Design & Analysis Of H∞ Controller For Blood Glucose Regulation In Type-1 Diabetes Patient

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Abstract: The target is to achieve some adaptive & robust controller for blood glucose regulation in presence of all sorts of disturbances in terms of physiological parameter variations,process and measurement noises. The state of the art in closed loop control of drug delivery using implant able has been reviewed & H∞ controller for the device has been designed & tested. The designed of the controller is mainly based on non linear modeling & robust structure constrained controller & also related problems like sample data control etc. The robust closed loop control algorithms for insulin infusion to maintain normoglycaemia in patient have been developed in one important method, that is H∞ control for the state feed back design with parameter uncertainties & external disturbances to assure robust closed loop stability in all possible patient conditions.

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1. Introduction

Diabetes Mellitus is one of the most common chronic diseases. The disease is caused by the inability of the pancreas to produce a sufficient amount of insulin, which leads to *hyperglycemia* or uncontrolled increase of blood glucose (BG) level exceeding 144 *mg/dl,* unless the patient administers insulin externally. For intensive treatment of diabetes, controlled release of insulin into the bloodstream at programmed rate is necessary for an extended period of time. The glucose metabolism of a diabetic patient is a complex nonlinear process closely linked to a number of internal factors, which are not easily accessible for measurement. Only with accessible information like occasional blood glucose measurements, information about food intake and physical exercise - the system appears highly stochastic and the quantity of interest, the BG concentration is difficult to model and predict. Different models of the diabetic patient has been used in several literature [1 - 7] to find the dynamics of various preparations of insulin to regulate BG.

A suitable H∞ controller for closed loop adjustments of discrete time insulin infusion rate is used. The following sections give the clinical background of glucose-insulin interaction, model description, anatomical basis and mathematical equations governing the physiological process, insulin dispenser system and the SIMULINK realization of the whole system. A linearized patient model has also been proposed for possible linear controller applications.

2. Clinical background

Diabetes Mellitus is a major chronic disease in industrial countries. It is group of clinical disorders of carbohydrate, fat & protein metabolism characterized by chronic high blood glucose level due to either deficiency of insulin in the body or resistance of it's action or both. This occurs when the body is unable to use glucose effectively [4-6]. Glucose is the main source of energy, it is required to body for any type of function. The BG levels are closely regulated in health despite the varying demands of food, fasting and exercise. when we take meal our digestive system converts meal to glucose. That glucose is added to venous blood & hence glucose level in blood stream increases At that moment pancreas measures the glucose level in the venous blood, if the glucose is high (more than 81mg/dl), it generates insulin & injects it to venous blood at programmable rate to maintain proper insulin level. Insulin is the key hormone, some peripheral cells use insulin as a key to open the cells door for glucose transport to cells & it converts glucose to energy. So that peripheral cells utilize glucose to get energy supply with help of insulin as shown in figure-1.

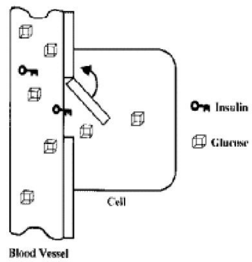

Figure 1: Insulin acting as a key to open the cell door.

When the glucose level is high liver absorbs glucose from blood stream with help of insulin & store it in form of glycogen. When glucose level is low liver converts glycogen to glucose & that Glucose is added to venous blood. In this way pancreas controls the glucose concentration in the venous blood. If pancreas is damaged or unable to inject proper amount of insulin to venous blood, peripheral cells do not utilize the glucose to get energy supply, liver does not utilize glucose & it produces internal sugar resulting in uncontrolled increase of blood glucose concentration in human body, that is type -1 diabetes. Extra glucose in blood stream is released through urine when glucose level is above the renal threshold level [8-12].

For treatment of diabetes controlled release of insulin into the blood stream at programmed rate is necessary. For treatment of diabetes doctors inject insulin externally by the help of injection time to time. That is not controllable, programmable and also very pain full treatment. To avoid this engineers design a H∞ controller for type -1 diabetes patient. Just like pancreas H∞ controller can estimate the Glucose concentration & inject insulin to venous blood at programmable rate. H∞ controller has three sections. These are sensor, insulin capsule & pump. H∞ controller estimates the glucose level in blood stream with help of sensor, if Glucose level is high it opens the insulin capsule gate, sufficient amount of insulin is injected to the blood stream by help of pump at programmable rate to maintain the perfect insulin level (As shown in figure-2).

