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Research Paper

Close Loop Design in Glucose Insulin Model with Effect of Physical Exercise

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Abstract. The minimal mathematical models for exercise and its extension is included the major exercise effects on plasma glucose and insulin levels. Model expectations for glucose and insulin dynamics are steady with current literature statistics. The extended model offers innovative disruption test stage for the enlargement of closed-loop glucose control algorithms. Stability analysis as well as qualitative analysis has been made for the model. We treat the controllability and observability of the system for glucose insulin regulatory system during feedback design. Numerical simulation has been carried out to check the effectiveness and actual behavior for the proposed system.

Keywords: Close-Loop designed; Exercise Minimal model; Controllability; Observability.

1. Introduction

With the passage of time, mathematics play an important role in the field of science as well as other disciplines. Mathematical biology is well organized field in the research of new areas with applications of mathematics to facilitate the researchers in interdisciplinary fields. This interdisciplinary research produces new areas between mathematical biology and mathematics for the qualitative as well as quantitative analysis. Also it is helpful for the complex problems of biological sciences with powerful research laboratories [1].

Diabetes is a major problem in the worldwide now a days which consists set of diseases caused by hormonal secretions for pancreatic endocrine in human life is known as diabetes mellitus. Chronic condition can be diagnosed as a diabetes mellitus in human when glucose level increased in human blood. According to the human energy requirement to absorb the extra glucose by the cells produced from insulin secretions. Normally insulin is secreted due to high glucose concentration in human body. On the similar way glucagon is secreted to regulate the hormone up to normal level to increase the glucose level in human blood when glucose level is very low. Diabetes is normally subdivided into two major parts known as type 1 and type 2 on the basis of insufficiency and deficiency.

In type 1, β cells of pancreas are destroyed reaction in the body, causes a very low amount of insulin is produced in the body (down to 10% of normal). Patients with this type have pancreas which produces a small amount of insulin or in some cases pancreas can produce insulin as for a healthy person. But this insulin is not be able to stimulate the body cells to increase the uptake of glucose which is known as insulin resistant. Insulin injection is used for such type of patient treated as type 1 diabetes which start increasing the diabetes cells when glucose level in blood rises above 270mg/dL. In this situation eating heavy meal is suggested to regulate the blood in human body. Hypoglycemia is the dangerous condition for diabetes patient when the amount of glucose (upto 60mg/dL or below) in the human blood [2-5].

Exercise model on separate dynamics on insulin concentration including plasma glucose seized the effects of mild-to-moderate. Haptic production for glucose tempted by exercise to capture the possibility of initial rise for glucose uptake. By the induction of mild-to-moderate exercise is necessary to capture the dynamic of complete observed glucose introducing a bilinear term for glucose uptake. The model of physical exercise from the circulatory system for the removal of plasma insulin is also efficaciously captured [6].

Controllability and observability are major questions in the analysis of a system before fixing on the best control approach to be practical, or whether it is even possible to control or steady the system. Controllability is associated with occasion of imposing the system into a specific state by appropriate control signal. Observability is associated with the state of a system to the possibility of inspecting through output capacity. A final step in the control system propose problem is, of course, to understand the mathematical model of the controller by an genuine physical device, often in the form of appropriate hardware and software, and to intersect this device with the to be controlled physical system [2,5,13].

On the new fractional derivative and application to nonlinear Fisher's reaction–diffusion equation and a very efficient numerical method to solve linear and nonlinear differential equations, including those with non-integer orders are studied in [14-

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19]. The use of new mathematical tools and definitions in this area of research will have a great impact on improving community health by controlling some diseases and related new results are discuss in [20-25]. The SIR model is a system of differential equations that arises in medical science to study epidemiology and medical care for the injured in [26]. The state function of a quantum mechanical system and gives a characterization of a system evolving with time and related real life problem can see in [27-30]. For patients with type 1 diabetes mellitus (T1DM), maintaining glycaemic control can be challenging. Artificial pancreata, which are closed-loop insulin delivery systems, monitor and detect changes in blood concentrations of glucose and deliver insulin when needed [31, 32]. Pivotal trials of new AP technologies are ongoing, and the first hybrid closed-loop system has been approved by the FDA for clinical use. Thus, the closed-loop AP is well on its way to become the digital-age treatment of diabetes [33]. We review the current status of insulin delivery, focusing on clinical evaluations of closed-loop systems [34].

