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A REVIEW ON MATHEMATICAL MODELING OF THE GLUCOSE–INSULIN SYSTEM

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Abstract: The only possibility to investigate the metabolic disease dynamics is by Mathematical models. The present review was performed in order to determine to what extent different mathematical models have been incorporated in understanding the homeostatic controls, for analyzing experimental data, for identifying as well as for evaluating diabetes disease progression. A silent epidemic Diabetes is sweeping the world contributing the growing burden of human activities' reducing levels as well as growing incidence of obese. In the earlier studies various models were proposed and investigated to interpret about aldohexose and hypoglycemic agent and rate of diabetes prevalence among the population with series health impacts. Several reviews have been studied about the significance of mathematical models in various aspects of disease progression. The variables required for the mathematical model includes the glycogen's concentration in the tissues/liver, glucose, hormone glucagon, and insulin in the venous blood plasma.

Keywords: Mathematical model, diabetes, glucose-insulin dynamics, disease progression.

Introduction:

The study of science is ubiquitous that deals with the spatial arrangement, quantity and it is the indivisible units of life for everything in our daily lives, including various appliance, ancient and modern designing and constructing buildings, art, economy, engineering, and even competitive physical activity. Biomathematics is a fast-growing with exciting modern applications such as differential equations one among them which has basic importance in mathematics due to many biological laws and relations. To study the molecular process of the cell species related to time of natural selection, ordinary differential equations methods are used to formulate. The process of diffusion in the cell is high enough to describe these equations particularly about the arrangement of a phenomenon across homogenous molecules. To study the relationship between the variables in large system, the most commonly as well as dependable mathematical technique is differential equation. Furthermore, molecular dynamics is generally utilized for modelling the biomolecules, at the molecular scale, moving as a Newtonian particles' system with interaction described through a force field, including several methods working for handling the solvent effects' challenges.

Predictions and analysis in life sciences' several areas, for instance expanding population in a systematic pattern, immunology, physiological processes, and neural networks are more reliable within the field of mathematics by modeling methods (R. Rakkiyappan, G. Velmurugan et al., (2015); S. Lakshmanan, et al., (2014); F. A. Rihan, (2014); F. A. Rihan and G. A. Bocharov, 2000). The time between cell's infection as well as also new visions' invention, the infectious period's duration, to initiate resistance, as well as so on can be studied by time lag models (F. A. Rihan, 2014). At the identical time instant, the unknown states as well as their derivatives are calculated in "Ordinary Differential Equations (ODEs)" but in "Delay Differential Equation (DDE)", although, at a specific time instant, the system's evolution is based on the earlier memory/history ends up in incorporate the delays of time during a differential model raises the complexities significantly. Hence, studying such models' qualitative behaviors, utilizing bifurcation or stability analysis, is critical (M. Gozen and C. Tunc, 2017). It involves providing solutions to mathematical problem as well as interpretation of such solutions within the real world language, conclusion validation through their comparison with the things, so either model is improved or, in case this is acceptable, and model is applied to related conditions for calculation and refinement. The flowchart for the method of mathematical model is given below: Bukova-Guzel, 2011).

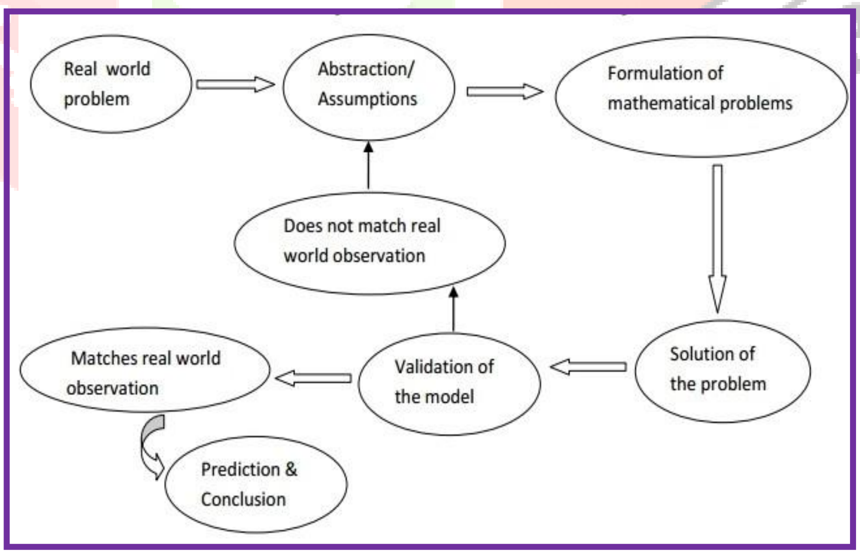


Figure 1- Flow chart for the process of mathematical modeling

Mathematical modeling is also classified in keeping with the mathematical techniques employed in solving them, the aim we've got for the model and per to their nature: linear or non-linear, stationary or energetic, random probability or deterministic, discrete or continuous. Essentially most realistic models are non-linear, dynamic and stochastic although linear, static or deterministic models are easier to handle and also give good approximate results.