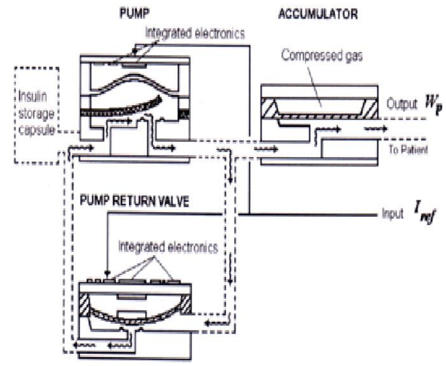

Figure 2: Schematic diagram of the micro-insulin dispenser

3. Physiological model of glucose-insulin interaction process

Figure-3 shows the flow-limited model of the physiological process of glucose-insulin interaction. In this model, the regulated output is the arterial glucose concentration and control input is the continuous insulin infusion at a regular interval of 5 minutes from the pump in closed loop. The variables 'glucose meal' to the 'gut' compartment and 'exercise condition' to periphery are added to the model as disturbances.

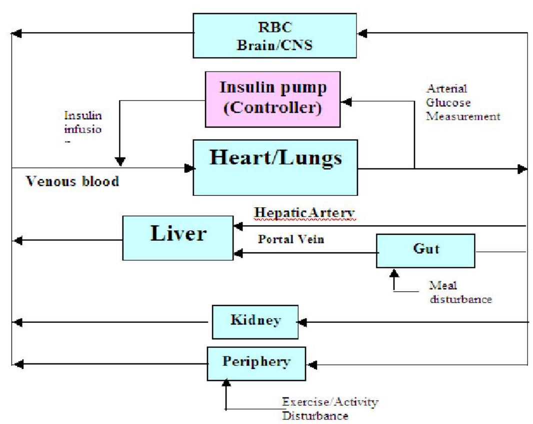

Figure-3: compartmental model of glucose insulin interaction with closed loop control

4. Linearized state space model of physiological process

The 'patient - model' of glucose - insulin process of figure - 3 is a non - linear one with three inputs & one output. Our purpose in this section is to find a linear state space model for blood glucose regulation process [13] & compare with figure – 4 to response with that of non linear model.

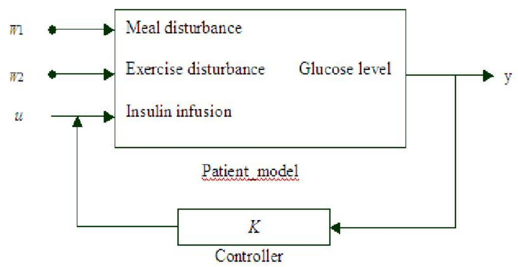

Figure - 4: Patient - model' block showing inputs & outputs with closed loop control

The state-space model of the corresponding LTI system is expressed as:

$$\left.\begin{aligned} \dot{x} &= Ax + Bu + Gw \\ y &= Cx + Du \end{aligned}\right\} \quad (1)$$

Where x is the state vector of the process, u is the insulin infusion inputs, w is the meal (w_1) and exercise (w_2) disturbance input vector. y is the measured output glucose level as shown in figure 4. A, B, G, C and D are the system matrices of appropriate order. The linearrized model of the system is obtained by using **linmod** command of MATLAB on the SIMULINK block '**patient_model**' with three inputs and one output. The continuous time system matrices of equation (1) for the linear model of present process and implantable pump with fixed parameters, thus obtained are:

$$A = \begin{bmatrix} -0.0001 & 0.000016 & -0.00008 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.0003 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.002 & 0 & 0 & 114.47 & 0 & 0 & 0 \\ 0 & 0 & 0.000007 & -0.0003 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -24.0 & -256.0 & 0 & 0 & 0.125 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -12.5 & -72.67 & -33.335 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

$$B = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix} \quad G = \begin{bmatrix} 0 & -0.057143 \\ 1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}$$

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

5. 'patient model' block diagram in algebraic framework

The plant transfer matrix P can be expressed as

$$p = \begin{pmatrix} p_{zw} & p_{zu} \\ p_{yw} & p_{yu} \end{pmatrix}$$

Where, the elements of the matrix are the transfer functions between inputs and outputs as shown in figure 4.