2. Bergman Minimal Model

The Bergman Minimal Model has three sub compartment $I(t)$, $X(t)$ and $G(t)$ represent in followings equation:

$$\frac{dI}{dt} = -n(I(t) - I_b) + p_5 u_1(t) \tag{1}$$

$$\frac{dX}{dt} = -p_2(X(t) - X_b) + p_3(I(t) - I_b) \tag{2}$$

$$\frac{dG}{dt} = -p_1 G(t) - p_4 X(t) G(t) + p_1 G_b + \frac{u_2(t)}{V_0 l_G} \tag{3}$$

Here I_b, G_b and X_b are the basal plasma insulin, basal plasma glucose concentration and basal remote insulin plasma, respectively.

$$\frac{d(PVO_2^{max})}{dt} = -0.8PVO_2^{max}(t) + 0.8u_3(t) \tag{4}$$

Here $PVO_2^{max}(t)$ and $u_3(t)$ represents the exercise level and ultimate exercise intensity respectively [6].

3. Minimal Exercise Model

The purpose for plasma glucose and insulin concentration to capture the effect of exercise which rise the glucose level in hepatic glucose production [8]. Due to increase in hepatic glucose production, glucose plasma initially start rising that demands the glucose by working tissue [11]. Pancreatic responsiveness and inslin sensitivity of diabatic patient using three compartment model such as insulin (I) , remote insulin (X) and plasma glucose (G) are shown in figure 1. The model as written as assume that all necessary insulin infused in modeling for diabetic patient. A protine of the infused insulin enter into the remote compartment, from the circulatory system. The remote insulin actively takes part in permoting the uptake of plasma gulocose into the hepatic and extrahepatic tissues.

The ordinary differential equations for the exercise minimal model is given by

$$\frac{dI}{dt} = -n(I(t) - I_b) + p_5 u_1(t) - I_e(t) \tag{5}$$

$$\frac{dX}{dt} = -p_2(X(t) - X_b) + p_3(I(t) - I_b) \tag{6}$$

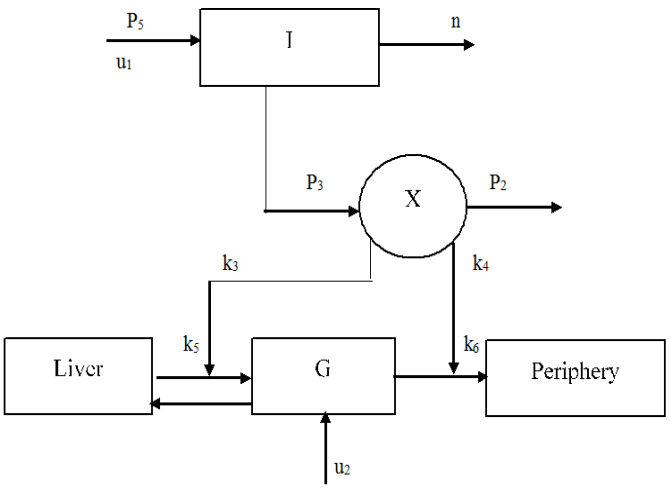

Fig. 1. Flow Diagram of the Model

Table 1. Table of Parameters used in the Model

Parameter	Value	Units
p_1	0.04	$1/min$
p_2	0.037	$1/min$
p_3	0.000012	$1/min$
p_4	1.0	$ml/min.\mu U$
p_5	0.000568	$1/ml$
n	0.142	$m1/min$
G_b	80.0	mg/dl
Vol_G	117	Dl
u_3	1/8	$1/min$

$$\frac{dG}{dt} = -p_1 G(t) - p_4 X(t) G(t) + p_1 G_b + \frac{u_2(t)}{V_0 l_G} + G_{prd}(t) - G_{up}(t) \tag{7}$$

$$\frac{dG_{prod}}{dt} = -a_1 PVO_2^{\max}(t) - a_2 G_{prod}(t) \tag{8}$$

$$\frac{dG_{up}}{dt} = -(a_3 PVO_2^{\max}(t) - a_4) PVO_2^{\max}(t) - a_5 G_{up}(t) \tag{9}$$

$$\frac{dI_e}{dt} = -a_6 PVO_2^{\max}(t) - a_7 I_e(t) \tag{10}$$

$$\frac{d(PVO_2^{\max})}{dt} = -0.8 PVO_2^{\max}(t) + 0.8 u_3(t) \tag{11}$$

Here $I_e(t)$ is the rate of insulin removal, $G_{up}(t)$ and $G_{prod}(t)$ are the rates of glucose uptake and hepatic glucose production induced by exercise respectively [8, 9]. Table of the parameters values used in the model given in Table 1.

