A LINEAR CONTROL OF HOVORKA MODEL

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ABSTRACT: *Efforts are being made to get an entire automated artificial pancreas. It would enable diabetic patients to control their disease with the help of an artificial pancreas. 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 linearised control system of human glucose insulin systems is used so that we can have a feedback control. Currently no fully automated artificial pancreas is available, although claims are being made to have it soon in market since more than ten years. We have treated a one existing model, i.e. Hovorka model. Hovorka model is treated for type 1 diabetes. This model is treated for linear controllability and Observability.*

Key Words: Automated Artificial Pancreas, Linearised Control System, Controllability, Observability, Hovorka Model

1. INTRODUCTION

Mathematics has always played a fundamental role in the advancement of science. With the passage of time every successive development is enhancing the importance of mathematics and its co-relation with other disciplines of science. As for as mathematical biology is concerned, it is a fast growing and well recognized subject that facilitates the researchers with a modern and an exciting view of mathematics applications. The complexity of the biological sciences has made interdisciplinary involvement essential. This interdisciplinary has made the biology more qualitative and quantitative. Both, for math and biology, it has opened a new world of research by providing a powerful laboratory technique. Mathematical-biology has revealed many thrilling aspects of research if it is used appropriately [1].

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 disorders of the pancreatic endocrine hormonal secretions in the human body. When the 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 [2]. Normally when the 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 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 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 [3].

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 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].

Several linearized models for glucose, insulin regulation in diabetic patients with type 1 are discussed in the literature to check the controllability and Observability of the models for feedback control. The purpose of treatment of controllability and Observability 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 linearised for diabetes to check controllability and Observability. This type 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 [5].

2. CONTROLLABILITY AND OBSERVABILITY

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) are 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 is closed interval, $I = [t_0, t_e]$, $t_0 < t_e < \infty$, respectively $I = [t_0, \infty)$. We suppose the elements of the matrices A (.), B (.) and C (.) are in $L^2(I; \mathbb{R})$ [6].

The function u (.) is also supposed to be in $L^2(I; \mathbb{R}^p)$ is called the input respectively the control of the system. For a given initial value $x_0 \in \mathbb{R}^n$ and input $u(.) \in L^2(I; \mathbb{R}^p)$ of equation $\dot{x}(t) = A(t)x(t) + B(t)u(t)$ also called the state equation of the system. This system has a unique solution of x(.) , and x(.) is absolutely continuous on I with $x(t_0) = x_0$ and the derivative x(.)exists almost everywhere on I. Furthermore equation $\dot{x}(t) = A(t)x(t) + B(t)u(t)$ is satisfied on I , x(t) , $t \in I$ is called a state of tsystem at time t. if we have the solution of x(.) of thequation $\dot{x}(t) = A(t)x(t) + B(t)u(t)$ with initial value x_0 and equation $y(t) = C(t)x(t), t \in I$ establish $y(t) \in L^2(I; \mathbb{R}^k)$ is called output of the system.[6]

1. 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. [4]

3. 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 output function. The additional output is taken as meal instead of intravenous glucose, which is used as clinical studies to recover from hypoglycemia. The model description, is shown in figure. A simple but comprehensive model consists of three subsystems. Glucose subsystem which describes the absorption of glucose, disposal and distribution of glucose. Insulin subsystem which shows the absorption of insulin, distribution and disposal of insulin [5].

