AN OVERVIEW ON DIABETES MELLITUS: MATHEMATICAL APPROACH

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Abstract

Diabetes mellitus, sometimes known as diabetes, is a widespread disease in the current technological period. Blood glucose levels in this condition are out of the normal range of 80 to 170 mg/dl, which puts the human body at risk for long-lasting illness. Diabetes raises a person's mortality risk. Many reviews have been written about mathematical modelling for diabetes. Various models have been presented in recent years for a number of diabetes-related topics, including glucose and insulin dynamics, management and the prevention of complications, and the epidemiology of diabetes in general. On a regular basis, reviews on mathematical models used for particular areas of diabetes are published. This study offers an overview of several mathematical models that deal with various elements of diabetes.

Keywords: Mathematical Modeling, Diabetes Mellitus, Type-1 diabetes, Type-2 diabetes, Gestational Diabetes, Glucose Insulin Dynamic and Control Algorithm.

INTRODUCTION

Mathematical modeling is defined as the conversion of real life problems into mathematical problems, formulating mathematical models necessary for solving a problem and interpretation of the results. Let us discuss about mathematical modelling in diabetics.

Diabetes Mellitus, also referred to as diabetes, is a syndrome of disturbed metabolism that typically results from a combination of inherited and environmental factors, leading to hyperglycemia, or abnormally high blood sugar levels. The hormone insulin, which is produced in the beta cells of the pancreas, interacts intricately with other hormones and substances in the body to regulate blood sugar levels. Diabetes is a collective term for a number of illnesses that increase blood sugar levels by impairing either insulin secretion or insulin activity. This concept is used to define a disorder characterized by persistently high blood plasma glucose levels and other abnormalities in carbohydrate and lipid metabolism that are frequently linked to the emergence of macrovascular and microvascular problems.

The main types of diabetes are:

Type 1 diabetes(T1D): It's an autoimmune disorder. In this situation, the pancreas' insulin-producing cells are killed. Type 1 diabetes affects up to 10% of patients with the disease. Although it can manifest at any age, it is typically identified in children and young people. Diabetes used to be more often known as “juvenile” diabetes. Patients with type 1 diabetes must take insulin daily. Diabetes that is dependent on insulin is another name for it.

Type 2 diabetes(T2D): In this type, the body either doesn't create enough insulin or its cells don't react to it properly. The most typical form of diabetes is this one, 90% of those who have diabetes are of Type 2 diabetes patients. People in their middle age and older tend to develop it. Adult-onset diabetes and insulin-resistant diabetes are two more names for Type 2 diabetes.
Gestational diabetes: Some women experience this kind of diabetes during pregnancy. After pregnancy, gestational diabetes typically disappears. The risk of getting Type 2 diabetes later in life is increased in pregnant diabetic people.

Increased thirst, weakness, fatigue, blurred vision, numbness or tingling in the hands or feet, slow-healing cuts or sores, unintended weight loss, frequent urination, frequent unexplained infections, and dry mouth are the main signs of diabetes.

Diabetic ketoacidosis (DKA) is a severe metabolic dysregulation condition that is typically brought on by type 1 diabetes. It is distinguished by the smell of acetone on the patient's breath, rapid, deep breathing known as Kussmaul breathing, vomiting, nausea, and abdominal pain, as well as altered states of consciousness or arousal like hostility and mania or, equally, confusion and lethargy. A coma and eventual death could occur in cases of severe DKA. DKA is a medical emergency that necessitates admission to the hospital right away.

The main cause of hyperosmolar nonketotic condition, which is more frequently observed in type 2 diabetes, is dehydration brought on by water loss from the body.

Diabetes increases a person's risk of having a heart attack. Long-term high blood glucose levels cause glucose absorption, which affects the curvature of the eye's lenses and impairs vision. As a result, people with diabetes are at risk for blindness and other vision issues. Renal damage and kidney failure are potential effects of diabetes. Damage to the body's nerves caused by diabetes is possible. Diabetes can lead to nerve damage, foot infections (such as ulcers), and issues with blood flow to the feet. Skin issues including itching, blisters, and infections can also be brought on by diabetes. Skin issues can occasionally be the first sign of diabetes. Diabetes can result in gingivitis and periodontitis, a condition that affects the gums and teeth.

According to B. M. Patil et al. (2010), diabetes mellitus is simply brought on by the body's inability to create enough insulin to keep blood sugar levels stable.

