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Research Article

Stability Analysis of Sorensen's Model for Controllability and Observability

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Abstract: 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. Sorenson's Model is used for this purpose because it is most comprehensive model for glucose, insulin and glucagon in humans. Equilibrium points for different case of concentration of glucose are calculated for stability of the system. Results are refined by using fsolve and fminsearch techniques in Matlab which turn out to be negative value of labile Insulin for all cases and techniques. In this situation we will be unable to find the control of the system in this model.

Keywords: Glucose, Insulin, Glucagon, controllability, observability, Sorenson's model

1. INTRODUCTION

Mathematics is a branch of science that has a great role in the development of other branches of sciences. Its involvement enriches in any field. Biomathematics is one of its major examples which are 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[1, 2]. 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 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 [4].

The level of blood glucose is mainly controlled by two hormones having opposite effects. While insulin clears out blood glucose by stimulating its uptake by muscles and adipose tissues and storing it as glycogen in the liver, glucagon supplies bloodstream by glucose produced through liver gluconeogenesis and glucogenolysis. In other words, insulin is secreted in order to avoid that the level of blood glucose goes beyond an upper bound after meals, whereas glucagon is secreted to counter hypoglycemia after fasting or meals without carbohydrates. Consequently, any dysfunction in the secretion of insulin or glucagon will lead to problems in the control of glycaemia [7].

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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. [6]

A physiological model using anatomical organ and tissue compartments was developed for simulating glucose metabolism and its regulation by insulin and glucagon in normal (non-diabetic) man in [3]. Physical parameters such as blood flow rates and distribution volumes were selected to represent a normal 70kg adult male. Hormonal regulation by insulin and glucagon were including in the model formulation. The model is a physiologically structured explanatory representation of the glucose regularity system and is used for generating predictions of response to a wide spectrum of glucose and insulin inputs. This model also has a few limitations. First hormonal effects of epinephrine (adrenalin) cortisol and growth hormone have been neglected. Second physiology related to changes in amino acid and free fatty acid sub travel levels has not been considered. Third, initial conditions for the model reflect normal basal post absorptive metabolism and changes in fuel utilization associated with prolonged fasting and starvation such as hepatic glycogen depletion and displacement of brain glucose utilization, have not been incorporated into the model formulation. Mass balance equations were written to account blood flow, exchange between compartments and the metabolic processes causing addition or removal of glucose, insulin and glucagon yielding simultaneous differential equations. The model is divided into three subsections named Glucose model, Insulin model and Glucagon model. The mass balance equations for each of models are written which yields a 22 nonlinear ODE's model with 42 parameters and11 nonlinear input functions.

In this paper we find the equilibrium point of the model to check whether the solution is in feasible region. We need point or equilibrium point to check the stability of the model.

2. MATERIALS AND METHODS

2.1 Glucose Model

The body has been divided into six physiological compartments: 1) Brain which represents the central nervous system, 2) Heart and lungs which represents the rapidly mixing vascular volumes of heart, lungs, and arteries, 3) Periphery which includes skeletal muscle and adipose tissue, 4) Gut, 5) liver, 6) Kidney. Arrows connecting 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. The mass balance in each compartment results in 8 ODE's with linear and nonlinear terms which are related to each specific metabolic rate.

Brain;

$$V_{BV}^{G}\dot{G}_{BV} = Q_{B}^{G}(G_H - G_{BV}) - \frac{V_{BI}}{T_B}(G_{BV} - G_{BI}) \quad (1.1.1)$$

$$V_{BI}\dot{G}_{BI} = \frac{V_{BI}}{T_B}(G_{BV} - G_{BI}) - r_{BGU} \quad (1.1.2)$$

Heart and Lungs:

$$V_{H}^{G}\dot{G}_{H} = Q_{B}^{G}G_{BV} + Q_{L}^{G}G_{L} + Q_{K}^{G}G_{K} + Q_{P}^{G}G_{PV} + Q_{H}^{G}G_{H} - r_{RBCU} \quad (1.1.3)$$

