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## Stochastic Modeling of Blood Glucose Levels in Type-2 Diabetes Mellitus

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### ABSTRACT

In this study we develop and analyze a stochastic model for blood glucose levels in type-2 diabetes mellitus patients. The optimal control policies of glucose regulatory system are derived. The sensitivity of the model with respect to the parameters is discussed. This model is useful for optimal drug administration among type-2 diabetes patients.

**Key words:** Stochastic modeling, glucose regulatory system, optimal drug administration, type-2 diabetes, sensitivity analysis

### INTRODUCTION

Food in take is the initial step of glucose entry in to blood plasma. Ingredients of the food namely carbohydrates, proteins, vitamins, fats, and minerals are added to the blood through hepatic porous system. In the process of metabolism the ingredients carbohydrates, proteins and fats will be converted to glucose and further conversion in to energy (Goel and Sastry, 1997). The consumption of glucose in the body/tissue cells will be carried out when the glucose is being transported by any five types of the glucose transporters (GLUTS). GLUT-1 is ubiquitously distributed in various tissues, GLUT-2 and GLUT-3 are in intestine, Kidney and Liver, GLUT -4 is in insulin sensitive tissues such as skeletal muscles and adipose tissues, GLUT -5 is in the Brain and Testis. Glucose consumption in the body is broadly categorized in to two ways namely insulin independent (Observed with GLUT-5) and insulin dependent (observed with GLUT 1 to GLUT-4) (<http://www.diabetes.org>). Insulin play a major role in facilitating the glucose entry to the cell through its membrane (e.g., Adipose tissue and muscle cells), stimulating the enzyme system for conversion of glucose to Glycogen (in liver and muscle cells), slowing down the gluconeogenesis process (liver and muscle cells), regulating the process of Lipogenesis (Liver and Adipose tissue) and promoting the protein synthesis and growth of the body. A major effect of insulin is to promote the entrance of the glucose and Amino acids in the cells of muscle tissue, Adipose tissue and Connective tissues. Glucose enters the cells by facilitated diffusion along an inward gradient created by low intra cellular free glucose and with the specific carrier of glucose (<http://www.endocrineweb.com>). The normal blood glucose concentration level in a healthy human being is in a narrow range (70-110 mg dL<sup>-1</sup>). The glucose metabolism in a healthy person leads to keep the glucose levels within the tight tolerance and it is also controlled by the secretion of insulin in pancreas. The high level plasma glucose signals the pancreas for a two fold action such as Alpha cells in Pancreas will convert some part of the glucose in to Glycogen and it will be stored in the liver; Beta cells in

pancreas to release insulin in to plasma and it lowers the serum glucose concentration level. The liver will convert the stored Glycogen in to glucose when the plasma glucose concentration levels come down.

The fluctuations of glucose levels in the blood are influenced by its varying requirements to the body functioning. When the glucose levels in plasma are high, some part of the glucose will be stored in the liver with a limited storage capacity and supplement the glucose by liver at the needy period of low glucose levels. Alternatively when there are high levels of plasma glucose then pancreas play an important role of releasing insulin and lower the glucose concentrations. Hence, the glucose levels of plasma are regularized to some extent by liver and large extent by Pancreas. Mass of beta cells in pancreas is directly proportional to the release of insulin quantum. In case of diabetic patients, the mass of beta cells is decreased and hence the quantity of insulin secretion comes down. Due to this reason the glucose transportation to insulin dependent tissues and cells will be passive. As a result of this phenomenon increasing levels of plasma glucose. Stochastic modeling of Glucose regulatory system is a suitable tool in studying the blood glucose levels in type-II diabetes mellitus (Fig. 1).

