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Research Article

Comparison of Glucose Insulin Model for Artificial Pancreas

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Abstract: The controllability and observability of a glucose-insulin system are checked for Bergman's minimal model, Sandhya model, Hovorka model, Sturis Tolic model and their modified form for a type 1 diabetic patient. These models are to simulate the glucose-insulin system for the treatment of type 1 diabetes mellitus. Models take the only insulin as input and glucose as an output. A control system can only be used in the form of closed-loop control to stabilize the system. It would enable diabetic patients to control their disease. Currently, no fully automated artificial pancreas is available. Comparison of controllability and observability are measured for this purpose. These models can be used to simulate a glucose-insulin system for the treatment of type 1 diabetes. This may play an important role in the development of the fully automatic artificial pancreas and stabilize the control loop system for the Glucose Insulin pump.

Keywords: Ordinary differential equation models, Artificial pancreas, Observability, Controllability, Linear control.

1. INTRODUCTION

Diabetes is a worldwide problem of the day. It is a group of diseases enclosed in a single term diabetes mellitus. It is caused by the disorder of the pancreatic endocrine hormonal secretions in the human body. When blood glucose level is too much increased in the body then a chronic condition known as diabetes mellitus is diagnosed in the body. Pancreas and its secretions insulin and glucagon are responsible to regulate the sugar level in our body. Normally when blood glucose concentration is too high in the body then insulin is secreted which stimulates the cells to absorb the extra glucose for the energy or fuel, that they need. Similarly, on the other hand when the blood glucose level is getting very low then stimulation will occur in the pancreas to secrete glucagon to increase the blood glucose level up to a normal level to regulate the system in the body. On the basis of deficiency and insufficiency diabetes is of two types called type 1 and type 2. Diabetes mellitus is a syndrome of diminished carbohydrate, fat, and protein metabolism might of the lack of insulin secretion or lesser sensitivity of the tissues to insulin. Metabolic disorders characterized by hyperglycemia causes diabetes mellitus. The hyperglycemia is the result of an insulin production problem. The chronic hyperglycemia of diabetes results from specific chronic complications and may become the cause of failure of various organs [1]. Type 1 diabetes is insulin-dependent and Type 2 diabetes which is insulin-independent [2]. Regarding a control system, there are two questions one usually came across. The first one is that in what way can we

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influence the system by choosing an appropriate control? Second is what information about the system can obtain from the output of the system? The concept of controllability answers. Controllability is concerned about the opportunity of forcing the system into a particular state by using suitable control of the signal. If a state is not convenient, then no signal will be capable to control the state. Observability is associated with 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. The final step in the control system proposed problem is of course to understand the mathematical model of a controller by a general physical device. A control system can only be used in the form of closed-loop controlled to stabilize the system [3, 4, 5].

Our basic objective was to check the controllability and observability of the exciting model with regard to diabetic patients and non-diabetic persons. The Bergman's minimal model, Sandya model, Hovorka model, and Sturis Tolic model was used for the non-diabetic persons and their modification for type 1 diabetes mellitus. The major mechanism that is involved in glucose regulation consisting of ordinary differential equations is explained in this nonlinear mathematical model [6, 7]. These models are used in the case of type 1 diabetes. There will be no production of insulin by the pancreas and as well as hepatic glucose. Several linearized models for glucose-insulin regulation in diabetic patients of type 1 are discussed in the literature to check the controllability and Observability of the models for feedback control. The minimal model is commonly used to analyze the results of glucose tolerance tests in humans. A minimal model that takes insulin in plasma concentration and glucose output concentrated in the model [8]. The Sandhya model for the glucose-insulin regulatory system describes the advance study to regulate the level of blood glucose for the diabetic and normal person. This model based on plasma insulin, plasma glucose concentration, and generalized insulin. The numerical solution of this model describes the complex situation of the different patients [9, 10].

