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An Approach for Artificial Pancreas to Control the Type-1 Diabetes Mellitus

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ABSTRACT

Currently Type 1 diabetes is worldwide issue and challenges for diabetes community for healthy life. Fully automatic artificial pancreas is better solution for diabetic patients to avoid the hyperglycemia/hypoglycemia as it provided the insulin/glucose when needed. For a controllable system a closed loop feedback control may be designed to normalize the blood glucose level. We convert the Sorenson model for Type 1 diabetes because this is the most comprehensive model in the Glucose Insulin Glucagon dynamics for human but the result show that this model has some deficiency in it since the equilibrium point is not in feasible region. We come up with the two cases, for case I: Insulin as the input only and glucose as an output and in case II: insulin and glucagon as an input and glucose as output only. A control system can only be used in the form of closed-loop control to stabilize the system. Controllability and observability of Glucose Insulin system is treated of the Sorensen's Model for type 1 diabetic patients. This may be play an important role in the development of fully automatic artificial pancreas and stabilize the control loop system for the Glucose Insulin Glucagon pump. It would be important for type 1 diabetic patients to control their diseases. We treated Sorensen's Model for type 1 diabetic's patient to check the linear controllability and observability.

KEYWORDS: Sorenson's model; Controllability; Observability; Artificial pancreas; Stability analysis

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 example which is a pioneer branch of Biology that is growing day by day. It is obvious that it cannot be developed without the help of a mathematician. Hence the involvement of mathematics in Biosciences is mandatory for its progress and development. New discoveries and developments are achievable only with the prime contribution of Mathematics [1, 2].

Diabetes is the one of the biggest diseases in the world nowadays. Many millions suffer from the disease and the number is growing. The grow is mostly due to extra use of unhealthy food and the lifestyle of the people in the world. Many researchers try to find methods for diagnosing and treating the disease to overcome such problems. A mathematical model is design to describe the glucose-insulin system. Diabetes is a malfunction in exactly this system.

These mathematical models can be used to diagnose, but also to create simulators to test different treatment types [7]. It is a group of diseases enclosed in a single term diabetes mellitus. It is caused by 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 blood glucose level is getting very low then stimulation will occur in 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 [5].

Close loop insulin delivery in type1 diabetes has been evaluated for treatment of adults and children [12]. Since diabetic patients depending on insulin require insulin administration to maintain blood glucose levels within the normal range, to reduce the burden of such open-loop insulin therapy have been studied by using automatic blood glucose control methods [11]. The compartmental models of glucose metabolism have had many scientific and clinical uses [7]. But in the case of technological application, in the last decades the development of the closed-loop therapy for type 1 diabetes mellitus, called artificial pancreas, has highlighted the need for a mathematical model

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which together with a control algorithm could reach a suitable automatic insulin delivery [8]. Even though the compartmental models are validated with a set of nominal parameters, one of the challenges of artificial pancreas is to deal with the high variability of glucose levels of a single patient [8]. One of the recent outpatient studies about artificial pancreas proposed a data-based mathematical model to synthetize a control algorithm for the full automation of insulin and glucagon administration [9, 10].

In 1970's, first experiment with an AP was made with large device with beneficial limitations. Over the last decade, several clinical studies were made. Insulin pumps used to administrate subcutaneous (SC) insulin and subcutaneous continuous glucose monitoring (CGM) with enzymatic technology. The AP in glucose measurement and insulin infusion occur in peritoneal cavity for example, through a port similar to that used is a promising [13]. The artificial pancreas [AP] or automated control system has been developed by researchers at last decades [14]. Continuous insulin dosing is allowed by continuous subcutaneous insulin infusion systems (CSII). Missing feedback of glucose sensing has fundamental drawback by closed loop control. The idea of closed loop control practically achieve by development of CGMs. Many plans made with the available feedback. Among others PID control [15], adaptive control, and fuzzy logic control. The model predictive control (MPC) 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 AP system is safe and prevented recovery from hypoglycemia episodes. The incorporation of insulin antagonist pancreatic hormone and glucagon into the control system is a best way to increase safety of these systems. The major problem is the absence of a stable glucagon formulation [15, 16]. An augmented minimal model was proposed that incorporate the glucagon effect [18].

The diabetes Mellitus is a metabolic disorder caused by either production or action of insulin. In type 1 diabetes mellitus there is no production of insulin by pancreas and its direct effect is hyperglycemias that increase a risk to life in the model purposed by Sorenson [3]. It is the modified to type 1 Diabetes Mellitus making assumption that there is no production insulin release [4].

