

LINEAR AND NON-LINEAR MATHEMATICAL MODEL OF THE PHYSIOLOGICAL BEHAVIOR OF DIABETES

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Abstract:

This paper's goals center on understanding the physiological behavior of diabetes, specifically type 2 diabetes, through mathematical modelling and in order to assess the health of diabetic patients and identify the most effective and practical blood glucose control strategies. Additionally, research on diabetes patients both those with and without complications is the main objective. Either a new model can be built or an existing model can be improved in order to develop a mathematical model for diabetes mellitus.

Keyword: Typical roots approach, The Direct Method of Lyapunov, Diabetes.

INTRODUCTION

The process of turning a problem from a practical one into a mathematical one, creating the mathematical models required to solve the problem, and interpreting the solutions is known as mathematical modelling (Berry and Nyman, 2002; Bukova-Guzel, 2011). It entails figuring out the mathematical puzzles, interpreting the answers in terms of the real world, validating the conclusions by contrasting them with the actual situation, and either improving the model or, if it is acceptable, applying the model to related situations for assessment and improvement.

Another definition of mathematical modelling is the use of mathematics to examine significant issues related to the seen world, test hypotheses, and make predictions about it. There are only better models; there is no best model. It is employed in the fields of engineering, including computer science and artificial intelligence, as well as the natural sciences, including physics, biology, earth science, and meteorology, as well as the social sciences, including political science, economics, psychology, and sociology. A mathematical model can be used to analyse a system, explore the interactions between its parts, and anticipate behaviour.

Dynamical systems, statistical models, differential equations, and game theoretic models are only a few examples of the many diverse types of mathematical models that exist. There are two sides to every field of knowledge: an analytical, mathematical, statistical, and computer-based one, and an empirical, experimental, and observational one. The first of these two aspects requires the use of mathematical modelling. 1988 in Kanpur. According to the mathematical methods used to solve them, the goal we have for the model, and their nature, mathematical models can be categorised as linear or non-linear, static or dynamic, deterministic or stochastic, discrete or continuous. Although linear, static, or deterministic models are simpler to handle and also produce reasonable approximations, non-linear, dynamic, and stochastic models are fundamentally more realistic.

Diabetes and its symptoms

Diabetes Mellitus, often known as diabetes or hyperglycemia, is a syndrome of disturbed metabolism that is typically brought on by a combination of inherited and environmental factors. The hormone insulin, which is produced in the beta cells of the pancreas, interacts intricately with other chemicals and hormones in the body to regulate blood sugar levels. Diabetes mellitus is a collective term for a number of illnesses that increase blood sugar levels by impairing either insulin secretion or action in the body. This phrase is used to describe a condition marked by persistently elevated blood plasma glucose levels and other abnormalities in lipid and carbohydrate metabolisms, which are frequently linked to the emergence of particular microvascular and macrovascular conditions.

Diabetes of type 2 develops when the body becomes resistant to the effects of insulin. Adult-onset or non-insulin-dependent diabetes mellitus are two names for it (NIDDM). When the liver, muscles, and other tissues stop responding

to insulin, type 2 diabetes develops. The pancreas makes an effort to make up for this by manufacturing more insulin, but for some people, this effort falls short. If the high blood sugar is left untreated, the beta cells eventually die or degenerate, which causes the pancreas to stop generating insulin. The most prevalent kind of diabetes, type 2, is linked to lifestyle factors like junk food, obesity, and inactivity as well as heredity. The recent increases in the prevalence of type 2 diabetes may be attributable to environmental exposures.

Diagnosis of Type 2 Diabetes

The most popular methods for identifying diabetes include

- 1) The hemoglobin A1c test, commonly known as the glycohemoglobin test
 - 2) The fasting plasma glucose test (FPG)
- Oral glucose tolerance evaluation (OGTT)

At routine medical checkups, a different blood test called the random plasma glucose (RPG) test is occasionally used to identify diabetes. If the RPG is 200 micrograms per deciliter or more and the patient additionally exhibits signs of diabetes, a medical professional may make the diagnosis of diabetes (World Health Organization, 2013). The blood test levels for diagnosing diabetes in people who are not pregnant as well as prediabetes are shown in the following table. (ML = deciliter; mg = milligrams).