Types of mathematical models (Kanpur, 1988) are listed below:

(i) Realism ofmodels,
(ii) Hierarchy of models,
(iii) Relative precision ofmodels
(iv) Robustness ofmodels
(v) Self-consistency of models
(vi) Complexity ofmodels

Many researchers (Dubey et al., 2011; Boutayeb and Kerfati, 1994; Brandeau, 2005; Eddy and Schlessinger, 2003; Freedman and Shukla, 1991) have utilized these models for understanding as well as predicting the Biological Systems' behavior.

Real life use of Differential Equations

The world around us was able to be predicted by the remarkable character of differential equations in wide selection of disciplines, from biological sciences, physical, chemical and social sciences and technology. These equations can describe the exponential growth phase and decline and introduce growth of species or changes reciprocally over time for investment a number of these variables may be solved (to get y= ...) and can be represented in the form dp/dt= … simply by integrating the differential equation but, others require much more complex process.

Population Models:

Differential equations can explain exponential population (p) and arithmetic food supply changes with respect to time growth dp/dt=rp. There will be some changes in constant r which depends on the species to be predicted that over time how that species will grow. Models can be deduced to explain the relation among prey and predators as variables of differential equations. For instance, with increase in predators there is decrease in prey which resulted in predators getting lesser to eat, thus, they started dying out, due to that resulted in survival of more prey, and such interaction among 2 populations are associated through differential equation.

Glucose metabolism:

The human body comprises of several organs. Every organ has a particular function as well as they significantly plays their responsibilities so that significant biological activities are maintained in human body. For carrying through their functions, every organ requires an adequate as well as stable supply of glucose from the blood. As hyperglycemia induces glucotoxicity It is significant keeping the optimal levels of blood glucose (Kaiser N, Nesher R, Leibowitz G, 2003) whereas organs' normal functioning is suppressed by the hypoglycemia. For such reason, under normal metabolic conditions, the human body is designed for maintaining the blood glucose levels in the 80 and 120mg/dL range.

The most abundant aldohexose in nature is glucose, its main energy source is cells of the human body. Diabetes is a disease of long-term complications evident across all sections of society in India with more than 72.9 million adults living (IDF, 2017). It is a condition when blood glucose level exceeds the normal range i.e., 75 -110 mg/dl for a long period of time. 4 million people died in 2017, due to diabetes and approximately 425 million adults in the world had diabetes. Prevalence rate by the year 2045 the diabetes people number will be increased to 629millions. In 2017, 21 million new born babies are affected by diabetes and approximately more than 1,106,500 children have type -1 diabetes and due to the increasing sedentary life habits nearly 352 million people may have the risks of type-2 diabetes development (International Diabetes Federation, 2017). India was ranked up from 11th (2005) to 7th (2016) due to number of deaths by diabetes (Hindustan times2017).

Furthermore, reproductive state, exercise, digestion rate, food intake etc. are affected by the blood glucose concentration levels. Also, the glucose concentration levels are controlled by the glucagon and insulin, pancreatic endocrine hormones. Insulin and glucagon are secreted by the pancreas's β-cells as well as α-cells. In high concentration of blood glucose, insulin is released by the β -cells that resulted in decreasing the concentration levels of blood glucose by making excess glucose to be utilized by the various cells (e.g., muscles). Hernandez, 2001 stated that glucagon is released by α-cells, in low concentration of blood glucose, which resulted in higher blood glucose levels through their action on liver cells into the blood.