Stability analysis of a model of glucose insulin glucagon system in humans is made which is one of the important factors for study of model for healthy life. If glucose, insulin or glucagon is negative then it will not be stable and cannot be treated for controllability or observability. Model is used for this purpose and consists of glucose, insulin and glucagon function in human body. Equilibrium points for different case of concentration of glucose are calculated by using Mathematica software for stability of the system. Results are refined by using Jacobean linearized method to check the stability of the model to design feedback control for artificial pancreas.

2. MATERIAL AND METHOD

2.1 Mathematical Model:

The physiological compartments of the human body are classified in six category: brain, heart, periphery, gut, liver and kidney. Arrows joining the physiological compartments represent the direction of blood flow. The heart and lungs compartment serves to close the circulatory loop, representing simply the blood volume of the cardiopulmonary system and the major arteries. Figure 1, which represents the mass balance of 8 ODE's in each compartment results with linear and nonlinear terms that are related to each specific metabolic rate. In Insulin model, the mass balance in each compartment results in 7 ODE's with linear and nonlinear terms represents in figure 2, which are related to each specific metabolic rate and glucagon mode is 1 ODE with linear and nonlinear terms, which are related to each specific metabolic rate represents in figure 3.

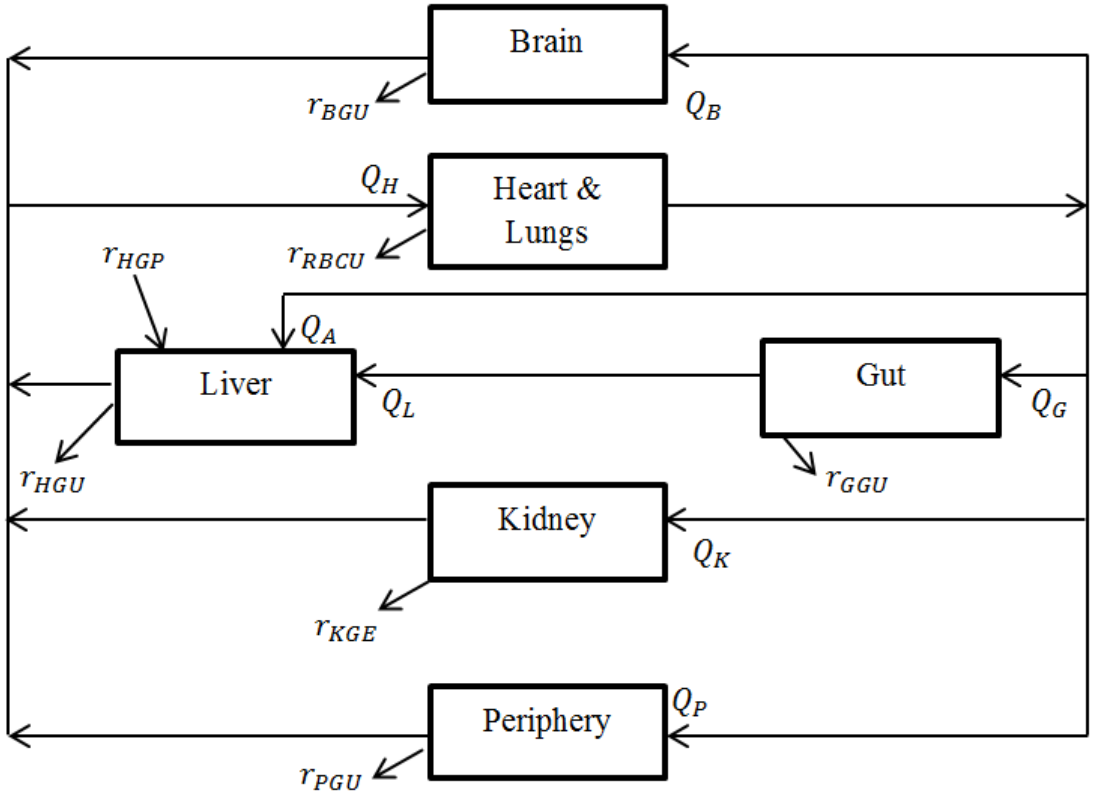

Fig. 1 Schematic representation of the Glucose Model

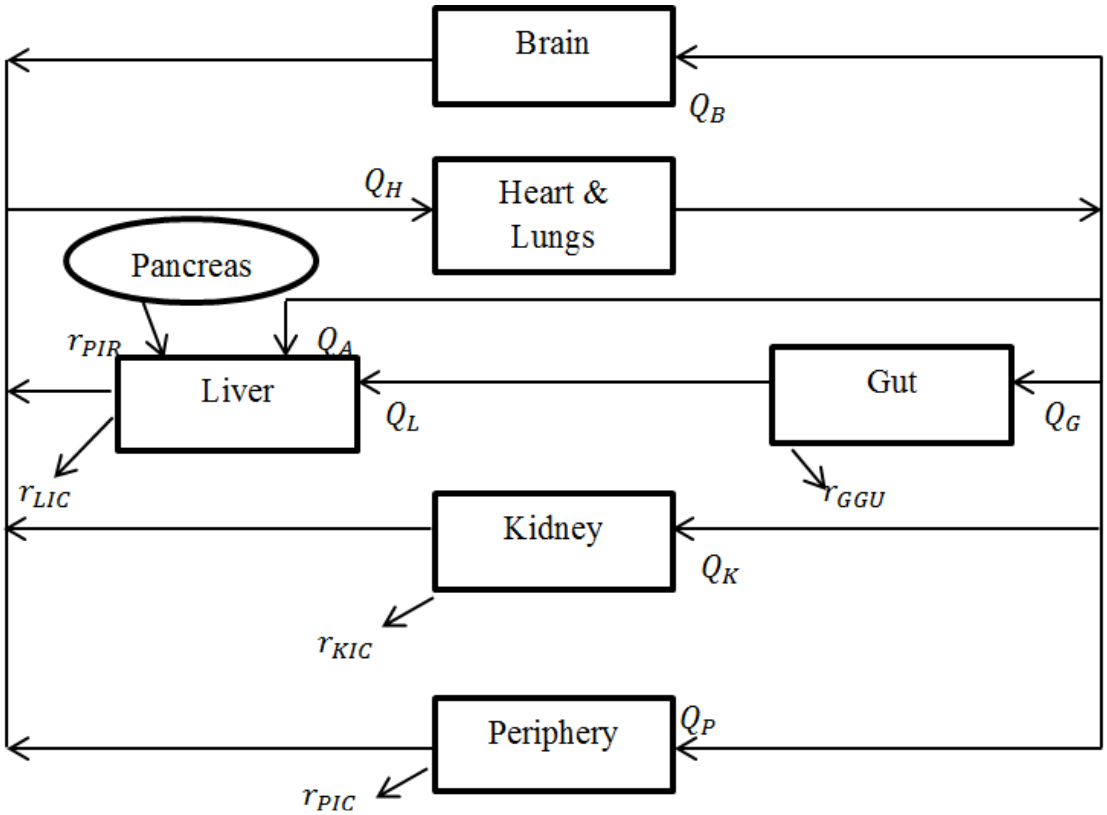

Fig. 2 Schematic representation of the Insulin Model

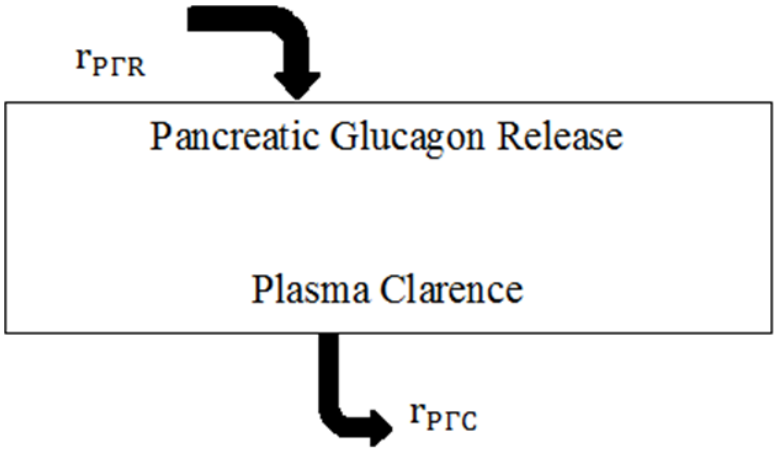

Fig. 3 Schematic representation of the Glucagon Model

Followings are the equations of the model

$$V_{BV}^{G}\dot{G}_{BV} = Q_{B}^{G}(G_H - G_{BV}) - \frac{V_{BI}}{T_B}(G_{BV} - G_{BI}) \quad (1)$$