Condition	A1c (percent)	Fasting plasma glucose (mg/dl)	Oral Glucose Tolerance Test (mg/dl)
Normal	About 5	99 or below	139 or below
Pre-diabetic	5.66 to 6.355	100 to 125	140 to 199
Diabetic	6.5 or above	126 or above	200 or above

Table 1.1 – Diabetes blood test levels

There are numerous approaches to diagnose diabetes mellitus, but the glucose tolerance test (GTT), an approach that is universally recognised, is always chosen. To determine if it is IDDM or NIDDM, more tests must be performed when diabetes mellitus is found. The amount of fasting blood sugar immediately reveals the extent of carbohydrate intolerance. Thus, depending on this classification, the severity of the condition can be determined, as shown in the table below:

SEVERITY	RANGE OF FASTING BLOOD SUGAR
Normal	60-100mg/dl
Mildly diabetic	60-105 mg/dl
Moderately diabetic	106-200 mg/dl
Severely diabetic	Above 200 mg/dl

Table 1.2 – Diabetes severity

The atypical oral glucose tolerance curve of moderate diabetes is similar to those seen in many non-diabetic

diseases, as seen in the above table. Because of this, understanding the patient's metabolic profile is necessary in order to properly evaluate a particular tolerance curve. It is necessary to establish the following details before analysing the blood for glucose levels:

- 1) The name of the actual technique utilised
- 2) Whether it accurately measures sugar
- 3) Whether whole blood, plasma, or serum will be used; and
- 4) The normal person's fasting glucose levels when any of these blood sample types are used.

METHODOLOGY

The formulation of mathematical models for the dynamics of glucose-insulin leaves out less important factors. The relative impact of system components on its dynamics is used to assess the relevance of the various components. After the mathematical issues are solved, interpretation is carried out by comparing the model's constituent parts and behaviour to those parts, traits, and behaviours of actual systems. The models are then verified using data from several sources as well as arbitrary parameter values. The dynamics of the disease can be explained using the models, and predictions regarding its rate of growth or decline can be made.

The two main methods used in our work for stability analysis are:

1. **The typical roots approach:** The eigenvalues of the variational matrix, a Jacobian matrix of first order derivatives of interaction-functions, determine a system's asymptotic stability. This method only examines the local stability of the system near its equilibrium state because the Jacobian is determined by Taylor expansion of the interaction-functions and neglects higher order terms. When examining the local stability of large-scale systems in homogeneous environments, the Gershgorin's theorem and the Routh-Hurwitz criterion (Lancaster and Tismanetsky, 1985) are both highly helpful. Only slight alterations of the initial state are stable under this technique. Thus, it is referred to as local stability.

2. **The Direct Method of Lyapunov:** The initial state and system dynamics are frequently subjected to significant disturbances in real systems. The direct Lyapunov method is the most effective analytical technique for analysing stability to finite perturbations of an ecosystem model's initial state (La Salle and Lefschetz, 1961; Rao, 1981). The creation of specific functions known as Lyapunov functions is necessary for this technique. The Lyapunov direct method generalises the idea that a system is stable if it dissipates energy continuously until it reaches equilibrium.

MODELLING THE SYSTEM THAT CONTROLS BLOOD SUGAR

Insulin and glucagon, two pancreatic hormones, are the two key players in the glucose control system. Together, glucagon and insulin regulate metabolism. When blood sugar (glucose) levels drop too low, the pancreas produces the hormone glucagon. The liver produces glucose when exposed to glucagon, which is then released into the bloodstream. Blood glucose levels are increased by glucagon, and fuel utilisation is organised by insulin for either storage or oxidation. Increased blood glucose levels trigger the production of insulin, which then acts on cells all over the body to promote glucose absorption, storage, and use.

