ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 2, Issue 11, November 2017

Mathematical Modelling of Blood Glucose Level by Glucose Tolerance Test

[1] Venkatesha P., [2] S. Abilash, [3] Abhishek S Shreyakar,[4] Ayana Chandran
[1] Assistant Professor, [2][3][4] 1st Semester
[1] Department of science and humanities Engineering, Sri Sairam college of Engineering, Anekal, Bengaluru, India. [2][3][4] Department of Electronics and communication Engineering, Sri Sairam college of Engineering, Anekal, Bengaluru, India.

Abstract:-- **A complete description of the response of man to large doses of glucose involves the use of more than sixteen rate constants the response of blood-glucose concentration (*G*) as a function of time (*t*) can be represented adequately by an equation involving only four constants in the equation: $G=G_0+Ae^{-\alpha}t \sin \omega t$. The values of these four constants are defined by the four measurements usually made in an ordinary glucose-tolerance test. A new mathematical model for Blood Glucose Regulatory System(BGRS) which includes epinephrine as a third variable in the form, $Y^{\cdot} = AY$, and whose solution has been analysed for equilibrium and stability to provide the blood glucose concentrations for diabetics and non-diabetics. The glucose-insulin regulatory system in relation to diabetes is given, enhanced with a survey on available software. The models are in the form of ordinary differential, partial differential, delay differential and integro-differential equations. The human body needs continuous and stable glucose supply for maintaining its biological functions. Stable glucose supply comes from the homeostatic regulation of the blood glucose level, which is controlled by various glucose consuming or producing organs. Commonly observed combinations of parameter values, the coupled model would not admit equilibrium and the concentration of active insulin in the "distant" compartment would be predicted to increase without bounds. For comparison, a simple delay-differential model is introduced, is demonstrated to be globally asymptotically stable around a unique equilibrium point corresponding to the pre-bolus conditions, and is shown to have positive and bounded solutions for all times.**

keywords:-- **Mathematical Modelling, Blood Glucose Regulatory System, Glucose Tolerance Test, Ordinary Differential Equations and Partial Differential Equations.**

I. INTRODUCTION

Diabetes Mellitus is a disease which is characterized by too high sugar levels in the blood and urine. It is usually diagnosed by means of a glucose tolerance test (GTT). Today, there are over 20 million diabetics in America, six million of whom must take injections of insulin daily, Reporter. It was established by the Kenya Diabetes Management and Information Centre during the free diabetes screening exercise at M. P. Shah hospital, Nairobi, Kenya that 3.3 million Kenyans sure from diabetes, Okwemba. Cases of diabetes in the country have increased from 3.5 to 10 per cent of the population in the past one year. Every 2 years 921 new cases are diagnosed in various clinics in Nairobi, Coast, Central, Nyanza, Eastern and Rift Valley provinces. Diabetic patients require supplement of insulin in the form of regular injections and tablets in addition to modified diet to regulate glucose input, Krimmel et al. The normal blood glucose concentration level in humans is in a narrow range (70–110 mg/dl). Exogenous factors that affect the blood glucose concentration level include food intake, rate of digestion, exercise, reproductive state.

II. MATHEMATICAL MODELLING

Glucose plays an important role in the food metabolism of any vertebrate tissue since it is a source of energy for all tissues and organs, Middleman. The majority of mathematical models were devoted to the dynamics of glucose-insulin, including Intra Venous Glucose Tolerance Test (IVGTT), Oral Glucose Tolerance Test, (OGTT) and Frequently Sampled Intra Venous Glucose Tolerance Test (FSIVGTT). It is quite conceivable, therefore that the body will interpret this as an extreme emergency and thereafter the hormones epinephrine and glucagon come in play. Epinephrine is secreted by the adrenal medulla in response to acute stress (fight or flight response), Duff and Jason. Important effects of epinephrine, some of which are highlighted in the appendix, include;

(a) Increased glucose production from glycogen breakdown
(b)Increased glucose production from lactate and amino acids
(c) Increased fat mobilization by stimulation of hormone sensitive lipase
(d) Small net stimulation of insulin secretion from pancreatic β-cells.

ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 2, Issue 11, November 2017

III. BLOOD GLUCOSE REGULATORY SYSTEM

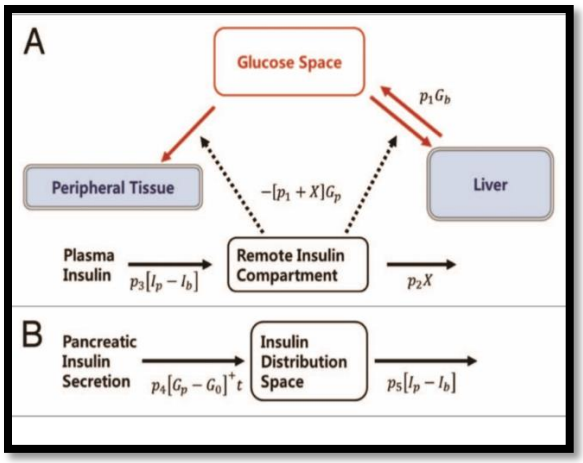

Fig.1

To understand the glucose homeostasis mechanism in the human body, many researchers have studied various mathematical models for the blood glucose regulation dynamics in the human whole-body system. With the help of those models, it has been reproduced that the plasma glucose concentration returns to its normal level from the hyperglycaemic state during the intravenous glucose tolerance test (IVGTT). In particular, since the study of the glucose insulin feedback action of the whole-body glucose regulation system by means of a simple model, a number of artificial models have been developed for understanding the glucose homeostasis in the human body. In the simple model by Bolie, plasma insulin increases due to production in the pancreas and exogenous insulin infusion, whereas plasma glucose diminishes due to various glucose consuming organs such as the liver and peripheral tissues.
If one's glucose concentration level is constantly out of the range (70–110 mg/dl), this person is considered to have blood glucose problems known as hyperglycaemia or hypoglycaemia. Diabetes mellitus is a disease of the glucose-insulin regulatory system hyperglycaemia. (see fig.1)

IV. GLUCOSE TOLERANCE TEST

]The glucose tolerance test is a medical test in which glucose is given and blood samples taken afterward to determine how quickly it is cleared from the blood. The test is usually used to test for diabetes, insulin resistance, impaired beta cell function, and sometimes reactive hypoglycaemia and acromegaly, or rarer disorders of carbohydrate metabolism. In the most commonly performed version of the test, an oral glucose tolerance test (OGTT), a standard dose of glucose is ingested by mouth and blood levels are checked two hours later. Many variations of the GTT have been devised over the years for various purposes, with different standard doses of glucose, different routes of administration, different intervals and durations of sampling, and various substances measured in addition to blood glucose. (see Fig.2)

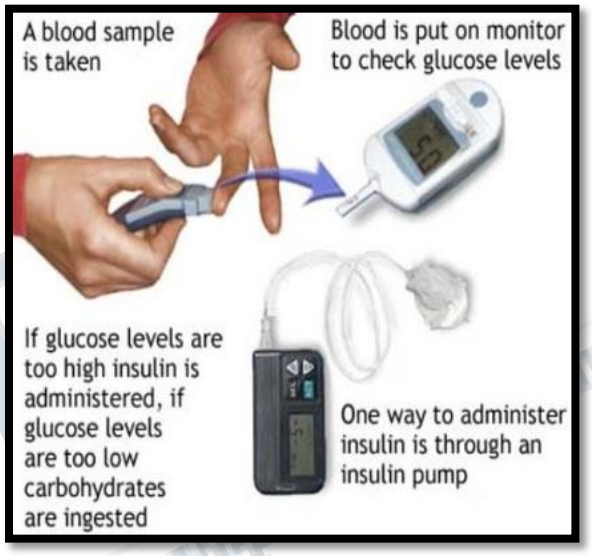

Fig.2

V. ORDINARY DIFFERENTIAL EQUATION

In mathematics, an ordinary differential equation (ODE) is a differential equation containing one or more functions of one independent variable and its derivatives. The term ordinary is used in contrast with the term partial differential equation which may be with respect to more than one independent variable.

ODEs that are linear differential equations have exact closed-form solutions that can be added and multiplied by coefficients. By contrast, ODEs that lack additive solutions are nonlinear, and solving them is far more intricate, as one can rarely represent them by elementary functions in closed form: Instead, exact and analytic solutions of ODEs are in series or integral form. Graphical and numerical methods, applied by hand or by computer, may approximate solutions of ODEs and perhaps yield useful information, often sufficing in the absence of exact, analytic solutions.

ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 2, Issue 11, November 2017

VI. PARTIAL DIFFERENTIAL EQUATIONS

In mathematics, a partial differential equation (PDE) is a differential equation that contains unknown multivariable functions and their partial derivatives. (A special case are ordinary differential equations (ODEs), which deal with functions of a single variable and their derivatives.) PDEs are used to formulate problems involving functions of several variables, and are either solved by hand, or used to create a relevant computer model.

PDEs can be used to describe a wide variety of phenomena such as sound, heat, electrostatics, electrodynamics, fluid dynamics, elasticity, or quantum mechanics. These seemingly distinct physical phenomena can be formalised similarly in terms of PDEs. Just as ordinary differential equations often model one-dimensional dynamical systems, partial differential equations often model multidimensional systems. PDEs find their generalisation in stochastic partial differential equations.

VII. MATHEMATICAL PART

Provided there is no recent digestion, glucose and insulin concentration will be in equilibrium. If g is taken to be excess glucose concentration and h is excess insulin concentration at time t, then at equilibrium, g = h = 0; positive value of g or h corresponds to concentrations greater than the equilibrium values while negative values corresponds to concentrations less than equilibrium values. If h or g is a non-zero value then the body tries to restore the equilibrium. It is assumed that the rate of change of Type equation here.these quantities depend only on the values of g and h. If there is an internal rate at which the blood glucose concentration is being increased, epinephrine is included as a separate variable in this model of blood glucose regulatory system. Thus, if it is assumed that there is no recent digestion, the following systems of differential equations results, Ackerman et al;

$g = -ag - bh + fe$

$h = cg - dh + ke$

$e = -lg - mh + ne$

where e represents epinephrine.
Thus, a, b, c, d, f, k, l, m and n are constants.
From the model in equation

$$\frac{dq}{dt} = -ag - bh + fe \cdots\cdots\cdots (1)$$

Differentiating (1) with respect to t,

$$\frac{d^2q}{dt^2} = -a\frac{dg}{dt} - b\frac{dh}{dt} + f\frac{de}{dt} \cdots\cdots\cdots (2)$$

Substituting for $\frac{dh}{dt} = cg - dh + ke \cdots\cdots\cdots (3)$ and

$$\frac{de}{dt} = -\lg - mh + ne \cdots\cdots\cdots (4)$$ in (1)

$$\frac{d^2q}{dt^2} + a\frac{dg}{dt} + (bc + fl)g + (bk - fn)e + (fm - bd)h = 0 \cdots\cdots\cdots (5)$$

From equation (1) and assuming h=0

$$e = \frac{1}{f}\left(\frac{dg}{dt} + ag\right) \cdots\cdots\cdots (6)$$

Substituting (6) in (5)

$$\frac{d^2q}{dt^2} + a\frac{dg}{dt} + (bc + fl)g + (bk - fn)\left(\frac{1}{f}\left[\frac{dg}{dt} + ag\right]\right) + (fm - bd) \times 0 = 0$$

$$\frac{d^2q}{dt^2} + \left(\frac{bk}{f} + a - n\right)\frac{dg}{dt} + \left(bc + fl + \frac{bka}{f} - na\right)g = 0 \cdots\cdots\cdots (7)$$

The above expression is of the form,

$$\frac{d^2q}{dt^2} + 2\alpha\frac{dg}{dt} + w_0{}^2 g = 0 \cdots\cdots\cdots (8)$$

Where $\alpha = \frac{bk}{f} + a - n$ and $w_0^2 = bc + fl + \frac{bka}{f} - na$

where the value of ω0, which is the system natural frequency is the basic descriptor of the response to a GTT. The model certainly conforms to reality in predicting that the blood glucose concentration tends to return eventually to its optimal concentration (1). It is assumed that α2−ω2 0 is negative, so α2−ω2 0 < 0. This means that characteristic equation of (2) has complex roots. If α2−ω2 0 > 0, then g(t) drops very rapidly from a fairly high value to negative ones below the equilibrium value. The body will interpret this as an extreme

ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 2, Issue 11, November 2017

emergency and large amounts of epinephrine will be secreted.