Gut:

$$V_{G}^{G}\dot{G}_{G} = Q_{G}^{G}(G_H - G_G) - r_{GGU} \quad (1.1.4)$$

Liver:

$$V_L^G \dot{G}_L = Q_A^G G_H + Q_G^G G_G - Q_L^G G_L + r_{HGP} - r_{HGU} \quad (1.1.5)$$

Kidney:

$$V_K^G \dot{G}_K = Q_K^G (G_H - G_K) - r_{KGE} \quad (1.1.6)$$

Periphery:

$$V_{PV}^G \dot{G}_{PV} = Q_P^G (G_H - G_{PV}) - \frac{V_{PI}}{T_P^G}(G_{PV} - G_{PI}) \quad (1.1.7)$$

$$V_{PI} \dot{G}_{PI} = \frac{V_{PI}}{T_P^G}(G_{PV} - G_{PI}) - r_{PGU} \quad (1.1.8)$$

Physiological processes leading to metabolic source, hepatic production, with rate function of live glucose (nonlinear), liver insulin (nonlinear) and plasma glucagon (nonlinear). The metabolic sinks and red blood cell uptake with rate function of constant, Brain uptake with rate function of constant, Gut uptake with rate function of constant, peripheral uptake with rate function of peripheral interstitial glucose (linear) and peripheral interstitial insulin (nonlinear), urinary excretion with rate function of kidney plasma glucose (nonlinear) and hepatic uptake, with rate function of liver glucose (nonlinear) and liver insulin (nonlinear).

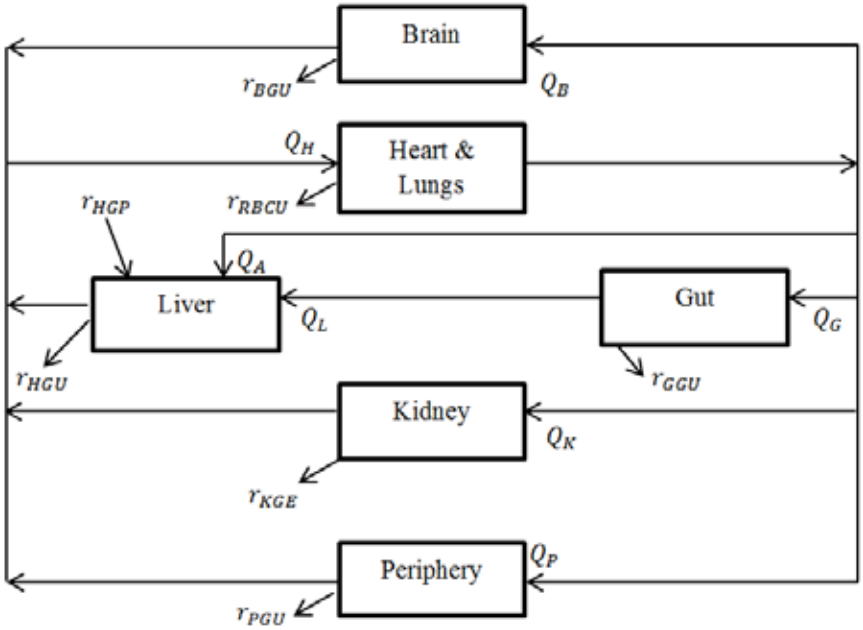

Fig. 1. Schematic representation of the Glucose model.