The broad paradigm for how insulin and glucose interact that we suggest is as follows:

$$\dot{x} = -p_1x - p_2xy + p_3$$

$$\dot{y} = q_1x - q_2y \dots \dots \dots (1.1)$$

Where $x \geq 0, y \geq 0$

x represents glucose concentration

y represents insulin concentration

p_1 is the rate constant which represents insulin-independent glucose disappearance

p_2 is the rate constant which represents insulin-dependent glucose disappearance

p_3 is the glucose infusion rate

q_1 is the rate constant which represents insulin production due to glucose stimulation

q_2 is the rate constant which represents insulin degradation

THE MODEL IS LINEARIZED

Consider the significant point of the coordination (1.1)

$$x' = 0 \Rightarrow -p_1x - p_2xy + p_3 = 0 = M(x, y)$$

$y' = 0 \Rightarrow q_1x - q_2y = 0 = N(x, y) \dots (1.2)$ The only equilibrium points are (0,0) and (x^*, y^*) .
Solving (1.2), we get

$$x^* = \frac{-p_1q_2 + \sqrt{(p_1q_2)^2 + 4p_2q_2p_3q_1}}{2q_1p_2}$$

$$y^* = \frac{-p_1q_2 + \sqrt{(p_1q_2)^2 + 4p_2q_2p_3q_1}}{2q_2p_2} \dots\dots\dots(1.3)$$

We are interested in the interior-equilibrium point (x^*, y^*) which always exist since all the parameters are considered positive.

Stability Analysis

Theorem 3.1: The trivial equilibrium point (0,0) is asymptotically stable locally.

Proof:

At (0,0)

$$K_{(0,0)} = \begin{pmatrix} -p_1 & 0 \\ q_1 & -q_2 \end{pmatrix}$$

Whose characteristic equation is given by $E^2 + (p_1 + q_2)E + p_1q_2 = 0$

Where $Trk_{(0,0)} = -(p_1 + q_2) < 0$ and $detJ_{(0,0)} = p_1q_2 > 0$, since $p_1 > 0, q_2 > 0$
As a result, the trivial critical point (0,0) is locally asymptotically stable according to Routh-Hurwitz criteria.

Theorem 3.2: If the interior-equilibrium point (x^*, y^*) is asymptotically stable locally,
 $(q_1 - p_2x^*)^2 < 4q_2(p_1 + p_2y^*)$

Proof: Consider the Lyapunov function

$$V = \frac{1}{2}(X^2 + Y^2)$$

Hence, $V' = -(p_1 + p_2y^*)X^2 + (q_1 - p_2x^*)XY - q_2Y^2$

$$V' = -1/2 AX^2 + BXY - 1/2 CY^2$$

Where $A = 2(p_1 + p_2y^*)$

$$B = q_1 - p_2x^*$$

$$C = 2q_2$$

That is a sufficient condition for V' to be negative definite.

$$B^2 < AC$$

i.e. $(q_1 - p_2x^*)^2 < 4q_2(p_1 + p_2y^*)$

Which is the requirement that the parameters satisfy in order for the critical point (x^*, y^*) to be locally asymptotically stable.

Lemma 3.1: The set $\bar{D} = \{(x, y) : 0 \leq x + y \leq \frac{p_3}{\delta} + ce^{-\delta t}, H = \min(p_1 - q_1, q_2)\}$, c is a constant that attracts all solutions that begin in the positive quadrant.

Proof:

From our model (1.1), we have

$$\frac{dx}{dt} = -p_1x - p_2xy + p_3$$

And $\frac{dy}{dt} = q_1x - q_2y$

Therefore, $\frac{d(x+y)}{dt} = -p_1x - p_2xy + p_3 + q_1x - q_2y$

$$\leq -p_1x + p_3 + q_1x - q_2y$$

$$= -(p_1 - q_1)x + p_3 - q_2y$$

$$\leq -\min\{(p_1 - q_1), q_2\} (x + y) + p_3$$

Let $H = \min\{(p_1 - q_1), q_2\}$

Then $\frac{d(x+y)}{dt} \leq -H(x+y) + p_3$

Or $\frac{d(x+y)}{dt} - p_3 \leq -dt$

Or $1/\delta \log\{H(x+y) - p_3\} \leq -t + \log r_1$

Or $x + y \leq p_3 / \delta + re^{-\delta t}$, where $r/\delta = r_1$

Theorem 3.3: If (x^*, y^*) is an interior-equilibrium point, it is globally asymptotically stable.

$$q_1 - p_2x^*)^2 < 4q_2(p_1 + p_2y^*) .$$

Proof: Consider the Lyapunov function $V = \frac{1}{2}(x - x^*)^2 + \frac{1}{2}(y - y^*)^2$