$$V_{BI}\dot{G}_{BI} = \frac{V_{BI}}{T_B}(G_{BV} - G_{BI}) - r_{BGU} \quad (2)$$

$$V_{H}^{G}\dot{G}_{H} = Q_{B}^{G}G_{BV} + Q_{L}^{G}G_{L} + Q_{K}^{G}G_{K} + Q_{P}^{G}G_{PV} + Q_{H}^{G}G_{H} - r_{RBCU} \quad (3)$$

$$V_{G}^{G}\dot{G}_{G} = Q_{G}^{G}(G_H - G_G) - r_{GGU} \quad (4)$$

$$V_{L}^{G}\dot{G}_{L} = Q_{A}^{G}G_{H} + Q_{G}^{G}G_{G} - Q_{L}^{G}G_{L} + r_{HGP} - r_{HGU} \quad (5)$$

$$V_{K}^{G}\dot{G}_{K} = Q_{K}^{G}(G_H - G_K) - r_{KGE} \quad (6)$$

$$V_{PV}^{G}\dot{G}_{PV} = Q_{P}^{G}(G_H - G_{PV}) - \frac{V_{PI}}{T_P^G}(G_{PV} - G_{PI}) \quad (7)$$

$$V_{PI}\dot{G}_{PI} = \frac{V_{PI}}{T_P^G}(G_{PV} - G_{PI}) - r_{PGU} \quad (8)$$

$$V_{B}^{I}\dot{I}_{B} = Q_{B}^{I}(I_H - I_B) \quad (9)$$

$$V_{H}^{I}\dot{I}_{H} = Q_{B}^{I}I_{B} + Q_{L}^{I}I_{L} + Q_{K}^{I}I_{K} + Q_{P}^{I}I_{PV} + Q_{H}^{I}I_{H} \quad (10)$$

$$V_{G}^{I}\dot{I}_{G} = Q_{G}^{I}(I_H - I_G) \quad (11)$$

$$V_{L}^{I}\dot{I}_{L} = Q_{A}^{I}I_{H} + Q_{G}^{I}I_{G} - Q_{L}^{I}I_{L} - r_{PIR} - r_{LIC} \quad (12)$$

$$V_{K}^{I}\dot{I}_{K} = Q_{K}^{I}(I_H - I_K) - r_{KIC} \quad (13)$$

$$V_{PV}^{I}\dot{I}_{PV} = Q_{P}^{I}(I_H - I_{PV}) - \frac{V_{PI}}{T_P^I}(I_{PV} - I_{PI}) \quad (14)$$

$$V_{PI}\dot{I}_{PI} = \frac{V_{PI}}{T_P^I}(I_{PV} - I_{PI}) - r_{PIC} \quad (15)$$

$$V^{\Gamma}\dot{\Gamma} = r_{P\Gamma R} - r_{P\Gamma C} \quad (16)$$

2.1.1 Description of Variables

G = Glucose Concentration (mg/dl),
T = Diffusion rate (min),
Q = Vascular Plasma flow rate (dl/min),
V = Volume (dl),
r = Metabolic source and sink rate (mg/min),
M = Multiplier of basal MR (dimensionless) and
τ = Time constant (min)
I = Insulin Concentration (mg/dl),
F = Fractional clearance (dimensionless) and
t = Time constant (min)
Γ = Glucagon Concentration (pg/ml),

2.1.2 First Subscript: Physiological Compartment

B = Brain,
G = Gut,
H = Heart and Lung,

L = Liver,
K = Kidney,
P = Periphery and
A = Hepatic artery
G = Glucose,
I = Insulin,
Γ = Glucagon,
B = Basal value and
N = Normalized value
I = Interstitial fluid space,
V = Vascular plasma space

2.1.3 Metabolic Rate Subscript

BGU = Brain glucose uptake,
GGU = Gut glucose utilization,
HGP = Hepatic glucose production,
HGU= Hepatic glucose uptake,
KGE = Kidney glucose excretion,
PGU = Peripheral glucose uptake and
RBCU = Red blood cell glucose uptake
KIC = Kidney Insulin clearance,
LIC = Liver insulin clearance,
PIR = Peripheral insulin release
PIC= Peripheral insulin clearance
PΓC = Plasma glucagon clearance,
MΓC = Metabolic glucagon clearance,
PΓR = Pancreatic glucagon release

Followings is the table of parameters and constant values given in [3,6] used in model