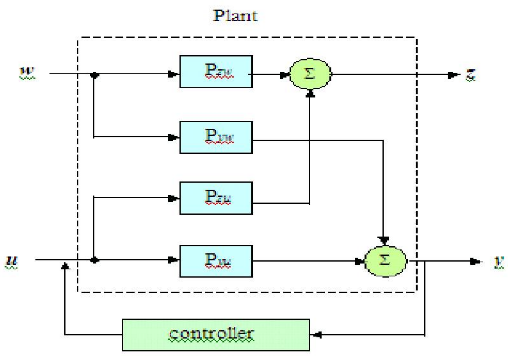

Figure 5. algebraic frame work

A transfer function representation of the system is given by

$$\begin{aligned} z &= p_{zw}w + p_{zu}u \\ y &= p_{yw}w + p_{yu}u \qquad (2) \\ u &= k\,y \end{aligned}$$

The closed loop transfer function between the regulated outputs and the exogenous inputs is obtained as follows. First we substitute for u in the equation for y.

$$y = p_{yw}\,w + p_{yu}\,k\,y \qquad (3)$$

and solve for y.

$$(1- p_{yu}k)\,y = p_{yw}\,w \rightarrow y = (1 - p_{yu}k)^{-1}\,p_{yu}\,w$$

Therefore, u becomes

$$u = k\,y = k\ (1 - p_{yu}k)^{-1}\,p_{yu}\,w \qquad (4)$$

Substituting this into the equation for z, we get

$$Z = p_{zw}\,w + p_{zu}k\ (1 - p_{yu}k)^{-1}\,p_{yw}\,w$$
$$= [p_{zw} + p_{zu}K\,(1 - p_{yu}k)^{-1}\,p_{yu}]\,w$$

Finally

$Z = T_{zw}\,w$, Where

$$T_{zw} = P_{zw} + P_{zu}K\,(1 - P_{yu}K)^{-1}\,P_{yw} \qquad (5)$$

The above expression for the closed loop transfer function Tzw is called the *linear fractional transformation (LFT)*. The plant can also be represented in state space form as

$$\begin{aligned} \dot{x} &= A\,x + B_1\,w + B_2\,u \\ z &= C_1x + D_{11}\,w + D_{12}u \qquad (6) \\ y &= C_2x + D_{21}\,w + D_{22}u \end{aligned}$$

Using the packed-matrix notation, we get.

$$P(s) = \begin{pmatrix} A & B1 & B2 \\ C1 & D11 & D12 \\ C2 & D21 & D22 \end{pmatrix}$$

6. Problem Formulation and Assumption

The H∞ control problem is formulated as follows: For stabilizing controller *K*(s) for the plant *P*(s) such that the ∞-norm of the closed loop transfer function Tzw is below a given level γ (a positive scalar). The problem is called the *standard H∞ control problem [14-16]*.The optimal H∞ control problem is

Optimal Problem $\min_{K(s)\ \text{stabilizing}} \|Tzw\|_\infty$

Standard Problem $\min_{K(s)\ \text{stabilizing}} \|Tzw\|_\infty \le \gamma$

For the problem to have a solution, certain assumptions must be satisfied. They are listed below after the dimensions of the various variables are given.

Dimensions: dim x = n, dim w = m_1, dim u = m_2, dim z = p_1, dim y = p_2

1. The pair (*A*, B_2) is stabilizable and (C_2, *A*) is detectable. This assumption is necessary for a stabilizing controller to exist. It simply guarantees that the controller can reach all unstable states, and these states show up on the measurements.
2. rank $D_{12} = m_2$, rank $D_{21} = p_2$. These conditions are needed to ensure that the controllers are proper. It also implies that the transfer function from *w* to *y* is nonzero at high frequencies. Unlike the first assumption, which is usually satisfied, this assumption is frequently violated (for example if the original plant is strictly proper; i.e if it has more poles than zeros, this condition will be violated) unless the problem is formulated such that this condition is satisfied.

3. $rank\begin{pmatrix} A - jwI & B_2 \\ C_1 & D_{12} \end{pmatrix} = n + m_2$

For all frequencies.