Then $V' = (x - x^*)x' + (y - y^*)y'$
 $= (x - x^*)(-p_1x - p_2xy + p_3 + p_1x^* + p_2x^*y^* - p_3 + p_2x^*y - p_2x^*y)$

$$\begin{aligned}
 & +(y - y^*)(q_1x - q_2y - q_1x^* - q_2y^*) \\
 = & (x - x^*)\{-p_1(x - x^*) - p_2y(x - x^*) - p_2x^*(y - y^*)\} \\
 & +(y - y^*)\{q_1(x - x^*) + q_2(y - y^*)\} \\
 = & (-p_1 - p_2y)(x - x^*)^2 + (-p_2x^* + q_1)(x - x^*)(y - y^*) - q_2(y - y^*)^2 \\
 = & -\frac{1}{2}P_{11}(x - x^*)^2 + P_{12}(x - x^*)(y - y^*) - \frac{1}{2}P_{22}(y - y^*)^2
 \end{aligned}$$

Where $P_{11} = 2(p_1 + p_2y)$

$$P_{12} = -p_2x^* + q_1$$

$$P_{22} = 2q_2$$

The condition for V' to be negative definite is that

$$P_{12}^2 < P_{11}P_{22}$$

$$\text{i.e., } (q_1 - p_2x^*)^2 < 4q_2(p_1 + p_2y)$$

If the interior-equilibrium point (x^*, y^*) is globally asymptotically stable,

$$(q_1 - p_2x^*)^2 < 4q_2(p_1 + p_2y) \text{ where } y \in \Omega.$$

Theorem 3.4: *The non-trivial significant point (C^*, N^*) is locally asymptotically stable if*

$$I < 2F + E + H + G \text{ and } E(F + H) > (I - F)\theta$$

Proof: Consider the Jacobian K at (C^*, N^*) connected with m and n of the IVP, which is provided by

$$K_{(0,0)} = \begin{pmatrix} -(E + \theta) & E \\ -(I + G) & (I - F) \end{pmatrix}$$

This matrix's characteristic equation is given by

$$X^2 - \text{trace}(K)X + \det(K) = 0$$

If the eigenvalues are negative or have negative real parts, the eigenvalues are negative.

$$\text{trace}(K) < 0 \text{ and } \det(K) > 0$$

And, according to the Routh-Hurwitz stability criterion, if the above conditions are met, the system will be locally asymptotically stable.

As a result, if our system of differential equations is locally asymptotically stable,

$$-E - \theta - I + F < 0 \text{ and } -(E + \theta)(I - F) + E(I + H) > 0$$

$$\text{i.e. if } I < 2F + E + H + G \text{ and } E(F + H) > (I - F)\theta$$

The Non-linear System

We now assume that E , the probability of a diabetic patient developing complications, is proportional to $W(t)$ and $N(t)$ and has the following form:

$$E = E(t) = \beta \frac{W(t)}{L(t)}, \dots\dots\dots (1.4)$$

Where β is a real positive constant.

The IVP is now a non-linear system that can be written as

$$C'(t) \in f(C, N) = (\beta - \theta)C(t) - \beta \frac{C(t)^2}{L(t)}, t > 0, C(0) = C_0$$

$$L'(t) \in N(W, L) = (I - F)L(t) - (I + H)C(t), t > 0, L(0) = L_0 \dots\dots\dots (1.5)$$

For simplicity sake, we write $W(t) = W$ and $L(t) = L$. Hence, we may write

$$W'(t) \in M(W, N) = (\beta - \theta)W - \beta/N W^2, t > 0, W(0) = W_0$$

$$L'(t) \in N(W, L) = (I - F)L - (I + H)W, t > 0, L(0) = L_0 \dots\dots\dots (1.6)$$

Taking $W'(t) \in M(W, L) = 0$ and $L'(t) \in N(W, L) = 0$, we get a non-trivial critical point

$$(W^*, L^*) = \frac{\beta(I - F)}{\beta(I - F) - (\beta - \theta)(I + H)} \frac{\beta(I + F)}{\beta(I - F) - (\beta - \theta)(I + H)}$$

Note that $W'(t) \in M(W, L) = 0 \Rightarrow (\beta - \theta)W^* - \beta/N^* W^{*2} = 0$
 $W^*/L^* = (\beta - \theta)/\beta$
 Now $W^* > 0, L^* > 0, \beta > 0$, therefore $\beta - \theta > 0$.

