EXPLORING MATHEMATICAL MODELS FOR THE TREATMENT OF TYPE-I DIABETES

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ABSTRACT: *An approach to check the Bergman's minimal model and its modifications for the study of diabetes mellitus. Models are treated for control of artificial pancreas. These models are to simulate glucose insulin system for the treatment of Type I diabetes. These models take into account plasma glucose concentration, generalized insulin and plasma insulin concentration. Models take the only insulin as an input and glucose as an output only. A control system can only be used in the form of closed-loop control to stabilize the system. The concept of controllability and observability for the linearized control is used to have a feedback control. It would enable diabetic patient to control their disease.*

Key words: Controllability, Observability, Diabetes Mellitus, Artificial Pancreas, Ordinary differential Equations.

1. INTRODUCTION

Mathematics is a beneficial branch of science because of its role in developing other branches of science. Its involvement enriches the field. Biomedical Science is one of its major examples which are a pioneer branch of Biology that is growing day by day. Biological science has opened doors for the mathematicians; hence you may say that the new age is era of Mathematics [4]. The scope of mathematics includes mathematical modeling, esoteric mathematics etc. The flow of work, its process, its predictions and outcomes can easily be measured with the help of Mathematical concepts and theory. Therefore, biologists are now extremely dependent on mathematics. This book shall show and prove the significance of Mathematics use in Biological Science [2].

Today diabetes becomes a biggest disease in the world. A large number of people suffering from this disease and the strength is growing day by day. The main reason of diabetes is due to unhealthy food. The researchers of the world try to treat the diabetes. One of them is to design a mathematical model represent glucose-insulin system. Bergman's minimal model is also a mathematical model which describes the glucose insulin system with some parameters. It has two parts one glucose kinetics and the other is insulin kinetics [1].

Controllability is concerned to the opportunity of forcing the system into a particular state by using suitable control the signal. If a state is not convenient, then no signal will be capable to control the state. Observability is associated to the possibility of examining through output capacity, the state of the system. If a state is not visible the controller will never be able to establish the behavior of an unobservable state, and hence cannot use it to claim the system. A control system can only be used in the form of closed loop controlled to stabilize the system [7].

The minimal model is commonly used to analyze the results of glucose tolerance tests in humans. A propose a mathematical model which takes into account all plasma glucose concentration, generalized insulin and plasma insulin concentration. This model shows a long-term diabetes progression but not considers the meals disturbance [1].

Our basic aim is to showing the different result of blood glucose regulatory system especially to healthy and diabetic person. Bergman's minimal model is used for healthy and diabetic person. Basically there are minimal model of Bergman's minimal model and its modification. First represent the glucose kinetics, how react the blood glucose concentration to the insulin concentration and the second is insulin kinetics, how react the insulin concentration to the glucose concentration. In a closed-loop model there is a full loop connection [5-6].The original model is an example of a closed loop model. Both models take insulin as an input and glucose as an output. These models can be used to simulate glucose insulin system for treatment of Type I diabetes. So it has more probability to concern simulations of insulin injections and meal disturbance. It is also use to test model predictive controllers and this gives us a tool in search of artificial pancreas. Controllability and Observability described the parts of advance control system theory. Controllability means what we want to do with this dynamic model under the control input and in Observability we will see what internal concept of model under observation.

2. CONTROLLABILITY AND OBSERVABILITY

The $n \times np$ controllability matrix is given by

$$R = [B, AB, A^2B, A^3B, \dots, A^{n-1}B]$$

The rank (i.e. $rank(R) = n$) , so the system is said to be controllable.