VIII. APPLICATION

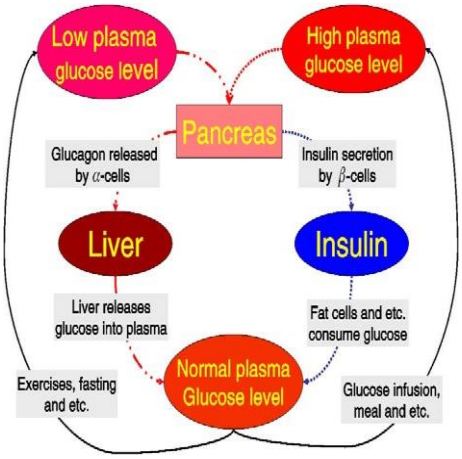

Fig.3

If one's glucose concentration level is constantly out of the range (70–110 mg/dl), this person is considered to have blood glucose problems known as hyperglycaemia or hypoglycaemia. Diabetes mellitus is a disease of the glucose-insulin regulatory system [1,3] which is referred to as hyperglycaemia.

(See Fig.3 for plasma glucose-insulin interaction loops.) Diabetes is classified into two main categories: Type 1 diabetes, juvenile onset and insulin-dependent, and type 2 diabetes, adult onset and insulin-independent. The relative interaction and contribution in the pathogenesis of this disease of various defects of the glucose-insulin regulatory system associated for example with β-cells mass, the responsiveness level of β-cells to glucose and the sensitivity of tissues to insulin, remains to be clarified [2,4]. Complications of the disease include retinopathy, nephropathy, peripheral neuropathy and blindness [7,8]. There are many diabetic patients in the world and diabetes mellitus is becoming one of the worst diseases with respect to the size of the affected population. This motivates many researchers to study the glucose-insulin endocrine regulatory system.

Various in-vivo and in-vitro experiments have shown that the insulin secretion rate (ISR) from pancreatic islets, oscillates in a number of different time scales: The fastest oscillations have a period of tens of seconds and they have been shown to be in phase with oscillations in the free Ca2+ concentration of β-cells; the second fast or rapid oscillations have a period of 5–15 minutes and the slow oscillations referred to usually as ultradian oscillations, have a period within the range of 50–120 minutes [5,6,7]. In addition to these types of oscillations, circadian rhythms have been also observed (cf. [10], originally Peschke and Peschke (1998) [5]).

The rapid oscillations are caused by coordinate periodic secretory insulin bursting from the β-cells. These bursts are the dominant mechanism of insulin release at basal states [5,7]. According to Bertram et al. (2004) [1,7], in some cases compound bursting occurs, the term referred to episodic bursts clustered together and they propose that the compound bursting is responsible for insulin oscillations with a period of approximately 5 minutes.
The ultradian oscillations of insulin concentration are associated to similar oscillations of the plasma glucose concentration, and they are best seen after meal ingestion, oral glucose intake, continuous enteral nutrition or intravenous glucose infusion [3,5].

Many mathematical models have been developed to better understand the mechanisms of the glucose insulin regulatory system. The most noticeable model is the so-called "minimal model" which contains minimal number of parameters [12,14] and it is widely used in physiological research work to estimate glucose effectiveness (SG) and insulin sensitivity (SI) from intravenous glucose tolerance test (IVGTT) data by sampling over certain periods. The IVGTT focuses on the metabolism of glucose in a short time period starting from the infusion of a big bolus (0.33 g/kg) of glucose at time t = 0. Models addressing insulin secretion oscillations include these presented in the papers [4,5,8,9]. A few models are based on the control through meals and exercise (cf. [8,9]). See also a review paper by Mari [5] for a classification of models.

Types of models which have been used in the literature can be classified mathematically as: ordinary differential equations (ODEs), delay differential equations (DDEs), partial differential equations (PDES), Fredholm integral equations (FIES) (in the estimation of parameters problem), stochastic differential equations (SDEs) and integro-differential equations (IDEs). Different software packages can be used for different types of models for numerical analysis and simulations.