2.1.1 Metabolic Source and Sink

$r_{BGU} = 70\ mg/min$ *(Constant)*

$r_{RBCU} = 10\ mg/min$ *(Constant)*

$r_{GGU} = 20\ mg/min$ *(Constant)*

$$r_{PGU} = M_{PGU}^I M_{PGU}^G \tau_{PGU}^B$$

$\tau_{PGU}^B = 35\ mg/min$

$$M_{PGU}^I = 7.03 + 6.52 tanh[0.338(I_{PI}^N - 5.82)]$$

$$M_{PGU}^G = G_{PI}^N$$

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

τ^{B}_{HGP} = *155 mg/min*

$$\dot{M}^{I}_{HGP} = \frac{1}{\tau_I}(M^{I_\infty}_{HGP} - M^{I}_{HGP}) \tag{1.1.9}$$

τ_1 = *25 min* $M^{I_\infty}_{HGP} = 1.21 - 1.14tanh[0.62(G^N_L - 0.89)]$

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

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

$$\dot{f}_2 = \frac{1}{\tau_\Gamma}[\left(\frac{M^{\Gamma_0}_{HGP} - 1}{2}\right) - f_2] \tag{1.1.10}$$

$$\tau_\Gamma = 65\, min$$

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

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

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

$$\dot{M}^{I}_{HGU} = \frac{1}{\tau_I}(M^{I_\infty}_{HGU} - M^{I}_{HGU}) \tag{1.1.11}$$

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

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

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

2.1.2 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),
t = Time (min),
M = Multiplier of basal MR (dimensionless) and
τ = Time constant (min)

2.1.3 First Subscript: Physiological Compartment

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

L = Liver,

K = Kidney,

P = Periphery and

A = Hepatic artery

2.1.4 Second Subscript: Physiological Compartment

I = Interstitial fluid space and

V = Vascular plasma space

2.1.5 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

2.1.6 First Subscript

G = Glucose,

I = Insulin,

Γ = Glucagon,

B = Basal value and

N = Normalized value

2.1.7 Second Subscript

0 = Initial value,

∞ = asymptotic or final steady state value [6]

2.2 Insulin Model

The body was divided into the same physiological compartments described for glucose model. But in terms of compartments, the insulin sub-system considers the pancreas as an additional compartment. Differences arise however, with respect to the extravascular fluid space access in the brain and liver compartments. The blood brain barrier capillary structure is impermeable to insulin passage into cerebrospinal fluid thus the brain interstitial space has been omitted from the insulin formulation. Also unlike the case for glucose the liver cell membrane is not freely permeable to insulin and the intracellular fluid volume has thus been omitted as insulin is degraded via binding to cell membrane receptors. The mass balance in each compartment results in 7 ODE's with linear and nonlinear terms which are related to each specific metabolic rate.

Brain:

$$V_B^I \dot{I}_B = Q_B^I (I_H - I_B) \tag{1.1.12}$$

Heart and Lungs:

$$V_H^I \dot{I}_H = Q_B^I I_B + Q_L^I I_L + Q_K^I I_K + Q_P^I I_{PV} + Q_H^I I_H \tag{1.1.13}$$

Gut:

$$V_G^I \dot{I}_G = Q_G^I (I_H - I_G) \tag{1.1.14}$$

Liver:

$$V_L^I \dot{I}_L = Q_A^I I_H + Q_G^I I_G - Q_L^I I_L - r_{PIR} - r_{LIC} \tag{1.1.15}$$

Kidney:

$$V_K^I \dot{I}_K = Q_K^I (I_H - I_K) - r_{KIC} \tag{1.1.16}$$

Periphery:

$$V_{PV}^I \dot{I}_{PV} = Q_P^I (I_H - I_{PV}) - \frac{V_{PI}}{T_P^I} (I_{PV} - I_{PI}) \tag{1.1.17}$$

$$V_{PI} \dot{I}_{PI} = \frac{V_{PI}}{T_P^I} (I_{PV} - I_{PI}) - r_{PIC} \tag{1.1.18}$$

Physiological processes leading to metabolic source, pancreatic insulin release, with rate function of heart and lung glucose (nonlinear). The metabolic sinks are, liver clearance, with rate function of liver insulin (linear), kidney clearance, with rate function of kidney insulin (linear) and peripheral clearance, with rate function of peripheral interstitial insulin (linear).