The artificial pancreas [AP] or automated control system has been developed by researchers in the last decades [11]. Among other proportional-integral design control [12], adaptive control and fuzzy logic control. The model predictive control is the most widely control approach because of its ability to classily handle a broad range of scheme constraints. It is still challenging to overcome the problems of insulin regulation in AP research. The main goal of the artificial pancreas system is safe and prevented recovery from hypoglycemia episodes. The incorporation of insulin antagonist pancreatic hormone and glucagon into the control system is the best way to increase the safety of these systems [13, 14].

The purpose of treatment of controllability and observability of a linearized Hovorka model is to treat the diabetic patients by introducing an artificial pancreas so that these patients can get rid of insulin injected treatment. This model is linearized for diabetes to check controllability and observability. This type of model is very useful due to its formulation but can also predict the system behavior over a range of inputs. Efforts are being made to get an entire automated artificial pancreas. It would enable diabetes patients to control their disease with the help of artificial pancreas.

2. MATERIALS AND METHODS

A mathematically linear control system is given by the following two equations:

$$\dot{x}(t) = A(t)x(t) + B(t)u(t), \qquad t \in I$$

$$y(t) = C(t)x(t), \qquad t \in I$$

Where $x(t) \in \mathbb{R}^n$, $u(t) \in \mathbb{R}^p$ and $y(t) \in \mathbb{R}^k$ for $t \in I$. The matrices A(t), B(t) and C(t) is defined on I and have correct dimensions (i.e., A(t) is $n \times n$, B(t) is $n \times p$ and C(t) is $k \times n$ matrix. I am closed interval, $I = [t_0, t_e], t_0 < t_e < \infty$, respectively. Suppose the elements of the matrices A(.), B(.) and C(.) are in L^2 (I; $\mathbb{R}$). The $n \times np$ controllability matrix is given by :

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

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

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

$$O = [C;\ CA;\ CA^2;\ CA^3 \ldots A^{n-1}C]^T$$

The rank (i.e. $rank(R) = n$), so the system is said to be observable [4, 5,13]

2.1 Bergman's Minimal Model

The body is termed as a chamber with basal absorption of insulin and glucose in this model. 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 the intravalence glucose tolerance test:

$$\dot{G}(t) = -(P_1 + X)G + P_1G_b \tag{1}$$

$$\dot{X}(t) = -P_2X + P_3(I - I_b) \tag{2}$$

$$\dot{I}(t) = P_6(G - P_5) + t - P_4(I - I_b) \tag{3}$$

Where $G(t)$ represents the plasma glucose concentration, plasma insulin variable for remote compartment and plasma insulin concentration are represented by $X(t)$ and $I(t)$ is, G_b is the basal pre-injection value of plasma glucose, I_b is the basal pre-injection value of plasma insulin.P_1, P_2, P_3, P_4, P_5 and P_6 are constant parameters of the model [8]. This model concluded that the rank of the controllability matrix is rank (R) = 3 and the rank of the observability matrix is rank (O) = 3. Hence the system is controllable and observable [14].

2.1.1 Modified form of Bergman's minimal model

The original minimal model is very good for interpreting IVGTT and is not good for another purpose. Thus in modification, it exchanges the pancreas with function $U(t)$, which describes the endogenous or exogenous insulin infusion. This model referred us to the modified model. The glucose-insulin model is described for type I diabetes mellitus. The modified model is

$$\dot{G}(t) = -(P_1 + X)G + P_1G_b + D(t) \tag{4}$$

$$\dot{X}(t) = -P_2X + P_3(I - I_b) \tag{5}$$

$$\dot{I}(t) = P_4 I + \frac{U(t)}{V_I} \tag{6}$$

$$\dot{D}(t) = -drate.D(t) \tag{7}$$

$$\dot{G}_{SC}(t) = \frac{G(t)-G_{SC}}{5} - R_{utln} \tag{8}$$

Where G_b and I_b represents the basal pre-injection value of plasma glucose and basal pre-injection value of plasma insulin, $U(t)$ and $D(t)$ are the insulin infusion rate and the rate of mg glucose pr. dL entering the blood [15]. The R_{utln} are the rate of utilization and the function $G_{sc}(t)$ is introduced to describes the glucose concentration in the subcutaneous layer of the body [8]. This model concluded that the rank of the controllability matrix is 4 and the system is not controllable. The rank of the observability matrix is 4. Hence the system is neither controllable nor observable [14].