4. $rank\begin{pmatrix} A - jwI & B_1 \\ C_2 & D_{21} \end{pmatrix} = n + p_2$

For all frequencies

5. $D_{11} = 0$ and $D_{22} = 0$

This assumption is not needed, but it will simplify the equations for the solution. It also implies that the transfer functions from w to z and u to y roll off at high frequencies, respectively.

7. Problem Solution

The controller is given by (*K*c corresponds to *K*, the controller gain in the LQG case)

$$u = -K_c\hat{x}$$

And the state estimator is given by

$$\dot{\hat{x}} = A\hat{x} + B_2u + B_1\hat{w} + Z_\infty K_e(y - \hat{y})$$

Where $\hat{w} = \gamma^{-2}B_1'X_\infty\hat{x}$ and

$$\hat{y} = C_2\hat{x} + \gamma^{-2}D_{21}B_1'X_\infty\hat{x} \quad (7)$$

The extra term ŵ is an estimate of the worst case input disturbance to the system and ŷ is the output of the estimator. The controller gain *K*c and estimator gain *K*e are given by

$$K_c = \tilde{D}_{12}(B_2'X_\infty + D_{12}'C_1) \quad (8)$$

Where $\tilde{D}_{12} = (D'_{12}D_{12})^{-1}$

$$K_e = (Y_\infty C_2' + B_1D_{21}')\tilde{D}_{21}$$

Where $\tilde{D}_{21} = (D_{21}D'_{21})^{-1}$

The term Z∞ is given by

$$Z_\infty = (I - \gamma^{-2}Y_\infty X_\infty)^{-1} \quad (9)$$

The terms *X*∞ and *Y*∞ are solutions to the controller and estimator Riccati equations; i.e

$$X_\infty = Ric\begin{pmatrix} A - B_2\tilde{D}_{12}D_{12}'C_1 & \gamma^{-2}B_1B_1' - B_2\tilde{D}_{12}B_2' \\ -\tilde{C}_1'\tilde{C}_1 & -(A - B_2\tilde{D}_{12}D_{12}'C_1)' \end{pmatrix}$$

$$Y_\infty = Ric\begin{pmatrix} A - B_1\tilde{D}_{21}D_{21}'C_2 & \gamma^{-2}C_1C_1' - C_2\tilde{D}_{21}C_2' \\ -\tilde{B}_1'\tilde{B}_1 & -(A - B_1\tilde{D}_{21}D_{21}'C_2)' \end{pmatrix}$$

Where $\tilde{C}_1 = (I - D_{12}\tilde{D}_{12}D_{12}')C_1$

and $\tilde{B}_1 = B_1(I - D_{21}'\tilde{D}_{21}D_{21})$

The closed loop system becomes

$$\begin{pmatrix}\dot{x}\\ \dot{\hat{x}}\end{pmatrix}=\begin{pmatrix}A & -B_2K_c\\ Z_\infty K_f C_2 & A-B_2K_c+\gamma^{-2}B_1B_1'X_\infty-Z_\infty K_f(C_2+\gamma^{-2}D_{21}B_1'X_\infty)\end{pmatrix}\begin{pmatrix}x\\ \hat{x}\end{pmatrix}+\begin{pmatrix}B_1\\ Z_\infty K_f D_{21}\end{pmatrix}w$$

$$\begin{pmatrix}z\\ y\end{pmatrix}=\begin{pmatrix}C_1 & -D_{12}K_c\\ C_2 & 0\end{pmatrix}\begin{pmatrix}x\\ \hat{x}\end{pmatrix}+\begin{pmatrix}0\\ D_{21}\end{pmatrix}w$$

As we had promised, the equations are quite complicated and messy! Finally, it can be proved that there exists a stabilizing compensator if and only if there exist positive semi-definite solutions to the two Rickety equations and the following conditions:

$$\rho(X_\infty Y_\infty) < \gamma^2 \qquad (10)$$

Where ρ (X_∞, Y_∞) = spectral radius of (X_∞, Y_∞) = largest Eigen value of (X_∞, Y_∞) = λ_{max} (X_∞, Y_∞). *H∞* control systems are shown in figure 6. Compare these diagrams to see the similarities and difference between them. It should be fairly obvious that *H∞* problems cannot be solved manually. Computer programs such as MATLAB, programs CC, MATRIX and CTRL-C have special functions and utilities for solving these problems. For every value of γ two Riccati equations must be solved and in addition even if the plant is first order, we still may need to add weighs to the system to either satisfy design requirements or satisfy the necessary assumptions for a feasible solution. This increases the order of the equations and makes manual solution almost impossible. A summary of steps is given below.