Several models were recommended and reviewed in the field of diabetes to discuss diabetes' various aspects like diabetes prevalence as well as its symptoms; insulin as well as glucose availability; affordances to the cost of diabetes treatment, In the majority of reviews are focused on particular aspects of Sundell (2003), Mari (2002), Bergman, (2001), (1997); Nucci G, Cobelli (2000) mathematical and software aspects Kuang Y, Li J, Makroglou A (2006), glycemic index; Andersons, De Grandpre E, Kalergis M (2005); burden and cost of diabetes Boutayeb A (2006), Atun R, Gurol-Urganci I (2005). One review cannot express all the variables of various model published on diabetes models' various aspects. The present review paper is worth trying over viewing the mathematical model validation on glucose insulin dynamics. Hyperglycemia or hypoglycemia is a condition when concentration levels of glucose are beyond the normal range 70–110mg/dl, then the individual is believed to suffer from issues related to blood glucose. Furthermore, Diabetes mellitus is the glucose-insulin regulatory system's disease (Bergman, Finegood, Kahn 2001) that is known as hyperglycemia, for the interaction loops of glucose-insulin. Disease includes changes in retina, kidney diseases, diabetic nerve pain and other complications suffering various diabetic patients as well as regarding the affected population's size, among the world's worst diseases one is diabetes mellitus WHO, (2017).

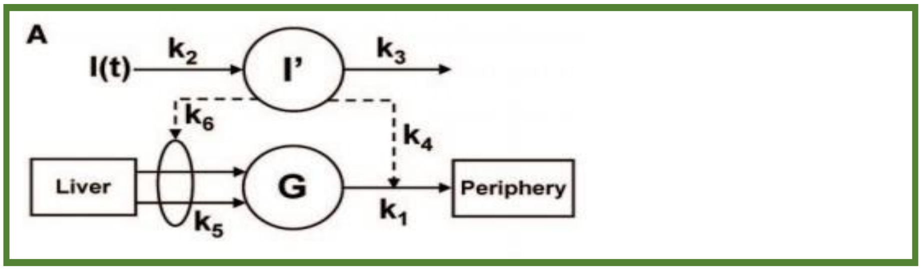
It encourages to review present paper to study the glucose-insulin endocrine regulatory system by minimal model. Many mathematical models were developed by many researches to study the regulatory pathway of insulin in utilizing glucose. The "minimal model" is the most noticeable model that comprises minimal parameters (Bergman, C. Cobelli 1980) such as for estimating "Insulin Sensitivity (SI)" and "Glucose Effectiveness (SG)" from "IVGTT (Intravenous Glucose Tolerance Test)" data through sampling over definite times, which focuses on glucose synthesis and breakdown and utilization in a short time period at time t = 0, starting from the intake of food. Other mathematical models like ordinary differential equation addressing the insulin secretion are based on controls by exercise and meals according to Mari(2002).

Differential equations that describe dynamically changing phenomena, evolution, and variations in the daily usage and in scientific fields as weather modeling, designing the reaction rates, genetic variations and even in market price analysis etc.

The minimal model: Fig. 2A represents the minimal model's diagrammatical representation; Fig. 2B explains the underlying minimal assumptions of insulin and glucose kinetics after injection. The following are included in the required processes:

1) Overnight fasting condition, leads to production of endogenous renal (and hepatic) glucose through basal glucose utilized by brain (total's 50%) as well as other tissue.
2) Post-Prandial Blood sugar explains the measures of glucose after two hours of eating any meal it means the ability of glucose for enhancing its own disposal as well as suppresses production of liver, which is independent activity of the plasma insulin response (Ader, (1997); Bergman(1979),
3) Carbohydrate intake causes a rapid response of insulin significant for renormalization of glucose leads to affect insulin levels on glucose uptake and production is not manifested immediately, however, in insulin's actions a considerable temporal delay is required by modeling.

How is the minimal model being useful? Various independent laboratories validated the model w Korytkowsk (1995) and, associated with experiment work, which helps to improve the physiology and pathophysiological conditions understanding paves to study the tools useful in the clinical and in epidemiological and genetic studies (Flanagan,2007).