2.2 Minimal Model for Type I Diabetes Mellitus

This also possible to increase the functionality of glucose minimal model, so it can use to simulate more and IVGTT, first of all, some additions can be made necessary for type 1 diabetes mellitus. So I is added $D(t)$ to the first equation which represents meal disturbance term.

$$\frac{dG}{dt} = -p_1 G - X\left(G - G_b\right) + D(t) \tag{9}$$

$$\frac{dX}{dt} = -p_2 X + p_3$$

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

$$\frac{dG_{sc}}{dt} = \frac{G(t) - G_{sc}}{5R_{utl}} \qquad G_{sc}^{(0)} = G(0) - 5_{ult}$$

where P_1, P_2, P_3, and V_G are parameters,

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

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

System (9) is stable according to the equilibrium point. In this model the rank of controllability matrix is 1 and the observability matrix is 2. Hence the system is not controllable, not observable [14].

2.3 Model Proposed by Sandhya

It would determine a model for all plasma glucose concentration, generalized insulin, and plasma insulin. Diabetes dynamics is a mathematical model. There are two other models of glucose/insulin use to explain interaction. These are valid to predict blood glucose because these are an inherent requirement of frequently updated information. In this model, take glucose level G, glucose uptake X, insulin level I [9].

The model is:

$$\dot{G}(t) = -m_1 G + m_2 I + m_1 G_b \tag{10}$$

$$\dot{X}(t) = -m_2 X + m_3 I - m_3 I_b + m_6 I_b \tag{11}$$

$$\dot{I}(t) = -m_3 I + m_4 G + m_4 m_5 - m_6 I + m_6 I_b \tag{12}$$

Here *G(t), X(t)* and *I(t)* represent the plasma glucose concentration, generalized insulin variable for the remote compartment and the plasma insulin concentration at time *t* respectively. G_b and I_b are shown the basal preinjection value of plasma glucose *(mg/dl),* and basal preinjection value of plasma insulin (μU/ml) [9]. Here it takes the only measured output of glucose concentration in plasma and the only input is insulin concentration. The rank of the controllability matrix is 3.The rank of the observability matrix is 2. Hence the system is controllable but not observable [16]. The above model for type 1 diabetes mellitus considers for controllability and observability. The model shows that at start time the level of glucose is very high but when give glucose then his level of glucose does not fall. After time passing from 250 mg/dl, it falls only about 275 mg/dl [9]. The rank of the controllability matrix and observability matrix is 3 and 2 respectively. Hence the system is controllable but not observable [16].

2.4 Hovorka Model

The glucose-insulin regulatory system is represented by the input-output relationship between subcutaneous, infused insulin and glucose concentration. Infusion of insulin is represented as input, and the concentration of glucose is taken as an output function. The additional output is taken as a meal instead of intravenous glucose which is used as clinical studies to recover from hypoglycemia. The model description is shown in Fig. 1. A simple but comprehensive model consists of three subsystems. The glucose subsystem describes the absorption of glucose, disposal, and distribution of glucose. The insulin subsystem shows the absorption of insulin, distribution, and disposal of insulin shown in figure [17].