Table 1: Table of parameters and constant value of the model

Parameter	Value	Parameter	Value
Q_B^G	*5.9 dl min*$^{-1}$	Q_H^G	*43.7 dl min*$^{-1}$ [3,6]
Q_A^G	*2.5 dl min*$^{-1}$	Q_L^G	*12.6 dl min*$^{-1}$ [3,6]
Q_G^G	*10.1 dl min*$^{-1}$	Q_K^G	*10.1 dl min*$^{-1}$ [3, 6]
Q_P^G	*15.1 dl min*$^{-1}$	V_{BV}^G	*3.5 dl* [3,6]
V_H^G	*13.8 dl*	V_L^G	*25.1 dl* [3,6]
V_G^G	*11.2 dl*	V_K^G	*6.6 dl* [3, 6]
V_{PV}^G	*10.4 dl*	V_{PI}	*67.7 dl* [3,6]
V_{BI}	*4.5 dl*	T_P^G	*5.0 min* [3, 6]
T_B	*2.1 min*	V^Γ	11310 *ml* [3, 6]
V_B^I	$0.26l$	Q_A^I	$0.18l/min$ [3, 6]
T_P^I	$20min$	V_H^I	$0.99l$ [3, 6]
Q_B^I	$0.45l/min$	V_G^I	$0.94l$ [3, 6]
Q_H^I	$3.12l/min$	V_L^I	$1.14l$ [3, 6]
Q_L^I	$0.90l/min$	V_K^I	$0.51l$ [3, 6]
Q_K^I	$0.72l/min$	V_{PV}^I	$0.74l$ [3, 6]
V_{PI}^I	$6.74l$	Q_G^I	$0.72l/min$ [3, 6]
Q_P^I	$1.05l/min$	α	$0.0482\ min^{-1}$[3, 6]
β	$0.931min^{-1}$	K	$0.00794min^{-1}$[3, 6]
M_1	$0.00747min^{-1}$	M_2	$0.0958min^{-1}$[3, 6]
γ	$0.575\ U/min$	Q_0	$6.33U$ [3, 6]

Metabolic source and sink

$r_{BGU} = 70\ mg/min$ *(Constant)*, $r_{RBCU} = 10\ mg/min$ *(Constant)*,
$r_{GGU} = 20\ mg/min$ *(Constant)*, $r_{PGU} = M_{PGU}^I M_{PGU}^G \tau_{PGU}^B$
τ_{PGU}^B = *35 mg / min*, τ_{HGP}^B = *155 mg/min*, $\tau_\Gamma = 65\ min$, $F_{LIC} = 0.40$, $F_{KIC} = 0.30$, $F_{PIC} = 0.15$, $r_{PIR}^B = 4\ mU/min$, $r_{M\Gamma C} = 9.10$, $M_{PGU}^G = G_{PI}^N$
$M_{PGU}^I = 7.03 + 6.52tanh[0.338(I_{PI}^N - 5.82)]$

$$r_{HGP} = M^{I}_{HGP} M^{\Gamma}_{HGP} M^{G}_{HGP} \tau^{B}_{HGP}$$

$$\dot{M}^{I}_{HGP} = \frac{1}{\tau_I}(M^{I\infty}_{HGP} - M^{I}_{HGP}) \tag{17}$$

$$M^{I\infty}_{HGP} = 1.21 - 1.14tanh[0.62(G^{N}_{L} - 0.89)]$$

$$M^{\Gamma}_{HGP} = M^{\Gamma_0}_{HGP} - f_2$$

$$M^{\Gamma_0}_{HGP} = 2.7\, tanh[0.39\Gamma^{N}]$$

$$\dot{f}_2 = \frac{1}{\tau_\Gamma}[\left(\frac{M^{\Gamma_0}_{HGP} - 1}{2}\right) - f_2] \tag{18}$$

$$M^{G}_{HGP} = 1.42 - 1.41tanh[1.66(I^{N}_{L} - 0.497)]$$

$$r_{HGU} = M^{I}_{HGU} M^{G}_{HGU} \tau^{B}_{HGU}$$

$$\tau^{B}_{HGU} = 20\, mg/min$$

$$\dot{M}^{I}_{HGU} = \frac{1}{\tau_I}(M^{I\infty}_{HGU} - M^{I}_{HGU}) \tag{19}$$

$$M^{I\infty}_{HGU} = 2.0tanh[0.55I^{N}_{L}]$$

$$M^{G}_{HGU} = 5.66 + 5.66tanh[2.44(G^{N}_{L} - 1.48)]$$

$$r_{KGE} = \begin{cases} 71 + 71\, tanh[0.11(G_K - 460)], & 0 < G_K < 460\, mg/min \\ -330 + 0.83G_K, & G_K \geq 460 mg/min \end{cases}$$

