frac{z_0 (pl-rm+rz_0^2)}{prz_0^2+(m-z_0^2)} \right) + \frac{2j\pi}{z_0}, j = 0, \pm1, \pm2, \ldots.$$ (18)

Substituting $z_0^\pm$ into equation (12) and solving for $s$, we obtain

$$s_+^q = \frac{1}{z_+} \arctan\left( \frac{z_+ (pl-rm+rz_+^2)}{prz_+^2+(m-z_+^2)} \right) + \frac{2q\pi}{z_+}, q = 0,1,2,\ldots.$$ (19)

Now differentiating equation (9) w.r.t. $s$, we obtain

$$\left[ 2\xi + p + re^{-\xi s} - s(r\xi + 1)e^{-\xi s} \right] \frac{d\xi}{ds} = \xi e^{-\xi s}(r\xi + 1) \ldots.$$ (20)

Thus

$$\left( \frac{d\xi}{ds} \right)^{-1} = \frac{2\xi + p}{-\xi^2 + p\xi + 1} + \frac{r}{\xi(r\xi + 1)} - \frac{s}{\xi} \ldots$$ (22)

And by using

$$e^{-\xi s} = - \left( \frac{\xi + p\xi + m}{r\xi + 1} \right)$$

We obtain

$$\text{sign} \left( \frac{d(\text{Re} \xi)}{ds} \right) \bigg|_{\xi=-z} = \text{sign} \left( \text{Re} \left( \frac{d\xi}{ds} \right)^{-1} \right) = \text{sign} \left[ \frac{2(z^2-m+p^2)}{(-z^2+m)^2+z^2} - \frac{r^2}{l^2+r^2z^2} \right] \ldots$$ (21)

It follows that

$$\frac{d(\text{Re} \xi)}{ds} \bigg|_{s=s_0, z=z_0} > 0$$

Thus, the transversality condition holds, and hence, Hopf bifurcation occurs at $s = s_0$. Hence proof is completed.

4. Description of numerical method

Let $M$ be any positive integer and $g = \frac{T}{M}$. Let $t_i = i \cdot g$, for $i = 0, \ldots, M$.

Let $x^i \approx x(t_i)$ and $y^i \approx y(t_i)$. Then, we can approximate the model equations (1) & (2) by the non-standard finite difference formula:
\[
\frac{x^{i+1} - x^i}{g} = -p_1x^{i+1} + p_2 - p_2x^i y^i, \ i = 0, \ldots, M - 1
\]
\[
\frac{y^{i+1} - y^i}{g} = r_1 x^i - r_2 y^i, \ i = 0, \ldots, M - 1
\]
From which we obtain two relations:
\[
x^{i+1} = \frac{x^i + g(p_2 - p_2x^i y^i)}{1 + gp_1}, \ i = 0, \ldots, M - 1 \quad \text{(22)}
\]
\[
y^{i+1} = \frac{y^i + gr_1 x^i}{1 + gr_2}, \ i = 0, \ldots, M - 1 \quad \text{(23)}
\]
Where, \(x^i\) approximates \(x(t_i - s)\) and \(y^i\) approximates \(y(t_i - s)\).
Let
\[H = \left\lfloor \frac{s}{g} \right\rfloor,
\]
then \(s \approx H \cdot g\). Now \(x(t_i - s)\) can be approximated by \(x(t_{i-H})\) for \(i \geq H\) and \(y(t_i - s)\) can be approximated by \(y(t_{i-H})\) for \(i \geq H\).
Then,
\[y(t_i - s) = \begin{cases} 
\phi(t_i - s) & i \leq H \\
y^i_{i-H} & i \leq H \end{cases} \quad \text{(24)}
\]
and
\[y(t_i - s) = \begin{cases} 
\phi(t_i - s) & i < H \\
y^i_{i-H} & i \geq H \end{cases} \quad \text{(25)}
\]
5. Numerical Methods
In this segment, some numerical methods associated with the theoretical predictions are given. Also, our theoretical results are verified by providing examples and some numerical simulations or methods proved using MATLAB program.
We consider the system:
\[
\frac{dx}{dt} = -0.1134x(t) - 1.4x(t - s)y(t - s) + 1.0022
\]
\[
\frac{dy}{dt} = 0.21x(t) - 0.2971y(t).
\]
There is a positive equilibrium \((x^*, y^*)=(0.9506, 0.6719)\)