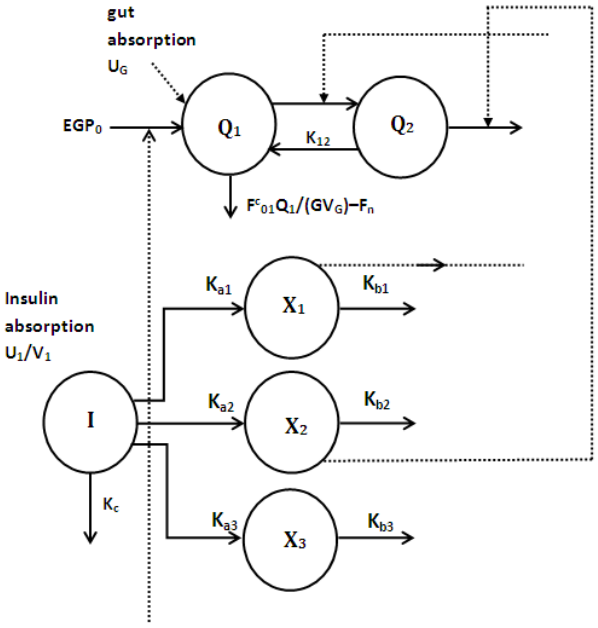

Fig-1: Hovorka Model

Table-1: Model constants and parameters:

Parameters	Values	Units
$*B^f_{IT}$	51.2×10^{-4}	$\min^{-1}\ per\ mUL^{-1}$
$*B^f_{ID}$	2W	$\min^{-1}\ per\ mUL^{-1}$
$*B^f_{IE}$	520×10^{-4}	$\min^{-1}\ per\ mUL^{-1}$
EGP_0	1.61×10^{-2}	$mmol\ Kg^{-1}\ \min^{-1}$
F_{01}	9.7×10^{-3}	$mmol\ Kg^{-1}\ \min^{-1}$
$t_{\max,I}$	55	min
k_{12}	6.6×10^{-2}	$\min^{-1}$
k_{a1}	6.6×10^{-2}	$\min^{-1}$
k_{a1}	6×10^{-2}	$\min^{-1}$
k_{a3}	3×10^{-2}	$\min^{-1}$
k_e	1.38×10^{-1}	$\min^{-1}$
V_I	1.2×10^{-1}	LKg^{-1}
V_G	1.6×10^{-1}	LKg^{-1}
A_G	0.8	$(unitless)$
$t_{\max,G}$	40	min
y^t	6.25	Unit less

$*B^f_{IT} = \frac{k_{b1}}{k_{a1}}, *B^f_{ID} = \frac{k_{b2}}{k_{a2}}$ and $*B^f_{IE} = \frac{k_{b3}}{k_{a3}}$.

Final form

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

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

$$\dot{B}_1(t) = u(t) - \frac{B_1(t)}{t_{\max,I}}$$

$$\dot{B}_2(t) = \frac{B_1(t)}{t_{\max,t}} - \frac{B_2(t)}{t_{\max,I}}$$

$$\dot{I}(t) = \frac{U_I(t)}{V_1} - k_e I(t)$$

$$\dot{x}_1(t) = -k_{a1}x_1(t) + k_{b1}I(t),$$
$$\dot{x}_2(t) = -k_{a2}x_2(t) + k_{b2}I(t),$$
$$\dot{x}_3(t) = -k_{a3}x_3(t) + k_{b3}I(t),$$

4. EQUILIBRIUM POINT

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.

5. LINEARISED MODEL

The linearised model about the equilibrium point is:

Case I :(G <4.5)

$$\dot{Q}_1 = -1.35\times10^{-2}Q_1 + 6.6\times10^{-2}Q_2 - 1.1926x_1 - 1.61\times10^{-2}x_3,$$

$$\dot{Q}_2 = -4.92\times10^{-1}Q_2 + 1.1926x_1,$$

$$\dot{B}_1 = 0$$

$$\dot{B}_2 = 0$$

$$\dot{I} = -1.38\times10^{-1}I,$$

$$\dot{x}_1 = -6\times10^{-3}x_1 + 3\times10^{-5}I,$$

$$\dot{x}_2 = -6\times10^{-2}x_2 + 5\times10^{-5}I,$$

$$\dot{x}_3 = -3\times10^{-2}x_3 + 1.56\times10^{-3}I,$$

Case II :(G ≥ 9)

$$\dot{Q}_1 = -3\times10^{-3}Q_1 + 6.6\times10^{-2}Q_2 - 3.5733x_1 - 1.61\times10^{-2}x_3,$$