In order to characterize the dynamic behavior of plasma glucose and insulin on diabetic individuals, Chen et al. (2010) suggested a novel mathematical model. Parameters are the components of the main physiological processes. According to their model, the dynamics and oscillation behavior of glucose-insulin on diabetes can be accurately captured. Confirming clinical data over a lengthy period of time. It is discovered that the obtained parameters can be used to determine the patient's major physiological function. They expected that this model will be helpful in developing appropriate treatment plans for diabetes patients.

For the study of diabetes, Sadhya and Kumar (2011) developed a new mathematical model that accounts for plasma insulin concentration, generalised insulin, and all plasma glucose concentrations. Their model demonstrated how a normal person's and a diabetic's glucose-insulin regulation systems differ. The fact that a diabetic patient's blood glucose concentration did not decrease after a particular period of time was discovered by the researchers as proof that the patient had diabetes.

A general mechanistic model that takes into account the dynamics of birth, mortality, migration, ageing, and diabetes incidence was proposed by Appuhamy et al. (2013). Their body mass index (BMI), which can be calculated using the Hill equation, was used to calculate diabetes incidence rates. The prevalence of diabetes in younger, middle-aged, and older individuals was accurately predicted by their model. They discovered that diabetes incidence and prevalence were each positively correlated with one another across all age groups, while the correlations among younger persons were stronger. In older persons compared to younger adults, the prevalence of diabetes was found to be more responsive to mortality rates. At younger ages, both diabetes incidence and prevalence were highly sensitive to BMI; however, sensitivity rapidly decreased with age.

A mathematical model was devised and examined by Samanta et al. (2013) to determine the impact of media awareness campaigns on the prevalence of infectious diseases and demonstrated that the system is significantly impacted by how quickly awareness initiatives are implemented, and continuous oscillation may result from raising this number above a threshold. Analyzed and described are the stable equilibrium that are logically possible. They noticed that informal information spreading is more likely to increase public awareness of a disease's local prevalence if it is not reported by the media or local health officials. If knowledge of the disease is appropriately spread throughout the population, people will change their behaviour in a way.

In order to describe how the Blood Glucose Regulating System (BRGS) functions during a glucose tolerance test, Singh (2014) developed a mathematical model (GTT). He came to the conclusion that a value of less than four hours for the time t₀, which corresponds to the Natural system frequency suggested normally, however significantly more than four hours suggested mild diabetes. He also noted that sociological aspects of BRGS are crucial.
According to Zheng et al. (2017), diabetic people have persistently high blood sugar levels that impact multiple body organs and cause major problems. Due to increased urbanisation, bad diets, decreased physical exercise, inadequate health care, and inadequate education, glycemic control is extremely poor in Asian countries like India.

In addition to developing a mathematical model to estimate the prevalence of diabetes, Purnami Widyaningsih et al. (2018) also created a DC model, which divided those who had the disease into two categories: uncomplicated diabetics (D) and difficult diabetics (C). The susceptible diabetic complication (SDC) model was created using the DC model. Risky interactions were calculated with the participation of susceptible persons. Since the SDC model is a first order nonlinear differential equation, it can accurately estimate the prevalence.

According to Boutayeb et al. (2019), a mathematical model controlled by ordinary differential equations is provided to explain how growth hormone, free fatty acids, insulin, and glucose interact in the case of type 1 diabetes. They came to the conclusion that this mathematical model describes the glucose dynamics based on subcutaneous insulin administration in a type 1 diabetic person after doing stability analysis and a simulation using different parameter values. They added that it provides theoretical and practical instructions for maintaining the regular blood sugar control required to prevent both hyperglycemia and hypoglycemia.

The paper by R Yadav and Maya (2020) focuses on a new method for studying diabetes mellitus. By including time delay, a new mathematical model of all glucose-insulin interactions is suggested. Following the formulation of the mathematical model, the model's analysis was discussed. They performed the numerical simulations to verify the theoretical findings. Computer simulations are utilized to assess how effective the suggested work is. Additionally, the behaviour of the suggested mathematical model for various time delay values will be demonstrated.

To understand various aspects of diabetes, including glucose-insulin dynamics, the epidemiology of diabetes, and its consequences, a number of mathematical models, computer algorithms, and statistical methods have been presented. Diabetes and mathematical models have received numerous reviews. Reviewing the various diabetes-related mathematical models that have been published.

Glucose-insulin dynamics

Mathematical models

In general, Mathematical models are used to estimate the glucose disappearance and insulin-glucose dynamics. Research on diabetes was started from 1939. Ker and Himsworth introduced the first approach to measure the insulin sensitivity in vivo.