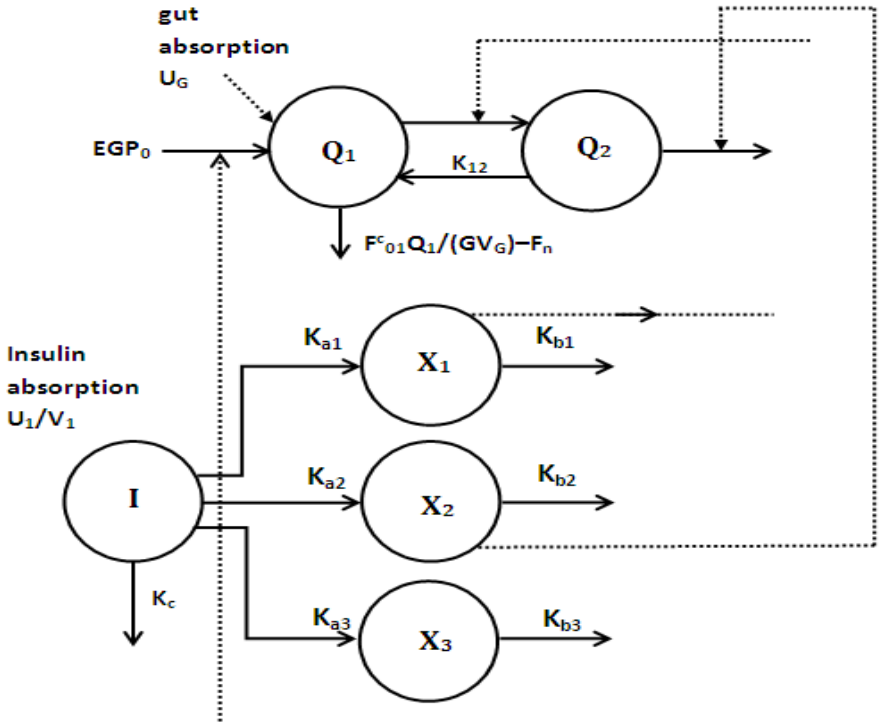

Fig. 1. Flow diagram of Hovorka model

$$\dot{Q}_1(t) = -\left[\frac{F_{01}^C}{V_G G(t)} + x_1(t)\right] Q_1(t) + K_{12} Q_2(t) - F_R + U_G(t) + EGP_0[1 - x_3(t)] \quad (13)$$

$$\dot{Q}_2(t) = x_1(t) Q_1(t) - [K_{12} + x_2(t)] Q_2(t) y(t) \quad (14)$$

$$\dot{B}_1(t) = u(t) - \frac{B_1(t)}{tmax.I} \quad (15)$$

$$\dot{B}_2(t) = \frac{B_1(t)}{tmax.I} - \frac{B_2(t)}{tmax.I} \quad (16)$$

$$\dot{I}(t) = \frac{U_I}{V_I} - k_e I(t) \quad (17)$$

$$\dot{x_1}(t) = -K_{a1} x_1(t) + K_{b1} I(t) \quad (18)$$

$$\dot{x_2}(t) = -K_{a2} x_2(t) + K_{b2} I(t) \quad (19)$$

$$\dot{x_3}(t) = -K_{a3} x_3(t) + K_{b3} I(t) \quad (20)$$

Case I :(G < 4.5)

In this case equilibrium points are (1.1926,0,0,0,0,0,0,0) and (0, -0.2439,0,0,0,0,0,0). The first one is feasible but not the second one.

Case II :(G ≥ 9)

In this case equilibrium points are (3.5733,0,0,0,0,0,0,0) and (0, -0.1624,0,0,0,0,0,0). The first one is feasible but not the second one.

Case III :(4.5 ≤G < 9)

In this case equilibrium points are (a,0,0,0,0,0,0,0) and (0, -0.0969,0,0,0,0,0,0). Where a is constant and a $\in (-\infty, \infty)$ and the first one is feasible but not the second one. The Linearized model about the equilibrium point is:

Case I: (G < 4.5)

$$\dot{Q}_1 = -0.0135Q_1 + 0.066Q_2 - 1.1926x_1 - 0.0161x_3$$

$$\dot{Q}_2 = -0.492Q_2 + 1.1926x_1$$

$$\dot{S}_1 = -0.0181S_1$$

$$\dot{S}_2 = 0.0181 - 0.0181S_2$$

$$\dot{I} = -0.138I$$

$$\dot{x}_1 = -0.006x_1 + 0.00003I$$

$$\dot{x}_2 = -0.06x_2 + 0.00005I$$

$$\dot{x}_3 = -0.03x_3 + 0.00156I$$

Case II: (G ≥ 9)