By substituting the parameter values, we get

$$\frac{dI}{dt} = -0.142 I(t) + 2.1306367 - I_e(t) \tag{12}$$

$$\frac{dX}{dt} = -0.037 X(t) + 0.555 + 0.00001 I(t) - 0.00018 \tag{13}$$

$$\frac{dG}{dt} = -0.04 G(t) - 1.6 X(t) G(t) + 3.2 + G_{prd}(t) - G_{up}(t) + 0.04700854701 \tag{14}$$

$$\frac{dG_{prod}}{dt} = -0.011 PVO_2^{\max}(t) - 0.9 G_{prod}(t) \tag{15}$$

$$\frac{dG_{up}}{dt} = -(0.000001 PVO_2^{\max}(t) - 0.00013) PVO_2^{\max}(t) - 0.00002 G_{up}(t) \tag{16}$$

$$\frac{dI_e}{dt} = -0.00025 PVO_2^{\max}(t) - 0.009 I_e(t) \tag{17}$$

$$\frac{d(PVO_2^{\max})}{dt} = -0.8 PVO_2^{\max}(t) + 0.8 u_3(t) \tag{18}$$

equilibrium point according to the source value is as: $(I, X, G, G_{prod}, G_{up}, I_e, PVO_2^{\max}(t)) = (14.847, 14.999, 0.56, 0.00977, -5.168, 0.0222, 0.8)$.

Equilibrium points are not lie in the feasible region, the production of glucose will be negative. Due to that reasons model is not fitted for glucose insulin feedback design, we cannot find its controllability and observability of the system.

4. Modified form of Minimal Exercise Model

Physical exercise affects the human body creating plasma insulin which may occurs metabolic changes from its basal level. Waser man with their colleagues studied by applying on dog that during dog exercises that insulin clamp at basal level creating the glucose level. Similar behavior is observed in study of human. Working tissue uptake the amplifies glucose by increasing the exercise also to maintain the plasma glucose which is the major source is contributed by prominent hepatic glycogenolysis.

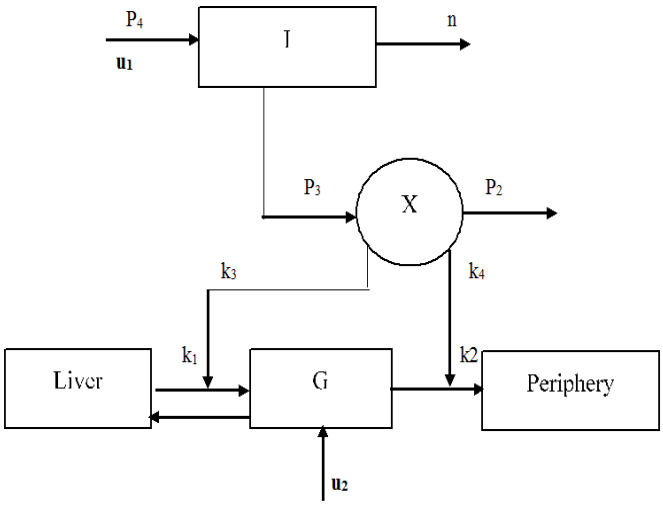

Fig. 2. Flow Diagram of Minimal Exercise Model

Hypoglycemia and plasma glucose decline due to imbalance between hepatic glucose and glucose uptake which causes the complications in regulation of glucose, it is also observed that that lever glucose content decline due to rapid increase of exercise [6,10,11].

We have

$$\frac{dI}{dt} = -n(I(t) + p_4 u_1(t)) - I_e(t) \tag{19}$$

$$\frac{dX}{dt} = -p_2 X(t) + p_3(I(t) - I_b) \tag{20}$$

$$\frac{dG}{dt} = -p_1[G(t)G_b] - X(t)G(t) + p_1 G_b + \frac{w}{V_0 l_G}[G_{prod}(t) - G_{gly}(t)] - \frac{w}{V_0 l_G} G_{up}(t) + \frac{u_2(t)}{V_0 l_G} \tag{21}$$