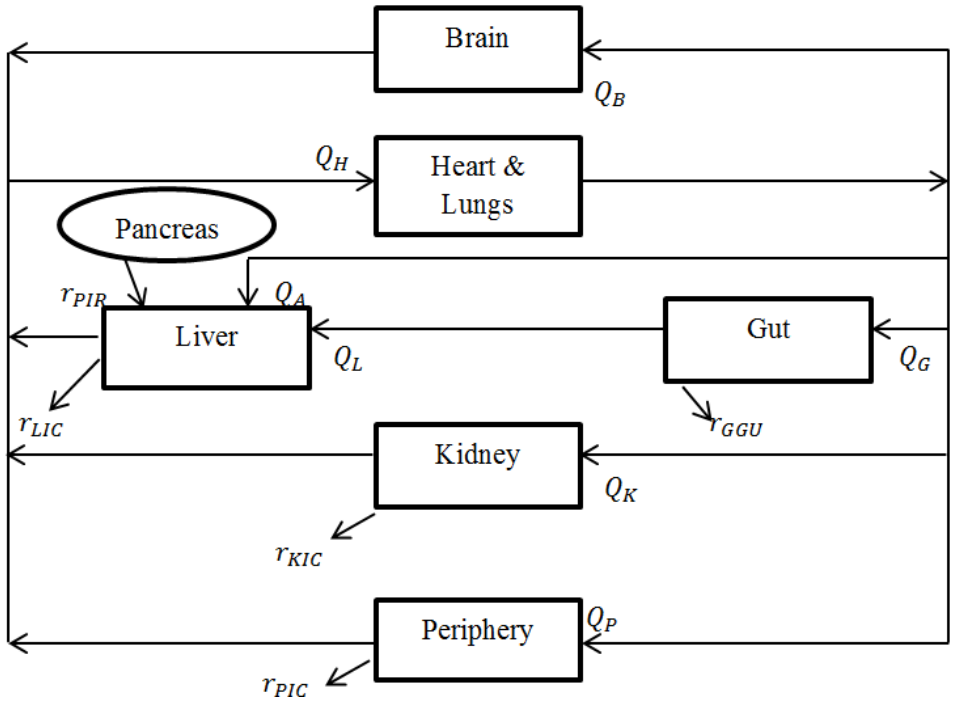

Fig. 2. Schematic representation of the Insulin model.

2.2.1 Metabolic Sink and Source

$$r_{LIC} = F_{LIC}[Q_A^I I_H + Q_G^I I_G + r_{PIR}]$$

$$F_{LIC} = 0.40$$

$$r_{KIC} = F_{KIC}[Q_K^I I_K]$$

$$F_{KIC} = 0.30$$

$$r_{PIC} = \frac{I_{PI}}{[(\frac{1 - F_{PIC}}{F_{PIC}})(\frac{1}{Q_P^I} - \frac{T_P^I}{V_{PI}})]}$$

$$F_{PIC} = 0.15$$

$$r_{PIR} = \frac{S(G_H)}{S(G_H^B)} r_{PIR}^B$$

$$r_{PIR}^B = 4\ mU/min$$

$$\dot{P} = \alpha[P_\infty - P] \tag{1.1.19}$$

$$\dot{I} = \beta[X - I] \tag{1.1.20}$$

$$\dot{Q} = K[Q - Q_0] + \gamma P - S] \tag{1.1.21}$$

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

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

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

P = Potentiator (dimensionless),

I = Inhibitor (dimensionless),

Q = labile insulin,

P_∞, Y, X = Intermediate variable (dimensionless)

2.2.2 Description of Variables

I = Insulin 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),

t = Time (min),

F = Fractional clearance (dimensionless) and

t = Time constant (min)