Numerical simulation

We consider arbitrary values for the parameters as follows:

$$I = 0.004, F = 0.000004, E = 0.05, H = 0.0009, G = 0.004,$$

$$\theta = F + H + G = 0.0049, \beta = 0.006,$$

The condition for local stability is satisfied as

$$I = 0.004 < 2F + E + H + G = 0.0549$$

And $E(F + H) = 0.0000452 > \theta(I - F) = 0.0000196$

For validate the global constancy condition, we consider the case as $t \rightarrow 0$ that is for $W + 1 \leq w$, i.e. $W \leq w$ and $L \leq w$. We again consider the scrupulous case when $w = 5000$. Let $L = 5800$ and $W = 0.00006$. We see that the condition for global constancy is also satisfied as

$$\left[\frac{w_1 \beta w^2}{5800L^*} - w_2(I + H) \right]^2 = 0.0000029 < 4w_1w_2(I - F) \left[(\beta - \theta) - \frac{\beta(0.00006 + W^*)}{L^*} \right] = 0.000087$$

Where $w_1 = 3$ and $w_2 = -0.35$.

Consider equation

$$\frac{dD(t)}{dt} = \dot{D}(t) = I D(t) - (E + F)D(t) + GC(t)$$

$$\frac{dC(t)}{dt} = \dot{C}(t) = ED(t) - \theta C(t)dt$$

We generate a graph for the equation using the initial values $D(0)=3$, $C(0)=3$, and the same parameter values but varying I .

When $I = 0.004$, the number of diabetics without complications drops to 1.35 (approximately) and the number of diabetics with complications rises to 2.755. (approximately). When $I = 0.00004$, we get the same result. However, when $I = 0.0004$, we see that both $D(t)$ and $W(t)$ grow exponentially, with $D(t)$ growing faster than $W(t)$ (t). When we increase I to $I = 4.0$, we see that $D(t)$ and $W(t)$ grow more quickly. This finding suggests that as the population of diabetics without complications grows at a constant positive rate, the population of diabetics with complications grows significantly as well.