1. Set up the problem to obtain the state space representation for *P*(s).
2. Check if the assumptions (the rank conditions) are satisfied. If they are not, reformulate the problem by adding weighs or adding (fictitious) inputs or outputs.

3. Select a large positive value for γ.
4. Solve the two Riccati equations. Determine if the solutions are positive semi-definite; also verify that the spectral radius condition is met.

If all the above conditions are satisfied, lower the value of γ. otherwise increase it. Repeat steps 3 and 4 until either an optimal or satisfactory solution is obtained.

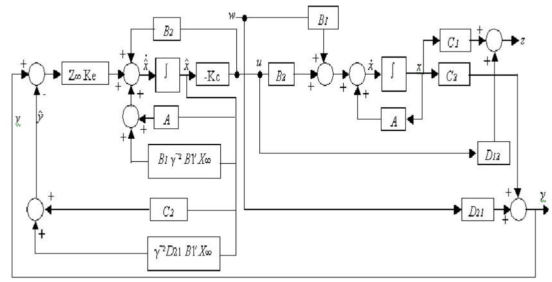

Fig 6. Block diagram showing the structure of H∞ controller system

8. H∞ Controller design for insulin delivery system in diabetic patient

Here we consider that linearized model of the physiological process glucose insulin interaction has linear ordinary differential equations. Hear the deterministic control input is the insulin infusion and we have identified at least two disturbance inputs as the meal disturbance (w_1) and exercise disturbance (w_2). Let us consider the state space representation of plant with x state vector; *u* the control input, *w* the identified process disturbance vector and *n* the measurement noise with zero mean as:

$$\left.\begin{aligned}\dot{x} &= Ax + Bu + Gw\\ y &= Cx + Du\end{aligned}\right\} \qquad (11)$$

For design of H∞ controller we have to convert given 9th order physiological system to following state space form

$$\begin{aligned}\dot{x} &= Ax + B_1 w + B_2 u\\ z &= C_1 x + D_{11} w + D_{12} u\\ y &= C_2 x + D_{21} w + D_{22} u\end{aligned} \qquad (12)$$

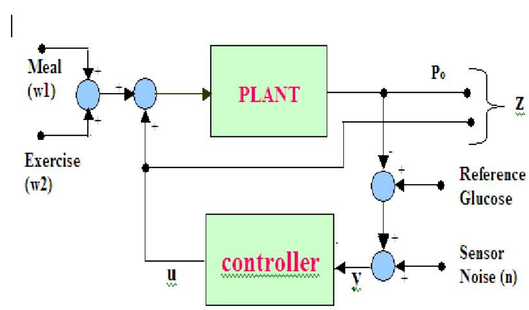

Figure 7. Block diagram of blood glucose regulation by H∞ control

The exogenous input vector that is denoted by *w*, where *w1* is the disturbance of meal, *w2* is the disturbance of exercise, *n* is the sensor noise. Po is the plant output (glucose level), *u* is the actuator signal (insulin dose). These are mentioned in matrix form.

$$w = \begin{pmatrix} W_1 \\ W_2 \\ n \end{pmatrix} \quad z = \begin{pmatrix} Po \\ u \end{pmatrix}$$

Step-1 :

$$\dot{x} = A\,x + B_1 w + B_2 u$$

$$\dot{x} = a \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ x_7 \\ x_8 \\ x_9 \end{bmatrix} + \begin{bmatrix} 0 & -0.057143 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} W_1 \\ W_2 \\ n \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix} u$$

Step-2:

$$= \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ x_7 \\ x_8 \\ x_9 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} W_1 \\ W_2 \\ n \end{bmatrix} + 0u$$

$$y = C_2 x + D_{21} w + D_{22} u = = p_0 + n$$

$$= x_1 + n$$

$$= p_0 + n \qquad \text{So that } Po = x_1, \text{ where } D_{22} = 0$$

Step-3:

$$z = \begin{bmatrix} p_0 \\ u \end{bmatrix} = \begin{bmatrix} x_1 \\ u \end{bmatrix}$$

$$z = C_1 x + D_{11} w + D_{12} u$$

$$= \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ x_7 \\ x_8 \\ x_9 \end{pmatrix} + \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} W_1 \\ W_2 \\ n \end{pmatrix} + \begin{pmatrix} 0 \\ 1 \end{pmatrix} u$$

$$= \begin{pmatrix} x_1 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ u \end{pmatrix} = \begin{pmatrix} x_1 \\ u \end{pmatrix} = \begin{pmatrix} p_0 \\ u \end{pmatrix}$$