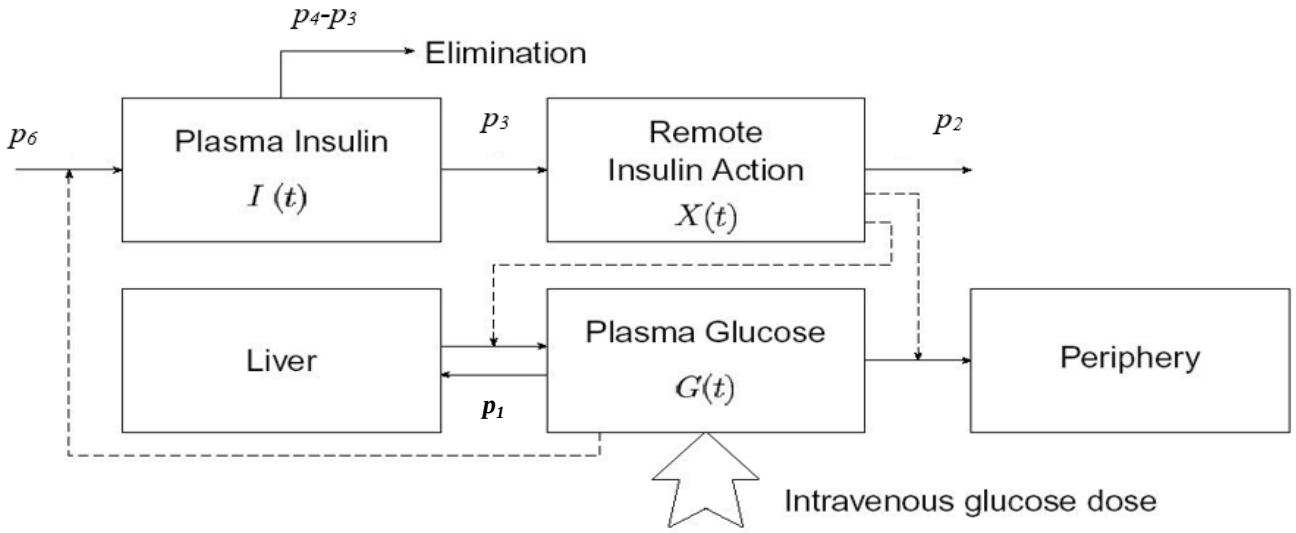
The $nk \times n$the Observabilitymatrix is given by

$$O = [C, AC, A^2C, A^3C, \dots, A^{n-1}C]^T$$

The rank (i.e. $rank(R) = n$) , so the system is said to be observable[8].

3. BERGMAN'S MINIMAL MODEL

In this model the body is described as a tank with basal concentration of insulin and glucose. It has exactly two minimal models. First describe the reaction of blood glucose to the blood insulin concentration and the second describe the reaction of blood insulin to the blood glucose concentration. These models take insulin as input and glucose as an output. These are mostly used to interpret the kinetics during intravalence glucose tolerance test [9].



Model

$$\dot{G} = -(P_1 + X)G + P_1 G_b$$

$$\dot{X} = -P_2 X + P_3 (I - I_b)$$

$$\dot{I} = P_6 (G - P_5) + t - P_4 (I - I_b)$$

Model after parameter substitution

$$\dot{G} = -0.028735G - XG + 2.3275$$

$$\dot{X} = -0.028344X + 0.00005I - 0.00075$$

$$\dot{I} = 0.003349G - 0.3I + 54.2$$

The equilibrium points of the models are

(27.9, 0.0547, 181)

Hence the linearized model is

$$\dot{G} = -0.0834G - 27.9X$$

$$\dot{X} = -0.028344X + 0.00005I$$

$$\dot{I} = 0.003349G - 0.3I$$

Linear Control System

The linear control system is

$$\dot{z} = Az + Bv$$

$$y = Cz$$

Then we have

$$z = \begin{bmatrix} G & X & I \end{bmatrix}^T$$

Where

$$A = \begin{bmatrix} -0.0834 & -27.9 & 0 \\ 0 & -0.028344 & 0.00005 \\ 0.003349 & 0 & -0.3 \end{bmatrix}$$

Controllability and Observability

Here we take the only measured output of glucose concentration in plasma and the only input is insulin concentration then

$$B = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}^T \text{ and } C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}$$

The controllability matrix is

R= [B AB A^2B] and rank (R) = [B AB A^2B] = 3

The observability matrix is

O=[C; CA; CA^2]^T and rank(O)=rank[C; CA; CA^2]^T=3

Hence the system is controllable and observable.

Modified form of Bergman's minimal model

The original minimal model is very good for interpreting to IVGTT and is not good for other purpose. One purpose is to describe the insulin kinetics for Type I diabetes with no endogenous insulin production. Thus in modification it exchange the pancreas with function U(t), which describe the endogenous or exogenous insulin infusion. This model referred us to the modified model. We can use it to glucose insulin system for Type I diabe (1.2) nnot attach it to single type test. [9].