$$\frac{dG_{prod}}{dt} = a_1 PVO_2^{\max}(t) - a_2 G_{prod}(t) \tag{22}$$

$$\frac{dG_{up}}{dt} = -a_1 PVO_2^{\max}(t) - a_4 G_{up}(t) \tag{23}$$

$$\frac{dI_e}{dt} = a_6 PVO_2^{\max}(t) - a_6 I_e(t) \tag{24}$$

$$\frac{d(PVO_2^{\max})}{dt} = -0.8 PVO_2^{\max}(t) + 0.8 u_3(t) \tag{25}$$

Here $I_e(t)$, $w(t)$ and $G_{gly}(t)$ represent the rate of insulin removal, weight of the body and the decline of glycogenolysis rate, respectively. Hence, the dynamics of glycogenolysis during prolonged exercise can be written as

$$\frac{dG_{gly}}{dt} = \begin{cases} 0 & if\ A(t)x < A_{TH} \\ k & if\ A(t)x \geq A_{TH} \\ \dfrac{G_{gly}(t)}{T_1} & if\ u_3(t) \end{cases} \tag{26}$$

Here A_{TH} is the critical threshold rate energy with decrease the rate of glycogenolysis. It can be written as

$$A_{TH} = u_3 t_{gly}(u_3(t))$$

It follows as

$$t_{gly} = -1.1621 u_3(t) + 87.47$$

where A(t) is the integrated exercise intensity which is calculated by the following equation

Table 2. Table of Parameters used in the Model

Parameter	Value	Units
p_1	0.04	$1/min$
p_2	0.037	$1/min$
p_3	0.000012	$1/min$
p_4	1.0	$ml/min.\mu U$
p_5	0.000568	$1/ml$
N	0.142	$m1/min$
G_b	80.0	mg/dl
Vol_G	117	dl
u_3	1/8	$1/min$
a_1	0.00158	$mg/kg.min^2$
a_2	0.056	$1/min$
a_3	0.00195	$mg/kg.min^2$
a_4	0.0485	l/min
a_5	0.00125	$\mu U/ml.min$
a_6	0.075	$m1/min$
k	0.0108	$mg/kg.min^2$
T_1	6	min

$$\frac{dA}{dt} = \begin{cases} u_3(t) & if\ u_3(t) \geq 0 \\ \dfrac{-A(t)}{0.001} & if\ u_3(t) = 0 \end{cases} \tag{27}$$

A(t) will increase at the rate proportional to $u_3(t)$. Mathematical model takes the form as

$$\frac{dI}{dt} = -n(I(t) + p_4 u_1(t)) - I_e(t) \tag{28}$$

$$\frac{dX}{dt} = -p_2 X(t) + p_3(I(t) - I_b) \tag{29}$$

$$\frac{dG}{dt} = -p_1[G(t)G_b] - X(t)G(t) + p_1 G_b + \frac{w}{V_0 l_G}[G_{prod}(t) - G_{gly}(t)] - \frac{w}{V_0 l_G} G_{up}(t) + \frac{u_2(t)}{V_0 l_G} \tag{30}$$

$$\frac{dG_{gly}}{dt} = -\frac{G_{gly}(t)}{T_1} \tag{31}$$

$$\frac{dG_{prod}}{dt} = a_1 PVO_2^{\max}(t) - a_2 G_{prod}(t) \tag{32}$$

$$\frac{dG_{up}}{dt} = a_3 PVO_2^{\max}(t) - a_4 G_{up}(t) \tag{33}$$

$$\frac{dI_e}{dt} = a_5 PVO_2^{\max}(t) - a_6 I_e(t) \tag{34}$$

$$\frac{d(PVO_2^{\max})}{dt} = -0.8 PVO_2^{\max}(t) + 0.8 u_3(t) \tag{35}$$

Model after putting the parameters, we get

$$\frac{dI}{dt} = -0.142I + 0.1098 - I_e(t) \tag{36}$$

$$\frac{dX}{dt} = -0.05X + 0.000028I - 0.00042 \tag{37}$$

$$\frac{dG}{dt} = -0.035G(t)G_b - 2.8 - X(t)G(t) + 0.81196[G_{prod}(t) - G_{gly}(t)] - 0.8119G_{up} + 0.047 \tag{38}$$