Considerable work has been reported on mathematical modeling of Diabetes Mellitus. The diffusion models of glucose in the blood stream using compartmental models were developed through ordinary differential equations to study the concentrations of glucose and insulin in the blood for diabetes by Kapur (1981). A Mathematical model of early diabetes mellitus by considering the manifestation of the disease as a function of time was developed by Mahan *et al.* (1987). Cavan *et al.* (1996) predicted unrecognized hypoglycemia with insulin dependent diabetes using DIAS model. Linear and non linear compartment models were used to develop a model on the blood glucose metabolism of diabetic by Tresp *et al.* (1999). Parker *et al.* (1999) developed a model based on predictive control algorithm to maintain normoglycemia in the Type-1 diabetic patients using compartment models. Simonyan and Pfunder (2001) had developed a computer model glucose balance system in humans by considering a five compartments model in the body like blood, carbohydrate intake, loss of glucose through renal excretion, insulin-dependent hepatic glucose, combined glucose uptake from the nervous system, muscles, fat etc. Briegel and Tresp (2002) developed a stochastic non-linear state space model for modeling the blood glucose concentration of a diabetic patients based on physiological prior knowledge like occasional blood glucose measurements and information about food in take, physical exercise etc. Mari (2002)

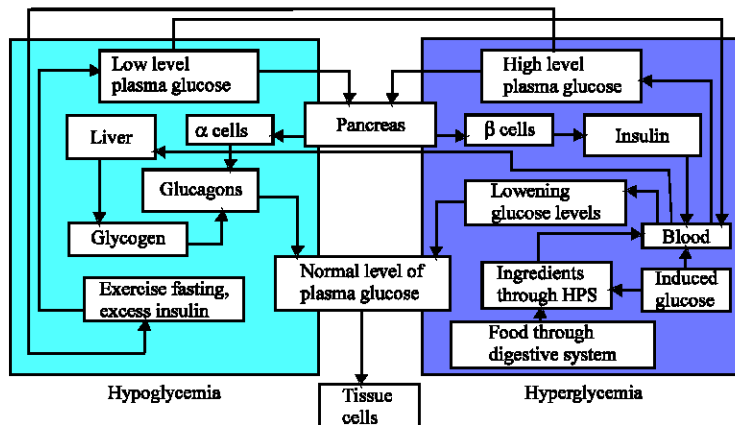


Fig. 1: The schematic diagram of glucose metabolism

developed mathematical models in glucose metabolism and insulin secretion provides a mechanism to govern the insulin glucose regulatory system. Makroglou *et al.* (2006) overviewed various mathematical models which are in the form of ordinary differential, Partial differential, Delay differential and Integro-differential equations assuming the glucose and insulin levels are governed by deterministic laws. Dallaman *et al.* (2006) modeled the glucose production during the meal. Picchini *et al.* (2006) considered stochastic differential equations in modeling the euglycemic hyperinsulinemic clamp. Makroglou *et al.* (2006) overviewed some of the mathematical models for use in the glucose-insulin regulatory system in relation to diabetes. Sparcino *et al.* (2007) predicted the Glucose concentration from continuous glucose monitoring sensor time series. Hovorka *et al.* (2008) developed a glucoregulatory model to create a virtual population of critically ill facilitating *in silico* testing of glucose controllers at the intensive care unit. Smith *et al.* (2009), developed Mathematical Models of Glucose Homeostasis and Its Relationship With Energy Balance and Body Fat. Li *et al.* (2010) developed a physiologically based, multiscale mathematical model of cellular metabolic dynamics in skeletal muscle. Gebregziabher *et al.* (2010) studied the Effect of Trajectories of Glycemic Control on Mortality in Type 2 Diabetes using A Semi parametric Joint Modeling Approach.

From the literature it is observed that there is a significant gap in the area regarding stochastic modeling of type-2 diabetes mellitus. In this study we develop and analyze a stochastic model on blood glucose levels in type-2 diabetes mellitus. It helps to understand the parameters like rates of arrival and consumption of glucose in the plasma i.e., existing plasma glucose levels at a point of time, duration of stay of glucose molecule in the plasma (i.e., the time from its arrival in the blood to its metabolism), energy requirements for various needs of body functions, excess energy for physical works etc. The rates of glucose release and consumption will generate the phases namely Booming (when the rate of glucose arrival dominates rate of glucose consumption), Recession (when the rate of glucose consumption dominates the rate of glucose arrival), Depression (when there is no arrival of food induced glucose, only consumption of existing glucose in plasma) and Recovery (observed during the rate of glucose arrival through liver).