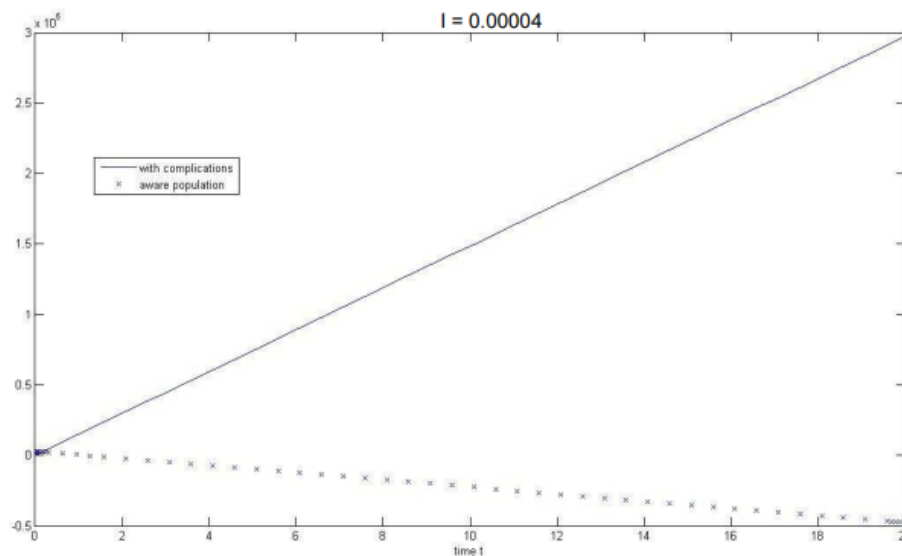


Fig 1

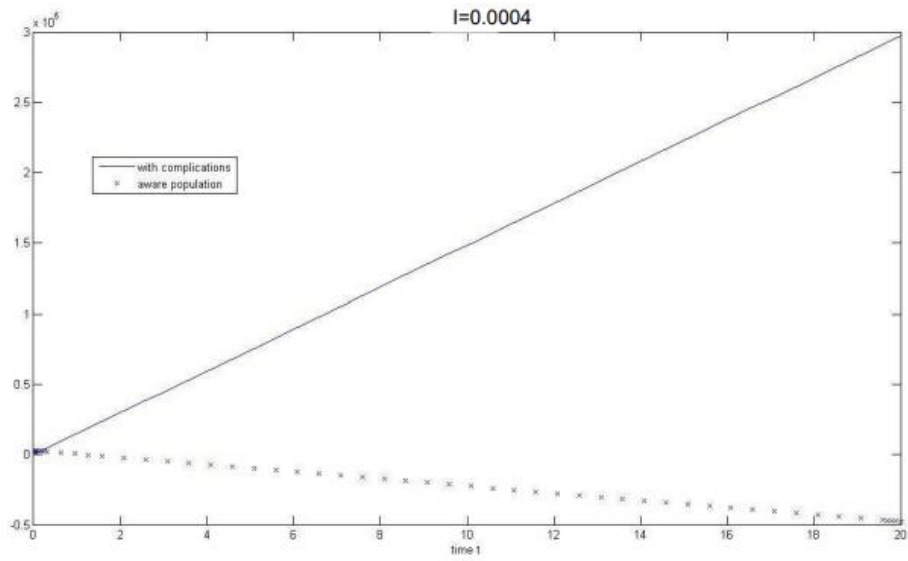


Fig 2

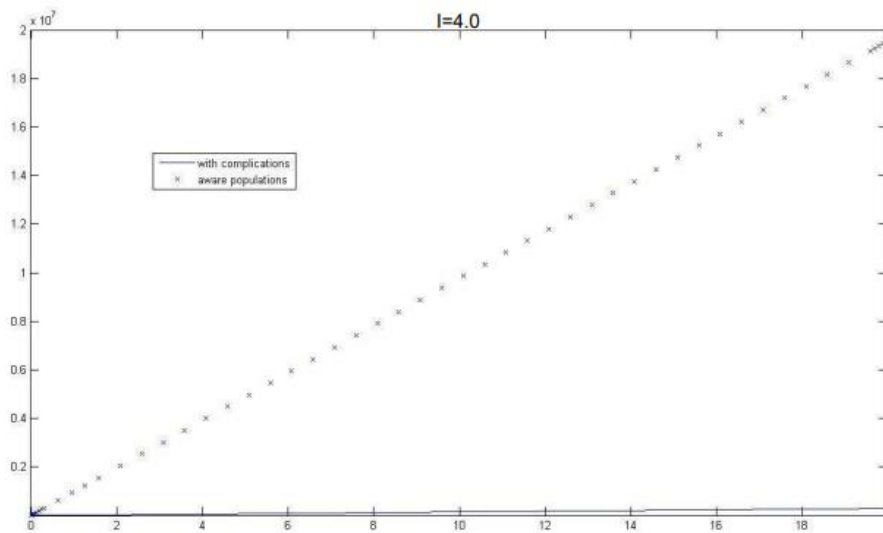


Fig 3

This finding is consistent with the real-world situation, demonstrating that our model is valid and in accordance with the real-world situation.

CONCLUSION

In this paper, we develop a mathematical model of the diabetic population and divide it into two groups: diabetics without complications and diabetics with complications. The Routh-Hurwitz Criterion and the Lyapunov function are used to establish local and global stability conditions. Numerical simulations are used to validate these conditions. Graphs are generated for the mathematical model, which shows that as the rate of diabetes increases, so does the number of diabetics with complications, and if this increase is at a positive integral rate, the population of diabetics with complications grows exponentially. Diabetes is sweeping the world as a global epidemic, and diabetes-related deaths are increasing at an alarming rate. Controllable factors that cause diabetes, such as unhealthy eating habits, obesity, and inactive lifestyles, should be prioritised, and the importance of raising awareness about the negative impact of such factors cannot be overstated. More research is needed to reduce the cost and burden of this disease.

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