$$\dot{Q}_1 = -0.003Q_1 + 0.066Q_2 - 3.5733x_1 - 0.0161x_3$$

$$\dot{Q}_2 = 3.5733x_1 - 1.474Q_2$$

$$\dot{S}_1 = -0.0181S_1$$

$$\dot{S}_2 = 0.0181 - 0.0181S_2$$

$$\dot{I} = -0.138I$$

$$\dot{x}_1 = -0.006x_1 + 0.00003I$$

$$\dot{x}_2 = -0.06x_2 + 0.00005I$$

$$\dot{x}_3 = -0.03x_3 + 0.00156I$$

Case III: (4.5 ≤ G < 9)

$$\dot{Q}_1 = 0.003Q_1 - x_1 - 0.0161x_3$$

$$\dot{Q}_2 = x_1 - 0.492Q_2$$

$$\dot{S}_1 = -0.0181S_1$$

$$\dot{S}_2 = 0.0181 - 0.0181S_2$$

$$\dot{I} = -0.138I$$

$$\dot{x}_1 = -0.006x_1 + 0.00003I$$

$$\dot{x}_2 = -0.06x_2 + 0.00005I$$

$$\dot{x}_3 = -0.03x_3 + 0.00156I$$

If consider the glucose concentration in plasma is the only measured output and the insulin concentration in plasma is the only input then for the case I, a rank of controllability and observability matrix is 7 and 8 respectively. For case II, the rank of controllability and observability matrix is 8 and 7 respectively. For case III, the rank of controllability and observability matrix is 7 and 7 respectively. The system in each case is controllable and observable [19].

2.4.1 Modification of Model

Since B_1 and B_2 are a two-compartment chain representing absorption of subcutaneously administrated short-acting insulin and u(t) is the infusion insulin administration so for the sake of simplicity ignore the 2nd and 3rd equation of the system. And the first term of the equation for the insulin concentration rate act as the control [17]. The model reduces to followings:

$$\dot{Q}_1(t) = -\left[\frac{F_{01}^C}{V_G G(t)} + x_1(t)\right] Q_1(t) + K_{12}Q_2(t) - F_R + U_G(t) + EGP_0[1 - x_3(t)] \quad (21)$$

$$\dot{Q}_2(t) = x_1(t)Q_1(t) - [K_{12} + x_2(t)]Q_2(t)y(t) \quad (22)$$

$$\dot{I}(t) = \frac{U_I}{V_I} - k_e I(t) \quad (23)$$

$$\dot{x_1}(t) = -K_{a1}x_1(t) + K_{b1}I(t) \quad (24)$$

$$\dot{x_2}(t) = -K_{a2}x_2(t) + K_{b2}I(t) \quad (25)$$

$$\dot{x_3}(t) = -K_{a3}x_3(t) + K_{b3}I(t) \quad (26)$$

If consider the glucose concentration in plasma is the only measured output and the insulin concentration in plasma is the only input for the case I, the rank of controllability and observability matrix is 5 and 5 respectively. For case II, the rank of controllability and observability matrix is 5 and 5 respectively. For case III, the rank of controllability and observability matrix is 5 and 5 respectively. The system in each case is controllable and observable [18].

2.5 Sturis Tolic Model

Delay differential equation model was proposed to introduce to time delays and model the glucose-insulin endocrine metabolic regulatory. The purpose of this model was to provide proper setup and machinery to the origin of the slow oscillation. This model includes glucose stimulate pancreatic insulin secretion, inhibits hepatic glucose production, insulin glucose uptake, and the glucose enhances own uptake. It is very well known that the increase in blood glucose concentration increases insulin secretion. This insulin increases glucose uptake and decreases glucose production. The purpose of the model was to provide possible machinery for the origin of the slow oscillation. The model includes glucose stimulate pancreatic insulin secretion, inhibits hepatic glucose production, insulin glucose uptake, and glucose enhance own uptake. The purpose of these two models was two provide a possible mechanism for the origin of the ultradian insulin secretion oscillation. It is well known that the

elevation of blood glucose concentration increases insulin secretion. That insulin enhances glucose uptake and inhibits glucose production. It consisting of four negative feedback loops and also positive feedback as glucose enhance its own uptake (see figure 2). Together these loops regulate the amount of insulin, glucose in the body towards an equilibrium which is not necessarily stable [19].