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

$$\dot{B}_1 = 0$$

$$\dot{B}_2 = 0$$

$$\dot{I} = -1.38\times10^{-1} I,$$
$$\dot{x}_1 = -6\times10^{-3} x_1 + 3\times10^{-5} I,$$
$$\dot{x}_2 = 6\times10^{-2} x_2 + 5\times10^{-5} I,$$
$$\dot{x}_3 = -3\times10^{-2} x_3 + 1.56\times10^{-3} I,$$

Case III: (4.5 ≤ G <9)

$$\dot{Q}_1 = 6.6\times10^{-2} Q_2 - x_1 - 1.61\times10^{-2} x_3,$$
$$\dot{Q}_2 = 1.474 Q_2 + 3.5733 x_1,$$
$$\dot{B}_1 = 0$$
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$$\dot{x}_2 = -6\times10^{-2} x_2 + 5\times10^{-5} I,$$
$$\dot{x}_3 = -3\times10^{-2} x_3 + 1.56\times10^{-3} I,$$

Linear Control System:

The Linear control System Is

$$\dot{x} = Ax + Bu$$
$$y = Cx$$

In this case we have

$$x = \begin{bmatrix} Q_1 & Q_2 & B_1 & B_2 & I & x_1 & x_2 & x_3 \end{bmatrix}^T$$

Controllability and Observability:

If we consider the glucose concentration in plasma is the only measured output and the insulin concentration in plasma is the only input then

$$B = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \end{bmatrix}^T,$$

and

$$C = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

Case I :(G <4.5)

The controllability matrix is

$$R = \begin{bmatrix} B & AB & A^2B & \ldots\ldots & A^7B & \end{bmatrix},$$
$$rank(R) = rank\begin{bmatrix} B & AB & A^2B & \ldots\ldots & A^7B & \end{bmatrix} = 8.$$

The observability matrix is

$$O = \begin{bmatrix} C; & CA; & CA^2; & CA^3 \ldots\ldots & ; & CA^7 \end{bmatrix}^T,$$

and

$$rank(O) = rank\begin{bmatrix} C; & CA; & CA^2; & CA^3 \ldots\ldots & ; & CA^7 \end{bmatrix}^T = 7.$$

Case II :(G ≥ 9)

In this case $rank(R) = 8.$ and

$rank(O) = 7.$

Case III: (4.5 ≤ G <9)

In this case $rank(R) = 8.$ and

$rank(O) = 7$

The only measured output is the concentration of glucose in plasma that we can easily measure. The system in each case is controllable but not observable.

6. MODIFIED FORM 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 we can ignore the 2nd and 3rd equation of system. And the first term of the equation for insulin concentration rate act as the control. [4]

Model

The model reduces to

$$\dot{Q}_1(t) = -\left[\frac{F_{01}^C}{V_G G(t)} + x_1(t)\right] Q_1(t) + K_{12} Q_2(t) - F_R + U_G(t) + EGP_0\left[1 - x_3(t)\right],$$
$$\dot{Q}_2(t) = x_1(t) Q_1(t) - \left[K_{12} + x_2(t)\right] Q_2(t) y(t),$$
$$\dot{I}(t) = \frac{U_I(t)}{V_1} - k_e I(t)$$
$$\dot{x}_1(t) = -k_{a1} x_1(t) + k_{b1} I(t),$$
$$\dot{x}_2(t) = -k_{a2} x_2(t) + k_{b2} I(t),$$
$$\dot{x}_3(t) = -k_{a3} x_3(t) + k_{b3} I(t),$$

Equilibrium points in each cases are

Case I :(G < 4.5)

(1.1926,0,0,0,0,0) and (0,-0.2439,0,0,0,0). The first one is feasible, but not the second one.