In 1960, Rosevear and Molnar of the Mayo clinic and Ackerman and Gatewood of the University of Minnesota proposed a simple model for blood glucose regulatory system (BGRS) where ‘g’ is taken to be excess glucose concentration and ‘h’ is excess insulin concentration at a time ‘t’ which is expressed as follows.

\[
\dot{g} = -ag - bh \tag{1}
\]
\[
\dot{h} = cg - dh \tag{2}
\]

Where a,b,c, and d are constants

In 1961, using ordinary differential equations, Bolie () proposed a simple model as follows

\[
\dot{G} = -a_1G - a_2 I + p \tag{3}
\]
\[
I = a_3 G - a_4 I \tag{4}
\]

Where G represents the glucose concentration, I represents the insulin and p,a_1,a_2,a_3and a_4 are parameters. Also various models were proposed by different authors based on the insulin sensitivity

In early 80’s, Bergemen et. al proposed minimal model as follows
\[ \dot{G}(t) = -[p_1 + x(t)]G(t) + p_1 G_B, \ G(0) = p_0 , \quad (5) \]
\[ x(t) = p_2 x(t) + p_3 (I(t) - I_b), \ x(0) = 0 \quad (6) \]
\[ I(t) = -p_4 (I(t) - I_b) + p_5 (G(t) - p_6)^{1/2} t, I(0) = p_7 + I_b \quad (7) \]
Where \((G(t) - p_6)^{1/2} = \begin{cases} G(t) - p_6, & \text{if } G(t) > p_6 \\ 0, & \text{otherwise} \end{cases} \)

\(X(t)\) denotes an auxiliary function representing insulin excitable tissue glucose uptake activity. \(I_b\) and \(G_b\) are the subject's baseline insulinemia and glyceamia. \(p_0\) to \(p_7\) are parameters. It should be stressed that, although equations (5) and (7) were developed for describing FSIGT data, these equations were presented into two parts. Part 1 with equations (5) and (6) and part 2 using (7). A large number of papers have been published, using modified versions of the glucose minimal model (5)–(6) for describing OGTT and meal tests, while insulin minimal models derived from (7) are still limited to IVGTT. It should also be stated that the major contribution of the glucose minimal model (5)–(6) has been to provide a means of estimating insulin sensitivity \(SI = p_3/p_2\), avoiding the glucose clamp.

Different versions based on the minimal model were considered by different authors. An example of this category was proposed by Derouich and Boutayeb who used a modified version of the minimal model to introduce parameters related to physical exercise:

\[ \dot{G} = (p_1 + q_1)(G_b - G(t)) - (1 + q_2)X(t)G(t) \quad (8) \]
\[ \dot{X} = -p_2 X(t) + (p_3 + q_3)(I(t) - I_b) \quad (9) \]

where \(p_1, p_2, p_3\) are parameters also \(q_1, q_2\) and \(q_3\) are parameters related to physical activity and defined as follows:

- \(q_1\) : the effect of physical exercise in accelerating the usage of glucose by muscles and the liver insulin
- \(q_2\) : the effect of physical exercise in increasing the muscular and liver sensibility to the action of insulin.
- \(q_3\) : the effect of physical exercise in increasing the usage of insulin. In other words, \(q_3\) increases insulin effectiveness in enhancing glucose disposal and consequently improving insulin sensitivity to become:

\[ S_{IL} = \frac{(p_3 + q_3)(1 + p_2)}{p_2} \]

In absence of physical effort the insulin sensitivity is \(\text{SI}_0 = \frac{p_3}{p_2}\). Sandhya and Deepak Kumar (2011) works on a new approach to regulate the blood glucose level of diabetes. They proposed a new mathematical model for the study of diabetes mellitus. The model takes into account all plasma glucose concentration, generalized insulin and plasma insulin concentration. The numerical solution presents the complex situation of diabetic patients. This model includes the basal values also i.e. \(G_B\) and \(I_B\). The modal is defined as:

\[ \begin{align*}
\dot{G} &= -m_1 G + m_2 I + m_4 G_b \\
\dot{X} &= -m_2 X + m_3 (I - I_b) + m_4 I_b \\
\dot{I} &= -m_3 I + m_4 (G + m_5) - m_6 I + m_6 I_b
\end{align*} \quad (10) \]

All the variables and parameters values used in mathematical models are described as:

- \(G(t)\) : The plasma glucose concentration at time \(t\) (mg/dl)
- \(X(t)\) : The generalized insulin variable for the remote compartment (min-1)
- \(I(t)\) : The plasma insulin concentration at time \(t\) (μU/ml)
- \(G_b\) : This is the basal preinjection value of plasma glucose (mg/dl)
\( I_b \) : This is the basal preinjection value of plasma insulin (μU/ml)

\( m_1 \) : Insulin independent rate constant of glucose rate uptake in muscles, liver and adipose tissue (min^-1).