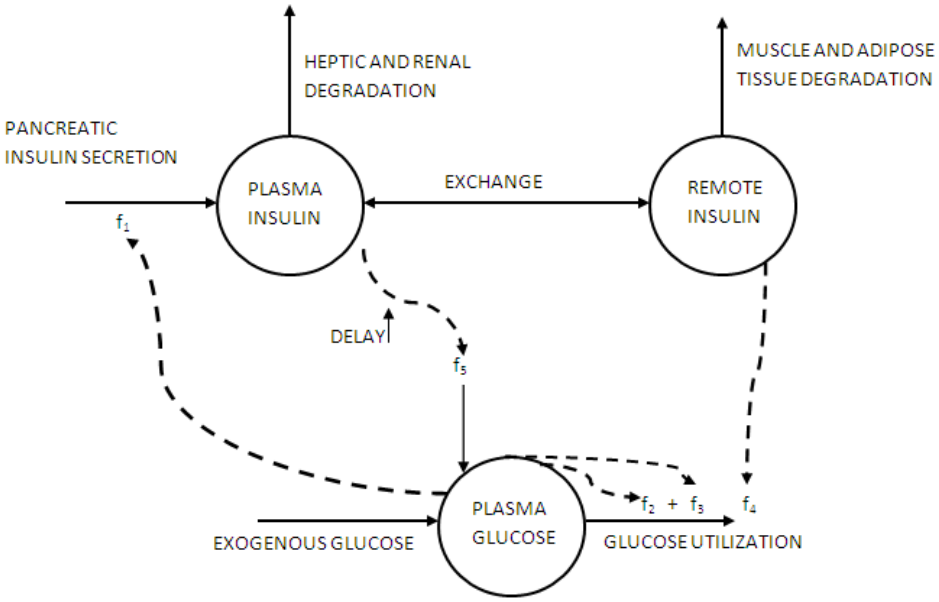

Fig. 2. Flow Diagram of Sturis Tolic Model

This model comprised two major negative feedback loops describing the effect of insulin of glucose production and glucose utilization respectively and both loops include the stimulatory effect on glucose on insulin secretion. The first delay of 5-15 min is due to insulin glucose utilization and another delay of 50-150 min is due to the time lag between the appearances of insulin in plasma. This delay is stimulated by three auxiliary variables which are called the third-order delay [19]. For the physiological regulatory system, the model takes the form:

$$\dot{G(t)} = G_{in} - f_2\left(G(t)\right)f_4\left(I_i(t)\right) + f_5\left(x_3(t)\right) \tag{27}$$

$$\dot{I_p(t)} = f_1\left(G(t)\right) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p} \tag{28}$$

$$\dot{I_l(t)} = E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_i(t)}{t_i} \tag{29}$$

$$\dot{x_1(t)} = \frac{3}{t_d}\left(I_p(t) - x_1(t)\right) \tag{30}$$

$$\dot{x_2(t)} = \frac{3}{t_d}\left(x_1(t) - x_2(t)\right) \tag{31}$$

$$\dot{x_3(t)} = \frac{3}{t_d}\left(x_2(t) - x_3(t)\right) \tag{32}$$

Model after parameters substitutions is given as:

$$\dot{G} = -61.2 + 72e^{-G/1440} - 0.00G - \frac{0.09G}{1+74963.05I_i^{-1.77}} + \frac{180}{1+0.00053e^{0.096x_3}}$$