Glucose regulatory system requires a suitable stochastic model for providing the guide spots for diabetes treatment. The optimality policies can be developed to obtain the quantity of food intake, the time gap between two successive food intakes, the energy consumption to physiological maintenance and for extra physical exercises, etc. The sensitivity analysis of the model is useful to get the affective indicators on the regulatory mechanism of diabetes mellitus. Health care industry can develop the decision making protocols on optimal drug administration, affective control and management of diabetes.

## ASSUMPTIONS AND NOTATIONS

The food taken through the digestive system will break the carbohydrates in to glucose. The processes of glucose release and its consumption in the blood per unit time are Markovian with continuous state space and continuous time space. They are assumed as a random variables with continuous state space. The inter arrival time between food intakes and time between two metabolisms are further assumed as continuous random variables. The rate of dissolving glucose per unit time is a continuous random variable follows weibull distribution. The inter arrival time for dissolving glucose is also a random variable follows negative exponential distribution. It is a special case of weibull distribution with  $\beta = 0$  and  $\alpha > 0$ . The induced glucose in the blood has to be disposed off by any of the methods like consumption for release of energy, leaving through renal or excretion passages, transformed to proteins or fats etc.

The rearrival of glucose in to the plasma is instantaneous by various methods of metabolism systems. Shortages in the supply of induced glucose are allowed and they are completely backlogged with liver. The unit release of energy is a function of glucose demand and is denoted by  $\ddot{e}(s)$ ,  $s$  is release of energy and  $s.\lambda(s)$  is a concave function of released energy so that the total expected energy consumption is a convex function. The rate of glucose arrival in to blood is finite and is equal to  $k$  (say  $k > \lambda(s)$ ). The duration of a glucose molecule in the blood stream is a random variable  $X$  that, follows a 3 parameter weibull distribution with p.d.f of the form  $f(t) = \alpha\beta(1-\gamma)^{\beta-1} e^{-\alpha(t-\gamma)^\beta}$ ;  $t \geq \gamma, \alpha, \beta > 0$ .

The distribution function of  $t$  is  $F(t) = P(X \leq t) = 1 - e^{-\alpha(t-\gamma)^\beta}$ . The probability that a glucose molecule will stay for a time period  $t$  in the blood is  $G(t) = P(X > t) = e^{-\alpha(t-\gamma)^\beta}$ .

The rate of glucose consumption from the blood is:

$$h(t) = \frac{f(t)}{G(t)} = \alpha\beta(t-\gamma)^{\beta-1} \text{ for } t > \gamma \tag{1}$$

The process of glucose formation and consumption will be started at  $t = 0$ . The process of glucose formation through food will be taken place up to  $t = A(t_1)$ . The supply of glucose from the food will be up to  $t = B(t_2)$ . The shortage in glucose through food will occur at  $t = B(t_2)$  But, the rate of consumption of the glucose is continued up to  $t = C(t_3)$  (as the glucose levels are at normal values). In order to keep the glucose levels in the normal limits the instantaneous supply of glucose from liver starts again at  $t = C(t_3)$  and continued up to  $t = D(t_4)$ ; the next cycle will be started by re induced food at  $t = D(t_4)$ , the back logged glucose requirement is satisfied.