Using the packed matrix notation, we will get

$$P(S) = \begin{pmatrix} A & B_1 & B_2 \\ C_1 & D_{11} & D_{12} \\ C_2 & D_{21} & D_{22} \end{pmatrix}$$

In this section, this problem is solved using H-infinity program. After several trials, we found that the value of γ could not be reduced below 649.164436497. hence we conclude that 649.164436497 is the optimal value (Note that the solution of the optimal H∞ control problem involves a search over γ and we can get as close to it as possible but not achieve it. I found these values of X∞, Y∞, Kc, Ke, K(s) through the MATLAB program.

9. Performance study with H∞ control

In the following sections we will study the response of the glucose-insulin process with H∞ control for the process disturbance of 60gm meal (carbohydrate) ingestion at t = 40000 sec and a half-an-hour exercise of 0.005 arbitrary unit at t = 90000 sec along with the additive sensor noise. In this section H∞ controller design has been applied on the simulated non - linear '**patient - model**' and the data from linearized system matrices have been used for on line design of closed loop estimator [18,20,21] and controller as shown in figure 15. The H∞ control gains have been computed by using MATLAB routines. The '**patient_ model**' block in figure 16 represents combination of the physiological process and the implanted insulin delivery device. The closed loop system compares the output plasma **BG** level with a reference glucose level of 4.5 mmol/l (81mg/dl) and H∞ controller generates insulin correction over the nominal (basal) rate 22.3mU/min to maintain *normoglycalmia.* The model has been tested in closed loop by varying glucose intake and exercise. In this section we study the transient response of blood glucose level for an controlled process with constant insulin infusion of 22.3 m U/min (basal dose) for the selected disturbances.

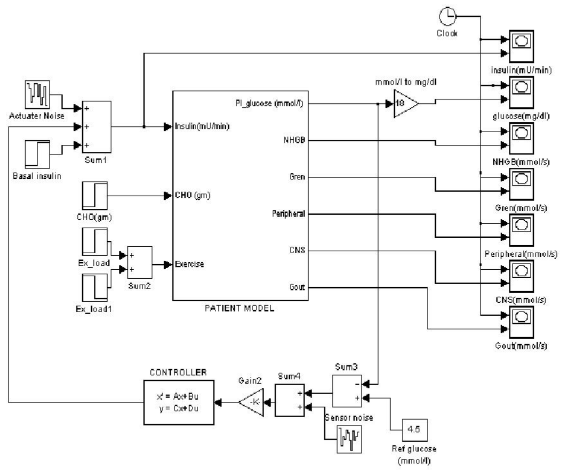

Figure 15. SIMULINK diagram of off line H∞ controller design on non - linear patient model.

The response of Glucose level (mg/dl), Insulin dose (mU/min), N H G B rate (mmol/s), Gren rate (mmol/s), Glucose utilization rate (mmol/s) in periphery, Glucose utilization rate (mmol/s) in the brain (CNS), Gout rate (mmol/s) with 60 gram meal injected at t=40000s & exercise noise is applied at t=80000s are shown in figure 16 at γ =649.164436497 (optimal value). Only at the optimal value of gamma the glucose level is low in the diabetes patient. Since H∞ controller is a robust, it is observed that the response of the model produce steady state glucose level and plasma insulin profile independent of initial value of simulation.

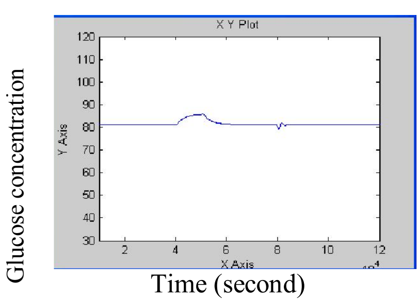

Figure 16 (a).Response of glucose level (mg/dl) with 60 gm meal injected at t=40000s & exercised is applied at t=80000s when γ =649.164436497.