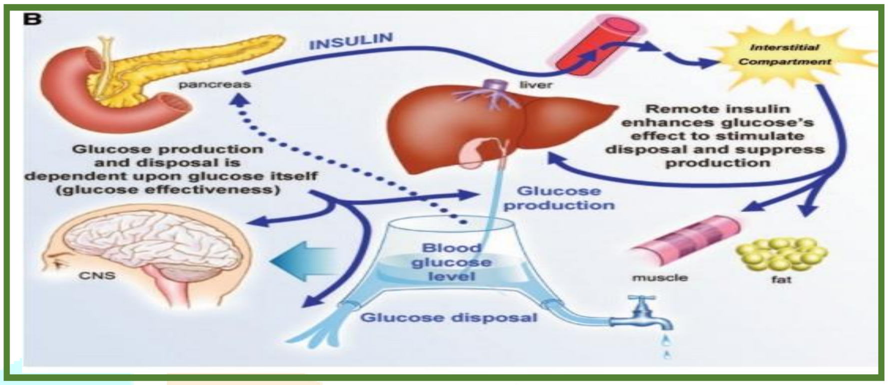


Fig2: Glucose Kinetics' Minimal model. 2A) Insulin in plasma [I(t)] crosses the endothelial barrier for entering interstitial fluid (I). Glucose Production (G) through liver as well as glucose disposal in periphery is remote controlled, (i.e., Interstitial) insulin concentration adapted from Chernick, et al., 1987. 2B) Minimal model's diagrammatic representation. Liver production and insulin dependent (Skeletal muscle) and insulin independent (brain) mechanisms are used to determine the fasting blood glucose level adapted from Bergman (1979).

Glucose-insulin dynamics' mathematical models: Numerous models were recommended to study the glucose-insulin energetics, including various Tolerance Tests. Bolie 1961 proposed Mathematical models were utilized for estimating the insulin-glucose and glucose disappearance dynamics in general, utilizing normal differential equation, as the following simple model:

$$\frac{dG}{dt} = -a_1 G - a_2 I + p, (1)$$

$$\frac{dI}{dt} = -a_3 G - a_4 I \ (2)$$

G = G (t) represent the concentration of glucose, I = I (t) represent the insulin as well as p, a_1, a_2, a_3, $a_4$are parameters respectively.

Parameter defines the characteristics of modeled objects as an amount of a quantity that impacts the output or behavior of a mathematical object which can be a number or function that holds as constant. Variables and Parameters are related to each other Variables are expressed and changeable but parameters typically won't change or change more slowly. For instance while executing many experiments variables are found to be differentiating in each experiment but the parameters are fixed during each experiment and only change between experiments. Parameters appear within function. For example, if $f(x)=ax^2+bx+c$, Where, the variable x is the input to the function. a, b, and c represents the parameters that determine the function behavior.

According to ordinary differential equation modeling started by naming as Minimal model which motivated to generate the modeling path of glucose-insulin dynamics. Bergman (2002) proposed based the pioneering works of Bolie (1961) and Derouich and Boutayeb (2002).

The form of the IVGTT *minimal model* was formulated as:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b, G(0) = p_0 \ (3)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3(I(t) - I_b), X(0) = 0 \ (4)$$

$$\frac{dI(t)}{dt} = p_4(G(t) - p_5)^+ t - p_6(I(t) - I_b), X(0) = 0 \ (5)$$

Where $(G(t) - P_5)^+ = G(t) - P_5$, if $G(t) > P_5$,0, if $G(t) \leq P_5$, P_0, P_1, P_2, P_3, P_4, P_5, P_6, P_7 are parameters Representing as I_b [lUI/ml] represents baseline insulinemia of subject; Gb [mg/dl] represents the baseline glycemia of subject; X(t) [min~1] represents an artificial non-observable variable which represents insulin-excitable tissue glucose uptake activities; I(t) [lUI/ml] represents concentration of blood insulin; G(t) (mg/dl) represent glucose concentration blood at time t minutes; The minimal model in a modified version where parameters related to physical exercise were introduced as an example proposed by Derouich and Boutayeb results as

$$\frac{dG(t)}{dt} = -(1 + q_2)X(t)G(t) + (p_1 + q_1)\big(G_b - G(t)\big), (6)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + (p_3 + q_3)(I(t) - I_b) \ (7)$$

q1, q2, q3 represents physical activity related parameters as well as represents as

q1: the glucose utilization through the liver insulin and muscles based the physical exercise's effect,

q2: effect of insulin with increasing the liver sensibility and physical activity of muscles,

q3: increasing the insulin utilization the physical exercise effect. Also, insulin effectiveness is increased by q3 for improving glucose disposal as well as thus enhancing insulin sensitivity for becoming:

SI = (p3 + q3) (1 + p2)/P2.

As stated by Makroglou,et al., (2006) and some other researchers discussed that the minimal method has minimum number of constants and also had drawbacks such as:

1) Measurable factors fitting the model to be performed in 2 steps: 1st as input data the insulin concentration is used, then by glucose as input data for parameter derivation in the 3rd equation.
2) This model produced results are not realistic (positive equilibrium problem as well as solution are not bounded).
3) To study the delay in insulin action, an artificial non-observable variable X (t) is presented.