$$r_{LIC} = F_{LIC}[Q^{I}_{A} I_H + Q^{I}_{G} I_G + r_{PIR}]$$

$$r_{KIC} = F_{KIC}[Q^{I}_{K} I_K]$$

$$r_{PIC} = \frac{I_{PI}}{[(\frac{1 - F_{PIC}}{F_{PIC}})(\frac{1}{Q^{I}_{P}} - \frac{T^{I}_{P}}{V_{PI}})]}$$

$$r_{PIR} = \frac{S(G_H)}{S(G^{B}_{H})} r^{B}_{PIR}$$

$$\dot{P} = \alpha[P_\infty - P] \tag{20}$$

$$\dot{I} = \beta[X - I] \tag{21}$$

$$\dot{Q} = K[Q - Q_0] + \gamma P - S] \tag{22}$$

$$S = [M_1 Y + M_2(X - I)^{0^+}]Q$$

$$S = \frac{(G_H)^{3.27}}{(132)^{3.27} + 5.93(G_H)^{3.02}}$$

$$P_\infty = Y = (X)^{1.11}$$

$$r_{P\Gamma C} = r_{M\Gamma C}\Gamma$$

$$r_{P\Gamma R} = M^{G}_{P\Gamma R} M^{I}_{P\Gamma R} \tau^{B}_{P\Gamma R}$$

$$\tau^{B}_{P\Gamma R} = r_{MTC}\boldsymbol{\Gamma^{B}}$$

$$M^{G}_{P\Gamma R} = 2.93 - 2.10tanh[4.18(G^{N}_{H} - 0.61)]$$

$$M^{I}_{P\Gamma R} = 1.31 - 0.61tanh[1.06(I^{N}_{H} - 0.47)]$$ [6]

3. Modified Form of Model in Type 1 Diabetes Mellitus

In this section model (1) – (22), convert into Type 1 Diabetes Mellitus and the details are given in [23]. The nomenclature, basal values, parameters values and metabolic rates are same like non diabetic model. After eliminating pancreatic insulin released model and r_{PIR} due to type 1 diabetes mellitus and substitution of parameters and basal values given in table 1, the model ends up 19 ordinary differential equations and takes the form

$$\dot{G}_{BV} = 1.685G_H - 2.297G_{BV} + 0.612G_{BI} \tag{23}$$

$$\dot{G}_{BI} = 0.476G_{BV} - 0.476G_{BI} - 15.555 \tag{24}$$

$$\dot{G}_{H} = 0.427G_{BV} + 0.913G_L + 0.731G_K + 1.094G_{PV} - 3.166G_H - 0.724 \tag{25}$$

$$\dot{G}_{G} = 0.901(G_H - G_G) - 1.785 \tag{26}$$

$$\dot{G}_{L} = 0.099G_H + 0.402G_G - 0.501G_L + 6.175M^{I}_{HGP}(2.7\tanh(0.389\Gamma) - f_2)$$
$$(1.42 - 141tanh((0.006G_L - 0.31)) - 4.5M^{I}_{HGU}(1 + \tanh(0.024G_L - 3.61)) \tag{27}$$

$$\dot{G}_{K} = 1.53G_H - 1.53G_K - 10.721 - 10.721(0.11G_K - 50.6) \tag{28}$$

$$\dot{G}_{PV} = 1.451G_H - 2.748G_{PV} + 1.296G_{PI} \tag{29}$$

$$\dot{G}_{PI} = 0.2G_{PV} - 0.2G_{PI} - 0.005G_{PI}(7.03 + 6.52\tanh(0.015I_{PI} - 1.967)) \tag{30}$$

$$\dot{M}^{I}_{HGP} = -0.04M^{I}_{HGP} + 0.048 - 0.045tanh(0.077I_L - 1.477) \tag{31}$$