IX. CONCLUSION

This paper presents a model for detecting diabetes Mellitus in the blood described by equation. Epinephrine

has been successfully incorporated as a third variable in this model of blood glucose regulatory system (BGRS). The importance of this third variable lies in its ability to help in conducting a reliable test for detecting diabetes in the blood. This leads to a system of linear homogenous equations, which are expressed in the form Y = AY and whose solution provides the blood glucose concentrations for diabetics and non-diabetics. This model has been found to be asymptotically stable since the eigenvalues of the coefficient matrix are complex numbers with negative real parts. Furthermore, the resonance period for this model which is T0 = 2.9847134 hrs, is far less than T0 = 3.5232581 hrs for the existing model. This shows that the glucose concentration returns to normal level within a shorter time. It is worth noting that the model developed in this study only considered an internal rate at which the blood glucose concentration is being increased. Future research may take into consideration an external rate at which the blood glucose concentration is being increased.
The model predicts that oscillations occur if there is sufficient diffusion (values of a scaled diffusion parameter (δ>0.1) to create adequate concentrations mixing in the reacting layers of the cells. With insufficient such mixing, the oscillations are inhibited. An 'unsolved dilemma' having to do with difficulty to produce large enough δ values (δ>0.1) from experimental values of the scaling parameters V, Lbed, where Lbed is the length of the islet bed and V is the velocity of the steady flow of the solution along the 1-dimensional reactor, and large physical diffusion (large DI coefficient) which is needed for the model to predict oscillations, is mentioned at the end of the paper. The software package AUTO97 was used for the simulations

The process of obesity could be described by the whole-body glucose regulation model. Accordingly, with the shortcomings improved, the approach based on modelling is very promising and expected to be beneficial to diabetic patients.

REFERENCE

[1] J. Li, Y. Kuang, C. Mason, Modelling the glucose-insulin regulatory system and ultradian insulin secretory oscillations with two-time delays, submitted for publication.

[2] J. Li, Y. Kuang, B. Li, Analysis of IVGTT glucose-insulin interaction models with time delay, Discrete Contin. Dyn. Syst. Ser. B 1 (1) (2001) 103–124.

[3] L.W. Maki, J. Keizer, Mathematical analysis of a proposed mechanism for oscillatory insulin secretion in perifused HIT-15 cells, Bull. Math. Biol. 57 (1995) 569–591.

[4] Mari, Mathematical modeling in glucose metabolism and insulin secretion, Curr. Opin. Clin. Nutr. Metab. Care 5 (2002) 495–501.

[5] Mukhopadhyay, A. De Gaetano, O. Arino, Modeling the intra-venous glucose tolerance test: A global study for a single-distributed-delay model, Discrete Contin. Dyn. Syst. Ser. B 4 (2) (2004) 407–417.

[6] G. Nucci, C. Cobelli, Models of subcutaneous insulin kinetics. A critical review, Comput. Methods Programs Biomedicine 62 (2000) 249–257.

[7] G. Pacini, R.N. Bergman, MINMOD: A computer program to calculate insulin sensitivity and pancreatic responsitivity from the frequently sampled intravenous glucose tolerance test, Comput. Methods Programs Biomedicine 23 (1986) 113– 122.

[8] R.S. Parker, F.J. Doyle III, N.A. Peppas, The intravenous route to blood glucose control, IEEE Engrg. Medicine Biol. 20 (2001) 65–73.

[9] E. Peschke, D. Peschke, Evidence for a circadian rhythm of insulin release from perifused rat pancreatic islets, Diabetologia 41 (1998) 1085–1092.

[10] G. Pillonetto, G. Sparacino, C. Cobelli, Numerical non-identifiability regions of the minimal model of glucose kinetics: Superiority of Bayesian estimation, Math. Biosci. 184 (2003) 53–67.

[11] N. Pørksen, M. Hollingdal, C. Juhl, P. Butler, J.D. Veldhuis, O. Schmitz, Pulsatile insulin secretion: Detection, regulation, and role in diabetes, Diabetes 51 (Suppl. 1) (2002) S245–S254.

[12] W.R. Puckett, E.N. Lightfoot, A model for multiple subcutaneous insulin injections developed from individual diabetic patient data, Amer. J. Physiol. 269 (1995) E1115–E1124, or Endocrinol. Metab. 32 (1995) E1115–E1124.

[13] E. Ruiz-Velázquez, R. Femat, D.U. Campos-Delgado, Blood glucose control for type I diabetes mellitus: A robust tracking H∞ problem, Control Engrg. Practice 12 (2004) 1179–1195.

[14] Simon, G. Brandenberger, Ultradian oscillations of insulin secretion in humans, Diabetes 51 (Suppl. 1) (2002) S258– S261.