2.2.3 First Subscript: Physiological Compartment

B = Brain,

G = Gut,

H= Heart and Lung,

L = Liver,

K = Kidney,

P = Periphery and

A=Hepatic artery

2.2.4 Second Subscript: Physiological Compartment

I = Interstitial fluid space,

V = Vascular plasma space

2.2.5 Metabolic Rate Subscript

KIC = Kidney Insulin clearance ,

LIC = Liver insulin clearance,

PIR = Peripheral insulin release and

PIC= Peripheral insulin clearance

2.2.6 First Subscript

I = Insulin,

B = basal value [6]

2.3 Glucagon Model

A schematic representation of an Insulin model. Here a simple one compartment formulation was employed, representing the whole body fluid distribution volume for glucagon. The mass balance in compartment results in 1 ODE with linear and nonlinear terms which are related to each specific metabolic rate.

$$V^{\Gamma}\dot{\Gamma} = r_{P\Gamma R} - r_{P\Gamma C} \tag{1.1.22}$$

Physiological processes leading to metabolic source, pancreatic glucagon release with rate function of heart and lung glucose (nonlinear) and heart and lung insulin (nonlinear). The metabolic sink is plasma clearance with rate function of plasma glucagon (linear).

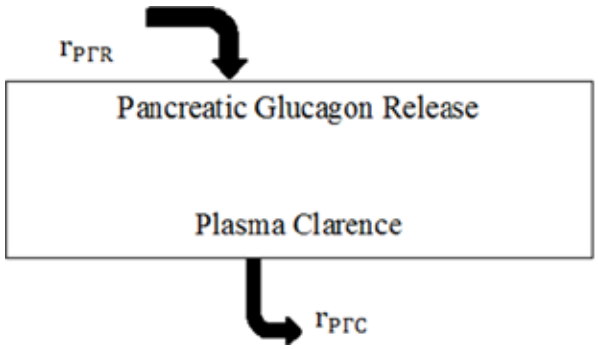

Fig. 3. Schematic representation of the Glucagon model.

2.3.1 Metabolic Sink and Source

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

$$r_{M\Gamma C} = 9.10$$

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

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

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

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

2.3.2 Description of Variables

Γ = Glucagon Concentration (pg/ml),

V = Glucagon volume (dl),

r = Metabolic source and sink rate (pg/min),

t = time (min), *M* = Multiplier of basal MR (dimensionless)and

t = time constant (min)

2.3.3 Metabolic Rate Subscript

$P\Gamma C$ = Plasma glucagon clearance,

$M\Gamma C$ = Metabolic glucagon clearance,

$P\Gamma R$ = Pancreatic glucagonrelease

2.3.4 First Subscript

G = Glucose,

I = Insulin,

Γ = Glucagon

B = basal value and

N = normalized value [6]

Table 1. Parameters values of the model.

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

Model after substitutions of constant and parameter values, we get model for different cases of *G*

Case I (0 < G < 460)

$$\dot{G}_{BV} = 1.69G_H - 2.3G_{BV} + 0.61G_{BI} \quad (1.1.1a)$$

$$\dot{G}_{BI} = 0.48G_{BV} - 0.48G_{BI} - 15.56 \quad (1.1.1b)$$

$$\dot{G}_H = 0.43G_{BV} + 0.91G_L + 0.73G_K + 1.09G_{PV} - 3.17G_H - 0.72 \quad (1.1.1c)$$

$$\dot{G}_G = 0.9(G_H - G_G) - 1.79 \quad (1.1.1d)$$

$$\dot{G}_L = 0.1G_H + 0.4G_G - 0.5G_L + 6.18M^I_{HGP}(2.7\tanh(0.389\Gamma) - f_2)(1.42 - 141tanh((0.006G_L - 0.31)) - 4.5M^I_{HGU}(1 + \tanh(0.024G_L - 3.61)) \quad (1.1.1e)$$

$$\dot{G}_K = 1.53G_H - 1.53G_K - 10.72 - 10.72(0.11G_K - 50.6 \quad (1.1.1f)$$

$$\dot{G}_{PV} = 1.45G_H - 2.75G_{PV} + 1.3G_{PI} \quad (1.1.1g)$$

$$\dot{G}_{PI} = 0.2G_{PV} - 0.2G_{PI} - 0.005G_{PI}(7.03 + 6.52\tanh(0.016I_{PI} - 1.97)) \quad (1.1.1h)$$