$$\dot{M}^{I}_{HGU} = -0.04M^{I}_{HGU} + 0.08tanh(0.025I_L) \tag{32}$$

$\dot{f}_2 = -0.015f_2 - 0.007 + 0.02tanh(0.389\Gamma)$ (33)
$\dot{I}_B = 1.73I_H - 1.73I_B$ (34)
$\dot{I}_H = 0.454I_B + 0.909I_L + 0.727I_K + 1.06I_{PV} - 3.151I_H$ (35)
$\dot{I}_G = 0.765I_H - 0.765I_G$ (36)
$\dot{I}_L = 0.094 + 0.378I_G - 0.789I_L$ (37)
$\dot{I}_K = 1.411I_H - 1.835I_K$ (38)
$\dot{I}_{PV} = 1.418I_H - 1.874I_{PV} + 0.455I_{PI}$ (39)
$\dot{I}_{PI} = 0.05I_{PV} - 0.111I_{PI}$ (40)
$\dot{\Gamma} = -0.08\Gamma + 0.08(2.93 - 2.10\tanh(0.041G_H - 2.55))(1.31 - 0.61\tanh(0.049I_H - 0.492)$ (41)

For equilibrium the left hand side of the equations (23) - (41) are substituted zero. By algebraic manipulations we can represent all the equations as a function of either G_K or I_B separately. The model represent a type 1 diabetes mellitus subject so it is not surprising to take insulin concentration in all compartments zero. The equation for kidney compartment provides $G_K = 197.1mg/dl$. The uniqueness of values provide in [4]. Hence we get a unique point of equilibrium for the Sorenson Model in type 1 diabetes mellitus.
(185.2, 152.5, 197.1, 195.1, 207.7, 197.1, 193.6, 189.9, 2.33, 0, 0.1, 0, 0, 0, 0, 0, 0, 0, 1.3).

3.1 Linearised Model

The linearised model about the equilibrium point is
$\dot{G}_{BV} = 1.685G_H - 2.297G_{BV} + 0.612G_{BI}$
$\dot{G}_{BI} = 0.476G_{BV} - 0.476G_{BI}$
$\dot{G}_H = 0.427G_{BV} + 0.913G_L + 0.731G_K + 1.094G_{PV} - 3.166G_H$
$\dot{G}_G = 0.901(G_H - G_G)$
$\dot{G}_L = 0.099G_H + 0.402G_G - 0.563G_L + 2.755M^I_{HGP} - 8.467M^I_{HGU} - 5.299f_2 + 4.354\Gamma$
$\dot{G}_K = 1.53G_H - 1.53G_K$
$\dot{G}_{PV} = 1.451G_H - 2.748G_{PV} + 1.296G_{PI}$
$\dot{G}_{PI} = 0.2G_{PV} - 0.204G_{PI} - 0.007I_{PI}$
$\dot{M}^I_{HGP} = -0.04M^I_{HGU} + 0.007I_L$
$\dot{M}^I_{HGU} = -0.04M^I_{HGU} + 0.002I_L$
$\dot{f}_2 = -0.015f_2 - 0.006\Gamma$
$\dot{I}_B = 1.73I_H - 1.73I_B$
$\dot{I}_H = 0.454I_B + 0.909I_L + 0.727I_K + 1.06I_{PV} - 3.151I_H$
$\dot{I}_G = 0.765I_H - 0.765I_G$
$\dot{I}_L = 0.094I_H + 0.378I_G - 0.789I_L$
$\dot{I}_K = 1.411I_H - 1.835I_K$
$\dot{I}_{PV} = 1.418I_H - 1.874I_{PV} + 0.455I_{PI}$
$\dot{I}_{PI} = 0.05I_{PV} - 0.111I_{PI}$
$\dot{\Gamma} = -0.08\Gamma + 0.0016I_H - 0.00000069G_H$

3.2 Stability Analysis:

Theorem 3.1: The linear $\dot{x}(t) = A(t)x(t)$, where $A(t)$ continuous and bounded for $t \geq t_0$, is uniformly asymptotically stable if and only if given a positive definite real matrix $A(t)$, there exists a symmetric positive definite real matrix $P(t)$, which satisfies
$\dot{P}(t) + A^T(t)P(t) + P(t)A(t) = -Q(t), t \geq t_0$
The linear time invariant system $\dot{x}(t) = A(t)x(t)$ the corresponding equation to be used as $A^TP + PA + Q = 0$. This is called Lyapunov equation [21], [22].

Proof:

Here A is matrix of coefficients of above linearized model and $Q = I$, where I is an identity matrix with the same order of A. By using the equation $A^TP + PA + Q = 0$ on Matlab. We find matrix P and its $\det(P) = 4.8878e^{11}$ which shows that P is symmetric positive definite real matrix P. The eigen values of A are
$(-4.6799, -2.5946, -2.0129, -1.0195 + 0.3193i, -1.0195 - 0.3193i, -0.3518, -0.1949,$
$-0.0118, -0.0152, -0.0800, -0.0400, -4.4302, -1.7618, -1.8580, -0.9559 + 0.3134, -$

$0.9559 - 0.3134i, -0.2154, -0.0779, -0.0400)$ negative real roots. Hence prove that the system is uniformly asymptotically stable.