Case 1:- For \(s = 0\). The numerical simulation in this case (figures 1 and 2) shows that both the insulin and glucose converge to their equilibrium values, \(x^* = 0.9506\) and \(y^* = 0.6719\) respectively, in finite time.
Figure 1: Glucose-insulin dynamics for \( s = 1.0738 \).

Figure 2: Phase plain of the Glucose-Insulin dynamics for \( s=1.0738 \)

Also in equation (12), the interior-fixed point \( B_1 \) is locally asymptotically stable when \( s = 0 \) since

\[
(r_1 - p_2x^*)^2 = 1.2562 < 4r_2(p_1 + p_2y^*) = 1.2526
\]
Case 2:- For $s \neq 0$, by Theorem 2a, there is a critical value $s_0 = 1.2738$. The computer simulations (figures 1-4), show that $B_1$ is asymptotically stable when $s = 1.0738 < s_0 = 1.2738$. When $s$ passes through critical value $s_0 = 1.2738$, $B_1$ loses its stability and a Hopf bifurcation occurs, i.e., a family of periodic solutions bifurcate from $B_1$. When $s > s_0 = 1.2738$, $B_1$ is unstable (figures 5 and 6).
Differential equations involving time delay are an exciting form of differential equations, having various kinds of applications, specifically in the biological and medical worlds. In this paper, a mathematical model is formulated and then analysed to study the glucose-insulin dynamics in the human body. Further, we implemented numerical simulations in order to demonstrate the obtained results. All the numerical results and graphs bestowed within the project were in agreement with those bestowed in the relevant corresponding papers. As a result, the constraints on the parameters are revealed such that the periodic answer encompassing the interior steady state exists. Thus, it can be seen that critical value of the parameter $s$ is $s_0$. Moreover, the stability of bifurcated periodic solutions and the direction of Hopf bifurcation are examined. All the above results can conclude that the model is anatomically consistent and should be a great tool for additional analysis on the chronic disorder i.e. diabetes.

References
[1] Kumar D, S 2011 Mathematical Model for Glucose-Insulin Regulatory System of Diabetes Mellitus Advances in Applied Mathematical Biosciences 2 39-46

[2] Hussain J, Z D 2014 A mathematical model for glucose-insulin interaction Sci Vis 14(2) 84-88

[3] D, Z 2014 Mathematical Modelling of Diabetes Mellitus Mizoram University Mathematics Tanhril Aizawl

[4] Devi Anuradha, K R 2016 A Mathematical Model of Glucose-Insulin regulation under the influence of externally ingested glucose (G-I-E model) International Journal of Mathematics and Statistics Invention 4(5) 54-58

[5] Widyaningsih P, R C 2018 A Mathematical Model for the Epidemiology of Diabetes Mellitus with Lifestyle and Genetic Factors Journal of Physics: Conference series

[6] Kwach B, O 2011 Mathematical Model for Detecting Diabetes in the Blood Applied Mathematical Sciences 5(6) 279-286

[7] Athena Makroglou, J L 2006 Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview Applied Numerical Mathematics 56 559-573

[8] Anirudh Nath, D D 2018 Blood glucose regulation in type 1 diabetic patients: an adaptive parametric compensation control-based approach IET Systems Biology 12(5) 219-225

[9] Preeti Kalra, Maninderjit Kaur 2019 Periodicity and stability of single species model with holling type III predation term using impulse Journal of Ecology, Environment and Conservation paper 25(3) 1327-1342