Model

The modified model is

$$\dot{G} = -[P_1 + X(t)]G(t) + P_1 G_b + D(t)$$

$$\dot{X} = -P_2 X(t) + P_3 (I - I_b)$$

$$\dot{I} = -P_4 I + \frac{U(t)}{V_I}$$

$$\dot{D} = -drate.\mathrm{D(t)}$$

$$\dot{G}_{SC} = \frac{G(t) - G_{SC}(t)}{5} - R_{ut\ln}$$

Hence equilibrium points are

(249.39, -0.016426, 5.56, 0.7388, 245.69)

Hence the linearized model is

$$\dot{G} = -0.0123G - 249.9X + D$$

$$\dot{X} = -0.028344X + 0.00005I$$

$$\dot{I} = -0.3I$$

$$\dot{D} = -0.05D$$

$$\dot{G}_{SC} = 0.2G - 0.2G_{SC}$$

Linear Control System

The linear control system is

$$\dot{z} = Az + Bv$$

$$y = Cz$$

Then we have

$$z=[G \quad X \quad I \quad D \quad G_{SC}]^T$$

Here we take the only measured output of glucose concentration in plasma and the only input is insulin concentration then

$$B=\begin{bmatrix}0 & 0 & 1 & 0 & 0\end{bmatrix}^T \text{ and } C=\begin{bmatrix}1 & 0 & 0 & 0 & 0\end{bmatrix}$$

The controllability matrix is

$$R=\begin{bmatrix}B & AB & A^2B & A^3B & A^4B\end{bmatrix}$$

$$rank(R)=rank\begin{bmatrix}B & AB & A^2B & A^3B & A^4B\end{bmatrix}=4$$

Hence the system is not controllable.
The observability matrix is
O=[C; CA; CA^2; CA^3; CA^4]^T and
rank(O)=rank[C; CA; CA^2; CA^3; CA^4]^T=4
Hence the system is neither controllable nor observable.

Modified form of minimal model for Type I diabetes

This also possible to increase functionality of glucose minimal model, so it can use to simulate more an IVGTT, first of all some additions can be made necessary for Type I diabetes. So we will add D(t) to first equation which represent the meal disturbance term. Where P_1, P_2, P_3, and V_G are parameters. [3]

Model

$$\frac{dG}{dt}=-p_1G-X\left(G-G_b\right)+D(t)$$

$$\frac{dX}{dt}=-p_2X+p_3$$

$$\frac{dI}{dt}=-n\left(I-I_b\right)+\frac{U_I(t)}{V_I}$$

$$\frac{dG_{sc}}{dt}=\frac{G(t)-G_{sc}}{5R_{utl}}$$

$$G_{sc}{}^{(0)}=G(0)-5_{ult}$$

where $D(t)=\frac{R_{abs}}{m_{BW}V_G}$, $R_{abs}=B.e^{(drate.t)}$ $T_{50}=a_iD_I+b_i$

, $U_I(t)=\frac{S_it^{si}T_{50}{}^{si}DI}{t\left[T_{50}{}^{si}+t^{si}\right]^2}$

After putting the parameter of the model and we get

equilibrium poits i.e
(194.635493, 44.396837, 37.0925, 194.635493)
Hence the linearized model is

$$\dot{G}=-44.4256G+5.3645X$$

$$\dot{X}=-0.028344X$$

$$\dot{I}=-0.22I$$

$$\dot{G}_{sc}=0.2703G-0.2703G_{sc}$$

Linear Control System

The controllability matrix is

$$R=\begin{bmatrix}B & AB & A^2B & A^3B\end{bmatrix}$$

and $rank(R)=rank\begin{bmatrix}B & AB & A^2B & A^3B\end{bmatrix}=1$

The observability matrix is
O=[C; CA; CA^2; CA^3]^T
Rank (O) = rank[C; CA; CA^2; CA^3]^T=2
Hence the system is neither controllable nor observable.

CONCLUSION

To make an artificial pancreas we are treated Bergman's minimal and its different modified form compare results for better solution to design feedback control. In this regard we need to check the controllability and observability of the model. The first model is Bergman's minimal model. This model keeps some problems. The first one is the original minimal model which is controllable and observable. Now Bergman's modified model and Adriana modified model which cannot be attached to single test. It is neither controllable nor observable. It gives us possibility to simulate the reaction for meal disturbance and reaction to insulin injection or a small change in insulin delivery. The main reason is that glucagon is not present in the model. Glucagon plays an important role in production of insulin and it helps to decrease the blood sugar. Hence in modified model we cannot design the feedback control. Glucose influence the liver to release glucose for blood glucose concentration rises. If glucose is increase then it goes to hyperglycemia a nonlinear. If a nonlinear system is controllable then linear system will also be controllable. If a nonlinear system is neither controllable non observable then we cannot control for artificial pancreas then new model will be design. Thus we conclude that the original minimal model is perfect because it is controllable and observable but glucagon is not present in this model that why we cannot design the feedback. Modified minimal model was not suitable for control design because these models are neither controllable nor observable. But these models are very important for treatment of type 1 diabetes because these models take insulin as an input and glucose as an output. These models can be used to simulate glucose insulin system for treatment of Type I diabetes.

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