$$\dot{M}^I_{HGP} = -0.04M^I_{HGP} + 0.05 - 0.045tanh(0.078I_L - 1.48) \quad (1.1.1i)$$

$$\dot{f}_2 = -0.05f_2 - 0.008 + 0.02tanh(0.389\Gamma) \quad (1.1.1j)$$

$$\dot{M}^I_{HGU} = -0.04M^I_{HGU} + 0.08tanh(0.026I_L) \quad (1.1.1k)$$

$$\dot{I}_B = 1.73I_H - 1.73I_B \quad (1.1.1l)$$

$$\dot{I}_H = 0.45I_B + 0.91I_L + 0.72I_K + 1.06I_{PV} - 3.15I_H \quad (1.1.1m)$$

$$\dot{I}_G = 0.77I_H - 0.77I_G \quad (1.1.1n)$$

$$\dot{I}_L = 0.1I_H + 0.378I_G - 0.79I_L + 0.53r_{PIR} \quad (1.1.1o)$$

$$\dot{I}_K = 1.41I_H - 1.83I_K \quad (1.1.1p)$$

$$\dot{I}_{PV} = 1.42I_H - 1.88I_{PV} + 0.46I_{PI} \quad (1.1.1q)$$

$$\dot{I}_{PI} = 0.05I_{PV} - 0.111I_{PI} \quad (1.1.1r)$$

$$\dot{P} = -0.05P + 0.05\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right]^{1.11} \quad (1.1.1s)$$

$$\dot{I} = -0.93I + 0.93\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right] \quad (1.1.1t)$$

$$\dot{Q} = 0.008Q + 0.58P - 0.008\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right]^{1.11} Q - 0.05 - 0.0958\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right]^{0^+} Q \quad (1.1.1u)$$

$$\dot{\Gamma} = -0.0008\Gamma + 0.0008(2.93 - 2.10\tanh(0.041G_H - 2.55))(1.31 - 0.61\tanh(0.05I_H - 0.5) \quad (1.1.1v)$$

The systemic nominal basal values [14] $G^B = 101.11mg/dl$, $I^B = 21.31mU/dl$, and $\Gamma^B = 1.002mg/dl$are used along parameter valued provided in [3].

For equilibrium the left hand side of the equations (1.1.1a)-(1.1.1v) are substituted zero. Using (1.1.1s), (1.1.1t) and (1.1.1u) we get, $r_{PIR} = 3.143PQ$and with this substitution to equation (1.1.1o). We end up 22 equations in 22 variables which are to solve simultaneously to get equilibrium points. After manual arrangement and simplifications we get

$0 = 0.813G_L - 55.136 + 34.59(1 + \tanh((0.024G_L - 3.61)) - 77.11(1.42 - 1.41\tanh(0.006G_L - 0.31))$ (1.1.2)

Solving on Matlab, we get a single real valued real solution for the equation (1.1.2), i.e.,

$G_L = 125.0046$. By using this value for rest variables. The equilibrium point we get

X_0 = (104.24, 71.82, 115.94, 133.95, 125, 136.48, 100.86, 83.48, 1.27, -0.13, 0.88, 1.38, 1.38,1.38, 4.26, 1.79, 1.07, 0.11, 0.26, 0.3, -17.02, 1.37).

To verify and refine the result we used fsolve and fminsearch by taking our manual solution as the starting value for fsolve and then its solution as starting value for fminsearch. Even tried with a couple of different choices of starting value for fsolve including all positive values and mixed values but result came out same although with different number of iterations. The results turn out are

Using fsolve

X = (104.24, 71.82, 115.94, 133.95, 125, 136.48, 100.86, 83.48, 1.27, -0.13, 0.88, 1.38, 1.38,1.38, 4.26, 1.79, 1.07, 0.11, 0.26, 0.3, -17.02, 1.37) with 9 iterations and function values multiple of 10^{-13}.