\( m_2 \) : The rate of decrease in tissue glucose uptake ability (min^-1).

\( m_3 \) : The insulin independent increase in glucose uptake ability in tissue per unit of insulin concentration \( I_b \) (min^-2(μU/ml)).

\( m_4 \) : The rate of the pancreatic β-cells’ release of insulin after the glucose injection and with glucose concentration above \( h \) [(μU/ml) min^-2 (mg/dl) - 1]

\( m_5 \) : The threshold value of glucose above which the pancreatic β-cells release insulin.

\( m_6 \) : The first order decay rate for insulin in plasma (min^-1) pancreatic β-cells release insulin.

Bergman’s minimal model, which is a third order nonlinear model and is comprises of three components shown in the following figure and the governing equations are (Al-Fandi et al, 2011; eigner et al 2015)

\[
\dot{G}(t) = -p_1[G(t) - G_b] - X(t)G(t) + D(t) \quad (13)
\]

\[
\dot{X} = -p_2X(t) + p_3[I(t) - I_b] \quad (14)
\]

\[
l = \gamma[G(t) - h] - n[I(t) - I_b] + u(t) \quad (15)
\]

where \( u(t) \) is the control variable, which is the insulin injection rate, \( D(t) \) is the disturbance, \( G_b, I_b \) are the basal glucose and insulin level, \( p_1, p_2, p_3 \) are the model parameters.

R Yadav and Maya (2020) 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 as follows:

\[
\dot{x} = -p_1x(t) - px(t - s)y(t - s) + p_3, t \in [0,T] \quad (16)
\]

\[
\dot{y} = r_1x(t) - r_2y(t), t \in [0,T] \quad (17)
\]

With initial conditions given as:

\[
x(\varphi) = \mu(\varphi), \varphi < 0 \quad (18)
\]

\[
y(\varphi) = \psi(\varphi), \varphi < 0 \quad (19)
\]

Control algorithm

In order to make the closing the loop strategy of glucose control a good algorithm need to be developed. Several algorithms were used in early days to design the infusion of insulin. Few of the algorithms, such as PID control, etc. As the development in the modern technology Fuzzy logic control with different rules and the MPC algorithm have made a good fame in the control design.
PID control

Proportional integral derivative type controller design(PID control) was widely used in process control and in several cases this has to be tuned accurately for good performance. ID algorithm can be given by Chee et al (2003) as follows:

\[ p(t) = \bar{p} + K_c e(t) + \frac{1}{\tau_1 \tau_0} \int_0^t e(t') dt' + \tau_d \frac{de}{dt} \]

where \( e(t) \) be the error of the deviation of measured blood glucose concentration from the set point. \( p(t) \) be the output of the controller. The P controller usually controls the infusion of the insulin; it gives the difference between the target and the sensed glucose level. The D controller measures the changes in the measured glucose and calculates the rate of infusion of the insulin and I controller connects with the value of P controller to improve the performance and to maintain proper regulation. This type of a control design gives magnificent control with average speed and very minimum overshoot. Although the PID controller fairly deals the regulatory problem, it cannot deal the announced meals and hence bolus needs to be calculated and separately conveyed.

IMC control

Internal model control controller also named as IMC control was designed with respect to the model parameters by Lunze et al., (2012). This algorithm takes in account the built in model to control the injection rate with respect to insulin concentration. The basic model was developed by using suitable dynamics. While developing the IMC algorithm for the control of infusion the process model is considered to be in Laplace domain and a filter is attached for the necessary corrections. The plant model considered for the algorithm to develop is the simple model which is first order with delay. IMC is recurrently used technique which can give evident mode for the device and results in only one tuning parameter. The close loop time constant principle states that “Control can be achieved if and only if the control summarizes either implicitly or explicitly, some representation of the process to be controlled.” This technique does not cover the disturbance rejection and hence the response obtained is stagnant. The parameters in the model depend on the filter time constant. For an acceptable limit as the time constant increases the overshoot decreases. The advantage like closed loop performance is related to the parameters in the controller which can have a line tuning very conveniently. The time delay compensation is provided in the design; at the steady state the controller gives offset free response.

Conclusion

During the last decades, an interesting number of papers have been published on mathematical models and control algorithms. In the present review, the author have tried to give a non-exhaustive panorama of the papers which have used mathematical modeling for different aspects of diabetes, including glucose-insulin dynamics, control algorithms, management and the burden of diabetes and its complications.

REFERENCES