$T$  is the duration of the cycle in which the formation and consumption of glucose takes place.  $Q$  is the required quantity of the glucose in one cycle of length  $T$ ;  $A$  is the consumption of energy to run the total body/all the physiological organs of the body.  $C$  is the energy consumption per unit time.  $C_1$  is the rate of energy consumption during which the excess requirement to the body (say the physical exercise);  $C_2$  is the energy consumption during the shortage of direct glucose obtained from the food (The energy consumption during this time is due to supplying of glucose from liver). The schematic diagram representing glucose levels in blood is shown in Fig. 2.

**STOCHASTIC MODEL**

Let  $I_g(t)$  be the glucose concentration level in the blood at time  $t$  ( $0 < t < T$ ). The differential equations describing instantaneous state of  $I_g(t)$  over the Cycle length  $T$  are:

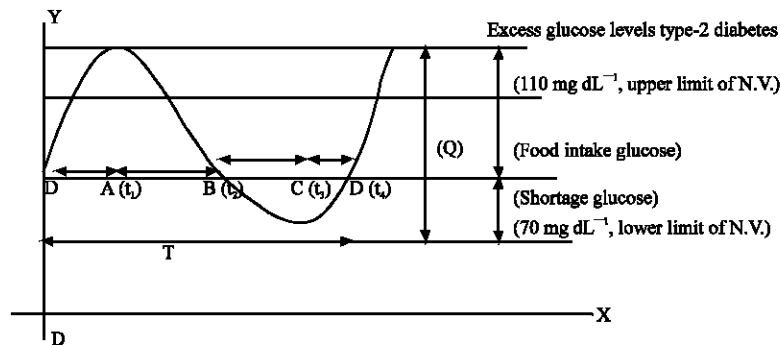


Fig. 2: The schematic diagram of glucose dynamics

$$\frac{d}{dt}I_g(t) = k - \lambda(s) \text{ for } 0 \leq t \leq \gamma \tag{2}$$

$$\frac{d}{dt}I_g(t) + h(t) \cdot I_g(t) = k - \lambda(s) \text{ for } \gamma \leq t \leq t_1 \tag{3}$$

$$\frac{d}{dt}I_g(t) + h(t) \cdot I_g(t) = -\lambda(s) \text{ for } t_1 \leq t \leq t_2 \tag{4}$$

$$\frac{d}{dt}I_g(t) = -\lambda(s) \text{ for } t_2 \leq t \leq t_3 \tag{5}$$

$$\frac{d}{dt}I_g(t) = k - \lambda(s) \text{ for } t_3 \leq t \leq t_4 \tag{6}$$

with the initial conditions  $I_g(0) = 0$ ;  $I_g(t_2) = 0$  and  $I_g(T) = 0$

Substituting  $h(t)$  and solving the above differential Eq. 2 to 6, the existing glucose stock in the blood at time  $t$  can be obtained as:

$$I_g(t) = [k - \lambda(s)]; 0 \leq t \leq \gamma \tag{7}$$

$$I_g(t) = e^{-\alpha(t-\gamma)\beta} \left[ \int_{\gamma}^t (k - \lambda(s)) e^{\alpha(u-\gamma)\beta} du + (k - \lambda(s))\gamma \right]; \gamma \leq t \leq \gamma t_1 \tag{8}$$

$$I_g(t) = e^{-\alpha(t-\gamma)\beta} \left[ \int_{t_1}^{t_2} \lambda(s) e^{\alpha(u-\gamma)\beta} du + \int_{t_1}^{t_2} \lambda(s) e^{\alpha(u-\gamma)\beta} du \right]; t_1 \leq t \leq \gamma t_2 \tag{9}$$

$$I_g(t) = \lambda(s) (t_2 \leq t \leq t_3) \tag{10}$$

$$I_g(t) = (k - \lambda(s))(t - T); t_3 \leq t \leq t_4 \tag{11}$$

The loss of glucose concentration level due to leaving the glucose molecule during the time interval

$$(0, T) \text{ is } L_g(T) = k \cdot t_1 - (s) \cdot t_2 \tag{12}$$

The requirement of glucose during the shortage in the specified level at time  $t$  ( due to the contribution of pancreas, by releasing glucagons through  $\alpha$  cells) is:

$$B(T) = (t) = (t_3 - t_1) \lambda(s) \text{ for } t_2 < t < t_3 \tag{13}$$

The stock of glucose in the blood in a cycle of length  $T$  is obtained as:

$$Q = k.t_1 + k.(T-t_3) \tag{14}$$

Let  $E(t_1, t_2, s)$  be the expected total energy consumption per unit time. Since the total consumption of energy is the sum of the energy consumption on (1) maintenance of body psychological organs, (2) requirement to physical exercise, and (3) overall consumption during shortage of direct glucose (i.e., supplied by liver).

$$E(t_1, t_2, s) = \frac{A}{T} + \frac{CO}{T} + \frac{C_1}{T} \left[ \int_0^{\gamma} h(t) dt + \int_{\gamma}^{t_1} h(t) dt + \int_{t_1}^T h(t) dt \right] + \frac{C_2}{T} \int_{t_2}^{t_3} I_g(t) dt \tag{15}$$

The expected total energy consumption per unit time is:

$$\begin{aligned} E(t_1, t_2, s) = & \frac{A}{T} + \frac{C}{T} [k.t_1 + k.(T - t_3)] + \frac{C_1}{T} \left\{ \int_0^{\gamma} (k - \lambda(s)) t dt \right. \\ & + \frac{C_1}{T} \int_{\gamma}^{t_1} e^{-\alpha(t-\gamma)\beta} \int_{\gamma}^t (k - \lambda(s)) e^{\alpha(u-\gamma)\beta} du + (k - \lambda(s)) \gamma \Big\} dt \\ & + \frac{C_1}{T} \int_{\gamma}^{t_1} e^{-\alpha(t-\gamma)\beta} \left[ \int_{t_1}^{t_2} (\lambda(s)) e^{\alpha(t-\gamma)\beta} dt - \int_{t_1}^t \lambda(s) e^{\alpha(t-\gamma)\beta} dt \right] dt + \frac{C_2}{T} \left[ \int_{t_1}^{t_3} \lambda(s) (t_2 - t) dt \right] \end{aligned}$$

on simplification  $E(t_1, t_2, s)$  can be obtained as:

$$\begin{aligned} E(t_1, t_2, s) = & \frac{A}{T} + \frac{Ck}{2T} [2t_1 + T - t_2] + \frac{C_1 k}{T} \left[ \frac{t_2^2}{2} + \frac{2(t_1 - \gamma)^{\beta+2} \alpha}{(\beta+1)(\beta+2)} - \frac{\alpha}{\beta+1} t_1 (t_1 - \gamma)^{\beta+1} \right] \\ & + \frac{C_1 \lambda(s)}{T} \left[ \frac{t_2^2}{2} - t_1 t_2 + \frac{\alpha}{\beta+1} (t_2 - t_1) (t_2 - \gamma)^{\beta+1} + \frac{\alpha}{\beta+1} t_2 (t_2 - \gamma)^{\beta+1} - \frac{\alpha \alpha (t_2 - \gamma)^{\beta+2}}{(\beta+1)(\beta+2)} \right] \\ & + \frac{C_2 \lambda(s)}{8T} [2Tt_2 - t_2^2 - T^2] \end{aligned} \tag{16}$$