Using fminsearch:

X = (104.24, 71.82, 115.94, 133.95, 125, 136.48, 100.86, 83.48, 1.27, -0.13, 0.88, 1.38, 1.38,1.38, 4.26, 1.79, 1.07, 0.11, 0.26, 0.3, -17.02, 1.37)

with 3386 iterations and function values are -0.000010.

Case II (G > 460)

$$\dot{G}_{BV} = 1.69G_H - 2.3G_{BV} + 0.61G_{BI} \quad (1.1.3a)$$

$$\dot{G}_{BI} = 0.48G_{BV} - 0.48G_{BI} - 15.56 \quad (1.1.3b)$$

$$\dot{G}_H = 0.43G_{BV} + 0.91G_L + 0.73G_K + 1.09G_{PV} - 3.17G_H - 0.72 \quad (1.1.3c)$$

$$\dot{G}_G = 0.9(G_H - G_G) - 1.79 \quad (1.1.3d)$$

$$\dot{G}_L = 0.1G_H + 0.4G_G - 0.5G_L + 6.18M^I_{HGP}(2.7\tanh(0.389\Gamma) - f_2)(1.42 - \text{-}1.41tanh((0.006G_L - 0.31)) - 4.5M^I_{HGU}(1 + \tanh(0.024G_L - 3.61)) \quad (1.1.3e)$$

$$\dot{G}_K = 1.53G_H - 1.66G_K + 49.5 \quad (1.1.3f)$$

$$\dot{G}_{PV} = 1.45G_H - 2.75G_{PV} + 1.3G_{PI} \quad (1.1.3g)$$

$$\dot{G}_{PI} = 0.2G_{PV} - 0.2G_{PI} - 0.005G_{PI}(7.03 + 6.52\tanh(0.016I_{PI} - 1.97)) \quad (1.1.3h)$$

$$\dot{M}^I_{HGP} = -0.04M^I_{HGP} + 0.05 - 0.045tanh(0.078I_L - 1.48) \quad (1.1.3i)$$

$$\dot{f}_2 = -0.05f_2 - 0.008 + 0.02tanh(0.389\Gamma) \quad (1.1.3j)$$

$$\dot{M}^I_{HGU} = -0.04M^I_{HGU} + 0.08tanh(0.026I_L) \quad (1.1.3k)$$

$$\dot{I}_B = 1.73I_H - 1.73I_B \quad (1.1.3l)$$

$$\dot{I}_H = 0.45I_B + 0.91I_L + 0.72I_K + 1.06I_{PV} - 3.15I_H \quad (1.1.3m)$$

$$\dot{I}_G = 0.77I_H - 0.77I_G \quad (1.1.3n)$$

$$\dot{I}_L = 0.1I_H + 0.378I_G - 0.79I_L + 0.53r_{PIR} \quad (1.1.3o)$$

$$\dot{I}_K = 1.41I_H - 1.83I_K \quad (1.1.3p)$$

$$\dot{I}_{PV} = 1.42I_H - 1.88I_{PV} + 0.46I_{PI} \quad (1.1.3q)$$

$$\dot{I}_{PI} = 0.05I_{PV} - 0.111I_{PI} \tag{1.1.3r}$$

$$\dot{P} = -0.05P + 0.05\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right]^{1.11} \tag{1.1.3s}$$

$$\dot{I} = -0.93I + 0.93\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right] \tag{1.1.3t}$$

$$\dot{Q} = 0.008Q + 0.58P - 0.008\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right]^{1.11} Q - 0.05 - 0.0958\left[\frac{(G_H)^{3.27}}{(132)^{3.27}+5.93(G_H)^{3.27}}\right]^{0^+} Q \tag{1.1.3u}$$

$$\dot{\Gamma} = -0.0008\Gamma + 0.0008(2.93 - 2.10\tanh(0.041G_H - 2.55))(1.31 - 0.61\tanh(0.05I_H - 0.5) \tag{1.1.3v}$$

Following the steps as in case I, we get equilibrium point

X_0 = (105.35, 74.04, 118.32, 129.59, 121.12, 136.68, 101.93, 87.83, 1.23, -0.13, 0.87, 1.26, 1.26,1.26, 4.18, 1.37, 1.36, 0.12, 0.29, 0.31, -18.51, 1.31).