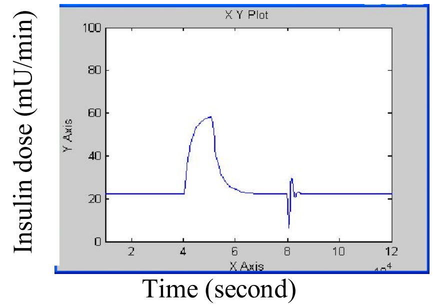

Figure 16 (b).Response of insulin dose (m U/min) with 60 gm meal injected at t= 40000s & Exercise is applied at =80000s when γ =649.164436497.

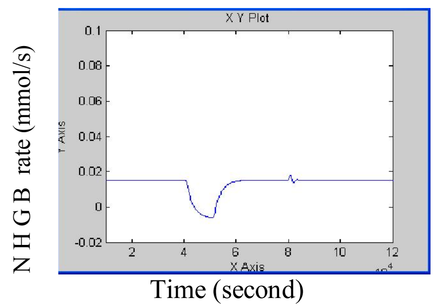

Figure 16 (c).Response of N H G B rate (mmol/s) with 60 gm meal injected at t=400000s & Exe is applied at t= 80000s when γ = 649.164436497.

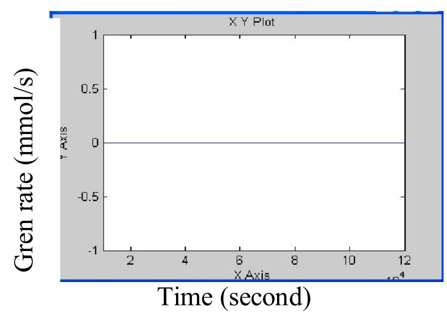

Figure 16 (d). Response of Gren rate (mmol/s) when γ =649.164436497.

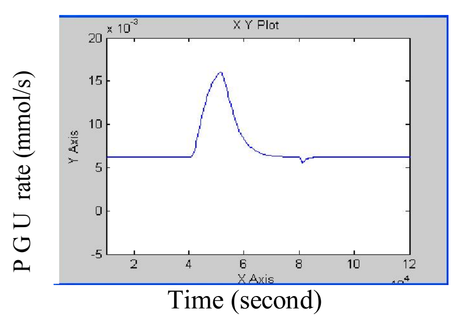

Figure 16 (e).Response of P G U rate with 60 gm meal injected at t=40000s & Exe is applied at t=80000s when γ =649.164436497.

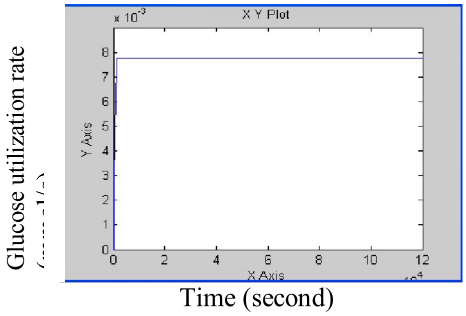

Figure 16 (f). Response of glucose utilization rate in C N

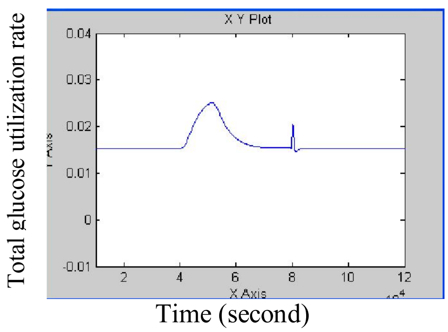

Figure 16.(g) Response of Gout rate with 60 gm meal is injected at t=40000s& Exe is applied at t= 80000s when
$\gamma = 649.164436497$.

9. Conclusion

The present investigation attempts to solve some major issues related to the complex control problems of implant able insulin delivery systems. Concentration is given on the problem of establishing a normal operating state and optimum setting of a robust controller for implantable insulin delivery systems. Which will produce optimal output at every possible physiological condition and disturbances. The present study is focused on the modeling and identification of the physiological process of glucose insulin interaction in **type-1** diabetes patient and design of adaptive controllers for implant able insulin delivery system in all possible physiological conditions and disturbances of a type-1 diabetic patient

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