The excess release of energy rate function  $P(t_1, t_2, s)$  is

$$P(t_1, t_2, s) = S.\lambda(s) - E(t_1, t_2, s) \tag{17}$$

Substituting Eq. 16 in Eq. 17

$$\begin{aligned} P(t_1, t_2, s) = & S.\lambda(s) - \frac{A}{T} - \frac{Ck}{2T} [2t_1 + T - t_2] - \left[ \frac{C_1 k}{T} + \frac{T_1}{2} + \frac{2\alpha(t_1 - \gamma)^{\beta+2}}{(\beta+1)(\beta+2)} - \frac{\alpha t_1 (t_1 - \gamma)^{\beta+1}}{\beta+1} \right] \\ & - \frac{C_1 \lambda(s)}{T} \left[ \frac{t_2^2}{2} - t_1 t_2 + \frac{\alpha(t_2 - t_1)(t_2 - \gamma)^{\beta+1}}{\beta+1} + \frac{\alpha t_2 (t_1 - \gamma)^{\beta+1}}{\beta+1} - \frac{2\alpha(t_2 - \gamma)^{\beta+2}}{(\beta+1)(\beta+2)} \right] \\ & - \frac{C_2 \lambda(s)}{8T} [2Tt_2 - t_2^2 - T^2] \end{aligned} \tag{18}$$

**OPTIMAL ENERGY RELEASE OF THE GLUCOSE STOCK LEVELS**

To find the optimal values of  $t_1$ ,  $t_2$  and  $s$ , equate first order partial derivatives of  $P(t_1, t_2, s)$  with respect to  $t_1$ ,  $t_2$  and  $s$  to zero.

$$\begin{aligned} \frac{\partial}{\partial t_1} P(t_1, t_2, s) &= 0 \\ \Rightarrow \frac{Ck}{T} + \frac{C_1 k}{T} \left[ t_1 + \frac{\alpha(t_1 - \gamma)^{\beta+1}}{\beta+1} + \alpha t_2 (t_1 - \gamma)^\beta \right] \\ &+ \frac{C_1}{T} \lambda(s) \left[ -t_2 - \frac{\alpha(t_2 - \gamma)^{\beta+1}}{\beta+1} + \alpha t_2 (t_1 - \gamma)^\beta \right] = 0 \end{aligned} \tag{19}$$

Similarly

$$\begin{aligned} \frac{\partial P(t_1, t_2, s)}{\partial t_2} &= 0 \\ \Rightarrow \frac{KC}{2T} - \frac{C2\lambda(s)}{4T} (T - t_2) - \frac{C_1}{T} \lambda(s) \left[ t_2 - t_1 + \frac{\alpha(t_2 - \gamma)^{\beta+1}}{(\beta+1)} + \alpha(t_2 - t_1)(t_2 - \gamma)^\beta \right] &= 0 \end{aligned} \tag{20}$$

and

$$\begin{aligned} \frac{\partial P(t_1, t_2, s)}{\partial s} &= 0 \\ \Rightarrow s = \frac{\lambda(s)}{\lambda(s)} + \frac{C_2}{8T} [2Tt_2 - t_2^2 - T^2] + \frac{C_1}{T} \left[ \frac{t_2^2}{2} - t_1 t_2 + \alpha(t_2 - t_1)(t_2 - \gamma)^{\beta+1} + \frac{\alpha}{\beta+1} t_2 (t_2 - \gamma)^{\beta+1} - \frac{2\alpha(t_2 - \gamma)^{\beta+2}}{(\beta+1)(\beta+2)} \right] \end{aligned} \tag{21}$$

From the Eq.19-21, it is observed that the optimal values of  $t_1$ ,  $t_2$  and  $s$  are influenced by the functional form of  $\lambda(s)$ .

Let  $t_1^0$  is the optimal time at which the food intake glucose is stopped, because it achieved the maximum released glucose stock level in the blood,  $t_2^0$  is the optimal time at which the shortage in the food intake glucose stock levels is occurred and  $s^0$  is the optimal energy released with existing glucose stocks. The optimal values of  $t_1^0$ ,  $t_2^0$  and  $s^0$  can be obtained by specifying the functional form of  $\lambda(s)$  and substituting it in Eq. 19-21 and solving them. The optimal values of  $P$  and  $Q$  say  $P^0$ ,  $Q^0$  are also obtained with the Eq. 18 and 14.

**NUMERICAL ILLUSTRATION**

As a numerical illustration, consider a linear function:

$$\lambda(s) = a - b.s \tag{22}$$

Let us consider  $a = 25$ ;  $b = 1$ , which represents the demand as a linear function of released energy.