$$\frac{dG_{gly}}{dt} = -0.8119G_{gly} \tag{39}$$

$$\frac{dG_{prod}}{dt} = 0.0015PVO_2^{\max}(t) - 0.056G_{prod}(t) \tag{40}$$

$$\frac{dG_{up}}{dt} = 0.00195PVO_2^{\max}(t) - 0.0485G_{up}(t) \tag{41}$$

$$\frac{dI_e}{dt} = 0.00125PVO_2^{\max}(t) - 0.075I_e(t) \tag{42}$$

$$\frac{d(PVO_2^{\max})}{dt} = -0.8PVO_2^{\max}(t) + 0.64 \tag{43}$$

For the equilibrium point left hand side of the equation 5.0.10 to 5.0.17 to zero. Consequently, there is a unique point of equilibrium. The coordinates of the equilibrium point $(I, X, G, G_{gly}, G_{prod}, I_e, PVO_2^{\max})$ under the source values of the parameters become

$$(0.6797, 0.00039, 80.25, 0.0226, 0.032164, 0.0133, 0.8)$$

We consider equilibrium point is lie in the feasible region. The linearized model is

$$\frac{dI}{dt} = -0.142I - I_e(t) \tag{44}$$

$$\frac{dX}{dt} = -0.05X + 0.000028I \tag{45}$$

$$\frac{dG}{dt} = -80.24X(t) - 0.0000133G(t) + 0.81196G_{prod}(t) - 0.8119G_{up} + 0.047 \tag{46}$$

$$\frac{dG_{gly}}{dt} = -0.16667G_{gly} \tag{47}$$

$$\frac{dG_{prod}}{dt} = 0.0015PVO_2^{\max}(t) + 0.056G_{prod}(t) \tag{48}$$

$$\frac{dG_{up}}{dt} = 0.00195I_e - 0.0485G_{up}(t) \tag{49}$$

$$\frac{dI_e}{dt} = 0.00125PVO_2^{\max}(t) - 0.075I_e(t) \tag{50}$$

$$\frac{d(PVO_2^{\max})}{dt} = -0.8PVO_2^{\max}(t) + 0.64 \tag{51}$$

5. Controllability and Observability

Consider the linear control system

$$\frac{dx}{dt} = D(t)x(t) + E(t)u(t),\ t \in I \tag{52}$$

$$y(t) = F(t)x(t),\ t \in I \tag{53}$$

where $x(t) \in R^n$, $u(t) \in R^p$ and $y(t) \in R^k$ for $t \in I$. I is the closed interval. Elements of matrices are in $L^2(I,R)$. $u(.) \in L^2(I,R^p)$ is called input/control, $y(.) \in L^2(I,R^k)$ is called output and $x(t) \in R^k$, $t \in I$ is called state [12,13]. In this case we have

$$x = [I, X, G, G_{gly}, G_{prod}, I_e, PVO_2^{\max}]^T$$

$$D=\begin{bmatrix} -0.142 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0.000028 & -0.05 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -80.24 & -0.0000133 & 0 & 0.811 & -0.811 & 0 & 0 \\ 0 & 0 & 0 & -0.1666 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -0.0562 & 0 & 0 & 0.00158 \\ 0 & 0 & 0 & 0 & 0 & -0.485 & 0 & 0.00195 \\ 0 & 0 & 0 & 0 & 0 & 0 & -0.075 & 0.00125 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -0.8 \end{bmatrix}$$

Here, considering the glucose concentration as an output and insulin in plasma as the input of the system, then we have

$$x=[00100000]^T$$

and

$$F=[10000000]^T$$

The controllability matrix is

$$R=[E\ DE\ D^2E\ D^3E\ \ldots\ D^7E]$$

and rank of controllability matrix is 1. The observability matrix is

$$O=[F;\ FD;\ FD^2;\ FD^3\ \ldots\ FD^7]^T$$

and rank of observability matrix is 4. The only measured output is concentration of glucose in plasma which we can easily measure. In this system, we observed that the system is neither controllable nor observable. Here, it also shows that rank is of observability matrix is improved and system lies in feasible region for control state.

4. Conclusion

In this article, we found the linear control of the model because if the system is linearly controllable then it may or may not be nonlinearly controllable. If the system is not linearly controllable, then it will never be nonlinearly controllable. In the first minimal exercise model, equilibrium points do not lie in the feasible region, the production of glucose will be negative. Due to that reasons, model is not fitted for glucose insulin feedback design, we cannot find its controllability and observability. In the extension of minimal exercise model, the concentration of insulin is input and glucose concentration is output in the system. We observed that the system is not controllable nor observable. The system is partially controllable and observable means that the exercise may have better impact on diabetes patient. In future work, we need to improve the model for close loop feedback design to control the diseases of diabetic patients.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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