Case II :(G ≥ 9)

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Case III :(4.5≤G<9)

(a,0,0,0,0,0) and (0,-0.0969,0,0,0,0). Where a is constant and $a \in (-\infty, \infty)$ and the first one is feasible, but not the second one.

7. LINEARISED MODEL

The linearized model about the equilibrium point is:

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$$\dot{Q}_2 = -4.92\times10^{-1} Q_2 + 1.1926 x_1,$$
$$\dot{I} = -1.38\times10^{-1} I,$$
$$\dot{x}_1 = -6\times10^{-3} x_1 + 3\times10^{-5} I,$$
$$\dot{x}_2 = -6\times10^{-2} x_2 + 5\times10^{-5} I,$$
$$\dot{x}_3 = -3\times10^{-2} x_3 + 1.56\times10^{-3} I,$$

Case II :(G ≥ 9)

$$\dot{Q}_1 = -3\times10^{-3} Q_1 + 6.6\times10^{-2} Q_2 - 3.5733 x_1 - 1.61\times10^{-2} x_3,$$
$$\dot{Q}_2 = 1.474 Q_2 + 3.5733 x_1,$$
$$\dot{I} = -1.38\times10^{-1} I,$$
$$\dot{x}_1 = -6\times10^{-3} x_1 + 3\times10^{-5} I,$$
$$\dot{x}_2 = 6\times10^{-2} x_2 + 5\times10^{-5} I,$$
$$\dot{x}_3 = -3\times10^{-2} x_3 + 1.56\times10^{-3} I,$$

Case III: (4.5 ≤ G <9)

$$\dot{Q}_1 = 6.6\times10^{-2} Q_2 - x_1 - 1.61\times10^{-2} x_3,$$
$$\dot{Q}_2 = 1.474 Q_2 + 3.5733 x_1,$$
$$\dot{I} = -1.38\times10^{-1} I,$$
$$\dot{x}_1 = -6\times10^{-3} x_1 + 3\times10^{-5} I,$$
$$\dot{x}_2 = -6\times10^{-2} x_2 + 5\times10^{-5} I,$$
$$\dot{x}_3 = -3\times10^{-2} x_3 + 1.56\times10^{-3} I,$$

Controllability and Observability

If we consider the glucose concentration in plasma is the only measured output and the insulin concentration in plasma is the only input

$$B = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 & 0 \end{bmatrix}^T,$$

and

$$C = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

Case I :(G < 4.5)

In this case $rank(R) = 6.$ and $rank(O) = 5.$

Case II :(G ≥ 9)

In this case $rank(R) = 6.$ and $rank(O) = 5.$

Case III: (4.5 ≤ G <9)

In this case $rank(R) = 6.$ and $rank(O) = 5.$

The only measured output is the concentration of glucose in plasma that we can easily measure. The system in each case is controllable but not observable.

8. CONCLUSION

For the purpose automatic artificial pancreas in the glucose regulatory system we discuss Hovorka model which have a simple but comprehensive model consist of three subsystems. For this purpose, we check the controllability and Observability of the system. In Hovorka Model for type 1 diabetes healthy persons, we consider that only measured output is the concentration of glucose in plasma that we can measured easily. The system is completely controllable but not observable. In its modified form for T1DM, we observe that system is controllable but not observable. The main reason is that glucagon is not present in the system. Glucagon plays an important role in production of insulin. Insulin helps to decrease blood sugar. Glucagon influences the liver to release glucose in blood and blood glucose concentration rises. If glucagon is in excess is in excess in the body, it will lead to hyperglycemia. For removing that problem, we use Hovorka Model for T1DM. Glucagon is a part of Hovorka model. But we observe that in each case, the system is controllable but not observable. That's why, we cannot feedback control for artificial pancreas. We treat 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 designed. Most of the models are nonlinear, we have done linear control system for these models In future, if we use a nonlinear control system for model and if model is controllable and observable then a feedback may be design. In that model seven variables are observable only one variable is not observable if we treat and make observable that variable then feedback design for automatic fully artificial pancreas.

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