Table 1: Optimal quantity of Q,s,P

a	b	C	C1	C2	$\alpha$	$\beta$	$\gamma$	k	T	A	T1	T2	Q	s	P			
25	1	0.2	0.2	2	0.2	4	0	4	10	50			13.884					
		0.5											14.392					
		0.8											14.76					
25	1	0.2	0.2	2	0.2	0.4	0	4	10	50		6.538	13.884					
			0.3										6.136	14.508				
			0.4										5.869	14.938				
25	1	0.2	0.2	1	0.2	4	0	4	10	50			13.884					
				2												13.9		
				3												13.908		
25	1	0.2	0.2	2	0.2	4	0	4	10	50	1.741		13.884		13.884			
											0.1					1.828	14.046	14.046
											0.2					1.917	14.312	14.312
											0.3					2.007	14.38	14.38
25	1	0.2	0.2	2	0.2	4	0	1	10	50	1.741		9.888	25				
								4			1.741					13.888	24.998	
								7			1.742					17.888	24.997	
25	1	0.2	0.2	2	0.2	4	0	4	8	50			3.472		11.812			
									10							13.884	12.408	
									12							24.304	13.004	
25	1	0.2	0.2	2	0.2	4	0	4	10	50					12.408			
																75	9.908	
																100	7.408	

By substituting Eq. 22 in Eq. 19, 20, 21, 18 and 14 the optimal values of  $t_1^o$ ,  $t_2^o$ ,  $s^o$ , P and Q for different values of the parameters  $\alpha$ ,  $\beta$ ,  $\gamma$  and costs are computed using the MATH CAD on PC and presented in Table 1 using these values the optimal values of the proposed glucose stock levels per cycle and release of energy per unit time are also computed and presented in Table 1.

From Table 1, it is observed that as energy consumption due to preparation of the physiological system say physical exercise ( $C_1$ ) increases, the time gap between the two successive normal glucose levels without shortage ( $t_2$ ) is decreasing, and the optimal glucose requirement (Q) is increasing. Hence it is suggested to have less time gap between two food intakes if the physical exercise is more. It is also suggestible to take more food when the consumption on physical exercise and the time gap between two successive food intakes is more.

The energy consumption during the shortage of normal glucose levels ( $C_2$ ) indicated the increase in optimal glucose requirements (Q). Hence, it is observed that there is more requirement of glucose intake during the supply of glucose by liver. It is observed that if there is an increase in the energy consumption to maintain the body physiological organs (A) then it decrease the extra release of energy (P).when the other parameters and factors remain non influencing. Hence, it indicates that the body composition with over weight and obesity will give the negative impact on the diabetes patients.

If there is an increase in the energy consumption per unit glucose molecule (C), then it increases the optimal glucose requirement quantity levels (Q) that are to be in the blood. Hence it is observed that per unit consumption of energy is directly proportional to the glucose levels when the other parameters are fixed. If there is an increase in the time gap between two food intakes (T), then it indicates the increase in the required optimal glucose levels (Q) assuming other factors remain constants. Hence, it is observed that the optimal glucose levels can be adjusted with time gaps between food intakes.

If there is an increase in the rate of formation of glucose from the food intake ( $k$ ) then it indicates the increase glucose levels ( $Q$ ) assuming other factors and the parameters are fixed. Hence, it is observed that the glucose optimal levels are regulated by the release rates of glucose from the food intake. As the rate of release of glucose from the food ( $k$ ) increases, the unit release of energy ( $s$ ) is decreasing for fixed values of other parameters. Therefore it is suggested to take the food rich in proteins and fibers so that the rate of glucose release is slow, in other words the time gap between the food intakes may be increased. It is also observed that if the capability of utilization of glucose making process by the body is maximum then the released energy ( $s$ ) and the required stock levels ( $Q$ ) are optimal.

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