4. RESULTS AND DISCUSSIONS

Achieving and maintaining normal blood glucose concentrations are critical issues for successful long term care of patients with diabetes mellitus. Serious attention is needed to maintain blood glucose level as close to the non-diabetic range as possible in individuals with T1DM to reduce the development and progression of micro-vascular and cardiovascular complications. Till now we don't have a fully automated artificial pancreas. An effort is made to answer the hurdles of having a fully automated artificial pancreas, since we need to have a feedback control for the system. First step in this direction is to check if we can stabilize the system by choosing an appropriate feedback control.

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

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

Here $x = [G_{BV}\ G_{BI}\ G_H\ G_G\ G_L\ G_K\ G_{PV}\ G_{PI}\ M^I_{HGP}\ M^I_{HGU}\ f_2\ I_B\ I_H\ I_L\ I_K\ I_{PV}\ I_{PI}\ \Gamma]^T$ and

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

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 observability matrix is given by

$O = [C, ACA;\ CA\text{^}2;\ CA\text{^}n - 1]^T$. The rank (i.e. $rank(R) = n$), so the system is said to be observable [2, 6, 19, 20].

For Case I

If we consider the insulin concentration in periphery vascular blood space as inputs and glucose concentration in extracellular fluid as the only output than

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

R is the controllability matrix, where R = [B, AB, A^2B, A^3B, A^4B,…, $A^{18}B$] and its rank is 12. The observability matrix is O = [C; CA; CA^2, CA^3, CA^4;…, CA^{18}] and its rank is 11. Hence the linear system is neither controllable nor observable.

For Case II

If we consider the insulin concentration in periphery vascular blood space and glucagon concentration as inputs and glucagon concentration in extracellular fluid as the only output than

$B = [0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 0\ 1]$ and $C = [0\ 0\ 0\ 0\ 0\ 0\ 1\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0]$. In this case rank of controllability and observability matrix is 13 and 11 respectively.

Stability analysis of A is checked by using Lyapunov equation and found that the system is stable because P is definite positive matrix and eigen values of A are negative real roots. So the system is uniformly asymptotically stable. Two cases are discussed according to input value, for case 1, insulin is an input only and glucose is output. For case 2, insulin and glucagon are input and glucose as an output only

5. CONCLUSION

The results obtained in this paper will have some impact on attempts to construct the artificial pancreas. Until now primarily one tries to implement a feedback control by taking glucose as the only input providing information on the system state and by using administration of insulin as the only control input. The use of insulin as the only control input may be insufficient in case of hypoglycemia, because a low glucose level cannot be raised by insulin action. It seems to be that in order to restore the desired glucose level that one has to include administration of glucagon as another control input. For instance, in case of Sorensen's model for T1DM we can see that the system improves its controllability when we consider glucagon as second input along with insulin. In our opinion one has to develop models for the glucose-insulin-glucagon system which pay special attention to the control mechanisms of the systems first for the healthy system in order to understand the working of the control loops in the healthy system which should be restored by the artificial pancreas. Our results indicate that such a feedback control will have to use administration of insulin and glucagon by a combined insulin-glucagon pump.

The system is uniformly asymptotically stable by using the Lyapunov equation because eigen values of A are all negative real roots. 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. If a nonlinear system is neither controllable nor

observable then linear may or may not be. This is the most comprehensive model in the history of Glucose Insulin Glucagon systems. Results show that the deficiency of the model can be improved if glucagon is used as input along with insulin. For this purpose, we check the controllability and observability of the system which further can be treated to design the feedback control for fully automatic artificial pancreas. In [2] it was concluded that the model was missing the glucagon and is verified as controllability and observability is improved by considering glucagon as another input since glucagon plays an important role in glucose regulatory systems. The system is neither controllable nor observable in both cases. The situation is improved when we consider insulin and glucagon as inputs than only insulin but still system is not controllable and observable thus we cannot design the feedback control for fully automatic artificial pancreas.

The discussion in the conclusion show that the following tasks should be considered for future research. Development and validation of a comprehensive model for the system including the important control mechanisms involving insulin and glucagon for the healthy system.

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