Again we used fsolve and fminsearch by taking our manual solution as the starting value for fsolve and then its solution as starting value for fminsearch. The results turn out are

Using fsolve

X = (131.35, 98.94, 143.05, 141.06, 139.06, 161.67, 140.51, 137.67, 0.63, -0.1, 1.21, 19.67, 19.67, 19.67, 26.93, 15.16, 16.70, 7.52, 0.36, 0.40, -31.72, 0.86) with 10 iterations and function values multiple of 10^{-12}.

Using fminsearch

X = (131.42, 99.01, 143.12, 141.13, 139.10, 161.73, 140.60, 137.79, 0.50, -0.09, 1.21, 19.69, 19.69, 19.69, 26.96, 15.17, 16.71, 7.51, 0.36, 0.40, -31.63, 1.17) with 3369 iterations and function values are -0.000144.

An equilibrium point is a constant solution to a differential equation. An equilibrium point of a dynamical system generated by an autonomous system of ordinary differential equations (ODEs) is a solution that does not change with time. For example, each motionless pendulum position in corresponds to an equilibrium of the corresponding equations of motion, one is stable, the other one is not. For linearized the model, we need point or equilibrium point to check the stability of the model. We did not linearizing the model since equilibrium point not lie in the feasible region. In this model f_2 is the degradation of the maximum response of the glucagon action on the hepatic glucose production and Q is the labile insulin. f_2 and Q both are negative in each case of the model and these are the concentration in healthy person which never be negative. If the equilibrium point lies in the feasible region then by using the Jacobian by taking the partial derivative with each variable, convert the nonlinear system of equation into linearized system.Because if a linear system is controllable and observable, then a nonlinear system may or may not be controllable and observable. If a linear system is not controllable and observable then nonlinear is not controllable and observable.

3. RESULTS AND DISCUSSION

In case I the equilibrium point includes two negative values one for $f_2$which is degradation of the maximum response of glucagon action on the hepatic glucose production and other for labile insulin Q. On using fsolve and fminsearch it turn out to be a single negative value only of Q. In case II again the equilibrium point has two negative values for same variables which also remain negative even after using fsolve and fminsearch.f_2 is the degradation of the maximum response of the glucagon action on the

hepatic glucose production and f_2 is positive or the maximum response is zero as glucose concentration is equal to the basal *BGL*. *Q* is the labile insulin and is taken in *Units* so it cannot have a negative value. This is the most comprehensive model in the *GIG* (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. The glucagon model considered is a very simple one as compare to model for insulin. Although the glucagon effect is not as complicated as the insulin but this can be one of the reasons.

f_2 and *Q* both are negative in each case in the model and these variables are the concentration in healthy person which never be negative. Since controllability and observability are sufficient conditions for the existence of a stabilizing feedback control further investigations should consider also the weaker properties of detectability and stabilizability for the models which provide a set of necessary and sufficient conditions for the existence of a stabilizing control. *Q* is dependent on P (periphery) and *G* both are in glucose subsystem can be improved.

As discussed in [5] under the nominal parameter values the Sorensen's Model can represent glucose metabolism for one subject with the assumption that parameter values remained unchanged with respect to time. Sorenson's Model can reproduce a systematic basal glucose level around *190 mg/dl* for any initial condition but basal level can reach more than *300 mg/dl* in diabetes patient. The equilibrium point can be modified but it is unique even if the parameter values have changed. Thus, a different basal level is reached as the parameter values change.

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