$$\dot{I}_p = \frac{210}{1 + 785.77e^{-G/3000}} - 0.2334I_p + 0.0182I_i$$

$$\dot{I}_i = 0.066\, I_p - 0.0282I_i$$

$$\dot{x_1} = 0.0833I_p - 0.0833x_1$$

$$\dot{x_2} = 0.0833x_1 - 0.0833x_2$$

$$\dot{x_3} = 0.0833x_2 - 0.0833x_3$$

If consider the glucose concentration in plasma is the only measured output and the insulin concentration in plasma is only input, then the rank of:

$$B = [0\ 1\ 0\ 0\ \ 0\ 0\ ]^T\ ,\ \text{and}$$

$$C = [1\ 0\ 0\ 0\ 0\ \ 0]$$

The controllability matrix is $R = [B\ AB\ A^2B \ldots A^5B]$

$$rank\ (R) =$$

$$rank[B\ AB\ A^2B \ldots A^5B] = 6$$

The Observability matrix is

$$O = [C; CA; CA^2; CA^3; \ldots.; CA^5]^T$$

$$rank(O) = rank[C; CA; CA^2; CA^3; \ldots.; CA^5]^T = 6$$

The only measured output is the concentration of glucose in plasma that can easily measure. The system is controllable and observable.

2.5.1 Modified form of Sturis-Tolic Model

In the case of type, I diabetes, there will be no production of insulin by the pancreas and as well as the hepatic glucose. For the modification of the model to type 1 diabetes mellitus the function modeling the pancreatic insulin production controlled by the glucose concentration, $f_1(G)$ and the function modeling the hepatic glucose production with the time delay t_d collaborated with auxiliary variables $x_1,\ x_2, x_3$ & $f_5(x_3)$ should be substituted zero in the system. Figure 3 shows the physiological glucose-insulin regulatory system in T1DM. The functions and the parameters are the same as in the case of a normal human.

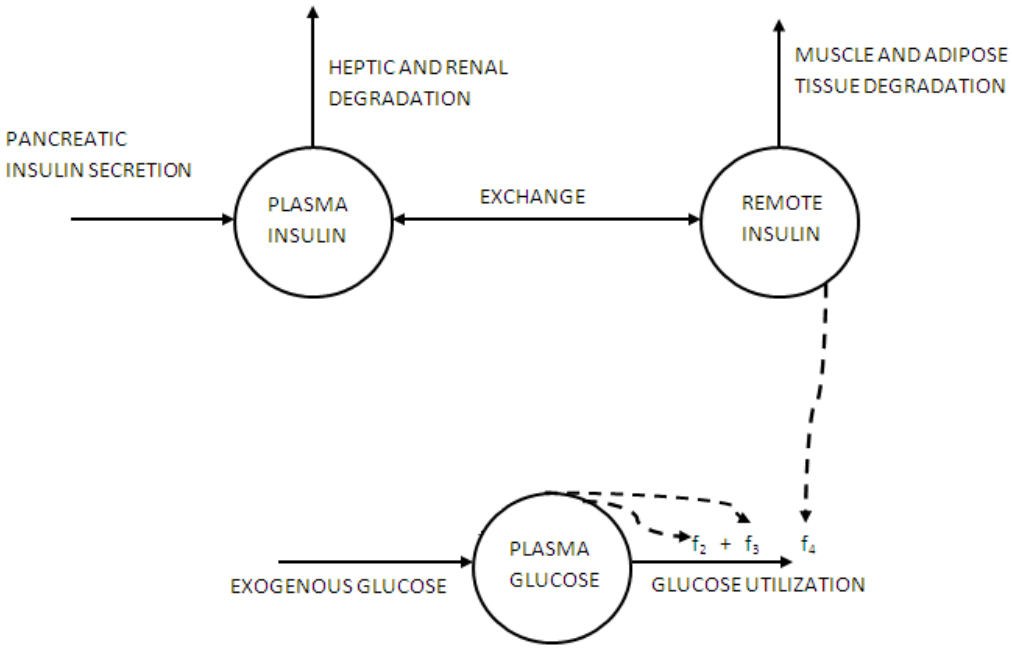

Fig. 3. Flow Diagram of Modified Sturis Tolic Model

The model takes the form:

$$\dot{G}(t) = G_{in} - f_2\left(G(t)\right)f_4\left(I_i(t)\right) \tag{33}$$

$$\dot{I_p}(t) = -E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p} \tag{34}$$

$$\dot{I_l}(t) = E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_i(t)}{t_i} \tag{35}$$

$$\dot{x_1}(t) = \frac{3}{t_d}\left(I_p(t) - x_1(t)\right) \tag{36}$$

$$\dot{x_2}(t) = \frac{3}{t_d}\left(x_1(t) - x_2(t)\right) \tag{37}$$

$$\dot{x_3}(t) = \frac{3}{t_d}\left(x_2(t) - x_3(t)\right) \tag{38}$$

After substitution, the parameter model takes the form:

$$\dot{G} = -61.2 + 72e^{-G/1440} - 0.00G - \frac{0.09G}{1 + 74963.05I_i^{-1.77}} + \frac{180}{1 + 0.00053e^{0.096x_3}}$$

$$\dot{I}_p = \frac{210}{1 + 785.77e^{-G/3000}} - 0.2334I_p + 0.0182I_i$$

$$\dot{I}_l = 0.066\, I_p - 0.0282I_i$$

$$\dot{x_1} = 0.0833I_p - 0.0833x_1$$

$$\dot{x_2} = 0.0833x_1 - 0.0833x_2$$

$$\dot{x_3} = 0.0833x_2 - 0.0833x_3$$

As a matter of fact, the coordinates of the equilibrium point under the nominal values of the parameters becomes (10988.0049, 52.11, 123.2498, 52.11, 52.11, 52.11). The controllability matrix rank is 5 and the observability rank is 1. The system is neither controllable nor observable.

3. RESULTS AND DISCUSSION

To make an artificial pancreas treated Bergman's minimal, model purposed by Sandhya, and Hovorka model and their modified form type 1 diabetes. Compare the results of all models for a better solution to design feedback control. In this regard, need to check the controllability and observability of these models. The first model is Bergman's minimal model. The first one is the original minimal model which is controllable and observable. But modified form is neither controllable nor observable. Sandya mathematical model is made for different conditions of diabetic individuals. The model shows the result is to different situations of progression of diabetes-related to time and severity of the disease. This model is controllable but not observable for both cases of normal and diabetic patients. This model is important in that sense insulin is controllable and two variables out of three are observable in each case. In Hovorka model for type 1 diabetes healthy persons, the system is completely controllable but not observable. Their modified forms for type 1 diabetes mellitus, here observe that the system is controllable but not observable. The Sturis-Tolic model is controllable and observable. In the Sturis-Tolic model for healthy persons, consider that only measured output is the concentration of glucose in plasma that can measure easily. The system is completely controllable and observable. Sturis-Tolic model modified for type 1 diabetes mellitus observes that the system is neither controllable nor observable.

But these models are very important for the treatment of type 1 diabetes because these models take insulin as input and glucose as an output. These models can be used to simulate the glucose-insulin system for the treatment of type I diabetes [3]. The model provides continues glucose measuring in limited time and solutions are bounded in normal values for a healthy person and type 1 diabetes. This is perhaps due to development in the biological approach for the new model: e.g. the hypothesis associated with internal insulin creation through a time-dependent model [20].

4. CONCLUSIONS

It would observe that the Hovorka model provides the best possible results from other models to design the closed-loop for the artificial pancreas. Glucose influence the liver to release glucose for blood glucose concentration rises. If glucose is increased, then it goes to hyperglycemia. If a nonlinear system is controllable then the linear system will also be controllable. If a nonlinear system is neither controllable nor observable, then the system cannot control for artificial pancreas then the new model will be designed. Consider the linear system because if a linear system is controllable and observable, then a nonlinear system may or may not be controllable and observable. So if a nonlinear system is neither controllable nor observable then a new model will be design or a new model for better study. In the future, use the mathematical models which have glucagon with insulin as an input in the system for the automatic artificial pancreas.

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