Considering the above said remarks De Gaetano and Arino (2000) stated dynamical model, which is an aggregated delay differential model, due to the glucose-insulin system was an integrated physiological dynamic system.

Dynamic model: In the dynamic model the parameters were renamed as a result the equation:

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t)G(t) + b_7, G(0) = G_b + b_0 \quad (8)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5}\int_{t-b_5}^{t} G(s)ds, I(0) = I_b + b_3 b_0 \quad (9)$$

With $G(t) = G_b$ for $-b_5 \leq t<0$.

The dynamic model recalled by Mukhopadhyay etal. (2004) stated that both glucose uptake and insulin secretion parameters simultaneous estimation is allowed by this model, and recommended an extension for the pancreatic response to glucose through organ weight function, w, which is introduced in the integral kernel's delay.

Thus, obtained new model is as below:

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t)G(t) + b_7, G(0) = G_b + b_0 \quad (10)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 \int_{0}^{\infty} \omega(s)G(t-s)ds, I(0) = I_b + b_3 b_0 \quad (11)$$

With $G(t) = G_b$ for $t<0$.

As minimal model problems are solved by the dynamical model, few assumptions are made explicitly or implicitly which are not realistic. Dynamical model was replaced by Li et al. (2001) proposed general model. For instance, it has been assumed by the word $b4I(t)G(t)$ that here mass action law is applied, whereas, a realistic, general and popular substitute is replacing the particular word with $b4I(t)G(t)/(\alpha G(t) + 1)$. In this model delay was restrictive with $G(t) = G_b$ for $-b5 \leq t < 0$ as well as $Gt(\theta) = G(t + \theta)$, $t > 0$, $-b5 \leq \theta < 0$.

Minimal Model Applications: Widely applied to physiological and pathophysiologic conditions, in subjects. Literature revealed that nearly 900 minimal model were performed in various subjects where mathematical treatments are implied (Godsland et al, (2006); Zheng Y, Zhao M (2005) among animals (Pacini et al., 2001) and humans (Flanagan et al., 2007). Various applications have employed based on the sampling for example IGTT resulting insulin secretory and sensitivity response. The minimal model utilization is still continuing still and successfully helpful to perform metabolic profile which may be utilized for population genetics, population dynamics, therapeutic regimens' comparison, and pathophysiologic and physiologic studies.

Discussion and Conclusions: Mathematical models are interesting tools to provide future predictions and for diseases progression understanding by providing visions, improving perceptions, for formal theory clarifying assumptions, allowing for study planning, parameters estimation, sensitivities determination. Comprehensive and simple models which deals with disease's various aspects, in the diabetes case, various model were discussed to date as simple models for example minimal model have advantages of utilizing a few measurable factors' small number. On the other hand, various comprehensive models attempts for representing the system (economic, clinical, biological, etc...) by considering every interaction as parameters. In this review paper, the primary goal was models' as well as studies' overview which deals with diagnosis's various aspects, diabetes progressions further care as well as management.

Seven models were discussed by Bergman et al. (1979) before they selected the "best one" which after that turn out to be most popular minimal model that was highly useful applications and selected based on physiologically activity, having parameters assessed with a moderate accuracy, parameters which can express physiological and reasonable interpretations, for simulating the system dynamics with identifiable parameters' smallest number. But minimal model's various versions were discussed by many researchers for example the physical exercise was taken as parameter considered as a remarkable tool which enhances sensitivity of insulin (SI = (p3 + q3)(1 + p2)/P2.Derouich and Boutayeb (2002). Regarding the practical usefulness of the model it was well acknowledged that in clinical patients the minimal model is used for the insulin sensitivity's routine evaluation. According to authors stated literature review of the present study focused on effective synthesis and utilization of aldohexose by IVGTT. In diabetes research, mathematical modeling's relative significance was studied in present review paper. One of the main problem is how clinically relevant data can be acquired for validating the model as well as implement simulation. In conclusion, present review represented that mathematical model deduced the progression of long-term diabetes. Also in human regulatory systems, a significant issue is diabetes management. The present reviewed paper can demonstrates the glucose-insulin regulatory system's difference among a diabetic person and a normal person. In diabetic patient, levels of glucose concentration after a certain time not easily comes down that indicates the evidences that person is diabetic. The actual medical observations can be interpreted by mathematical model depending on the debated or shared assumptions, suggesting to the critical readers a control for further experimentation as well as hypotheses. In the present review study the models described about the minimal models of Bergman's model was better used to interpret an IVGTT, further this can't be efficiently explained by dynamic model.

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