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Research Report

Presented By
Akshita JAIN
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Artificial Pancreatic System

Jury

Evaluators: Michel Malabre

Director of Research,
CNRS

Supervisors: Claude Moog

Director of Research,
CNRS

Emeric Scharbarg

Medical Doctor and
PhD student
(Automatic Control)

Abbreviations

1. APS : Artificial Pancreatic System
2. CGM : Continuous Glucose Monitoring
3. BG : Blood Glucose
4. FIT : Flexible Insulin Therapy
5. PID : Proportional Integral and Derivative
6. CHO : Carbohydrates
7. ISF : Insulin Sensitivity Factor
8. CIR : Carbs to Insulin Ratio
9. IOB : Insulin on board
10. SF : State Feedback
11. TDS : Time delay system
12. MIMO : Multiple Input Multiple Output
13. SISO : Single Input Single Output
14. MPC : Model Predictive control
15. LHP : Left half complex plane
16. RHP : Right half complex plane
17. ZOH : Zero order hold
18. TDI : Total daily insulin
19. SPD : Symmetric positive definite
20. UIO : Unknown Input Observer
21. DDE : Delayed Differential Equation
22. FDA : Food and Drug Administration

List of Symbols

1. x_g/x_1 = Glucose concentration in blood plasma
2. x_{ip}/x_2 = Insulin concentration in blood plasma
3. x_{is}/x_3 = Insulin concentration in subcutaneous compartment
4. x_s/x_5 = CHO content transferred to duodenum from stomach
5. x_d/x_4 = CHO content transferred to plasma from duodenum
6. u_i = Injected insulin rate
7. u_m = CHO from the Meal
8. θ_1 = Insulin independent glucose absorption
9. θ_2 = Insulin Sensitivity Factor
10. θ_3 = Time constant for insulin dynamics
11. θ_4 = Constant for glucose release from CHO digestion.
12. θ_5 = Time constant for digestion dynamics
13. τ_1 = Transport delay from subcutaneous to plasma
14. τ_2 = Glucose production delay for meal dynamics
15. τ_3 = BG Measurement delay
16. U_{BG} = Insulin required for BG difference
17. U_{basal} = Basal insulin - fasting BG insulin
18. U_{carb} = Insulin required for carbs intake
19. k = Safety tuning gain
20. x = State vector
21. \hat{x} = Observer state vector
22. y = System Output/Measurement
23. \hat{y} = Estimated output
24. τ = Time Constant of a system (Generalised)
25. τ_d = Time delay

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Abstract

The controlled injection rate of insulin to maintain plasma glucose at the desired target level is a necessary requirement in the absence of natural mechanism of blood glucose regulation for Type 1 patients with diabetes. Hence, effectiveness of a control algorithm lies in the fact that blood glucose (BG) regulation remains hypo-free such that the system under positive disturbance (e.g. meal) is regulated by driving BG from hyperglycaemia to euglycemia with an effective injection rate of insulin while maintaining the positivity of the system i.e. avoidance of hypoglycaemia. Besides, external disturbance like exercise drives the blood glycaemia to hypoglycaemia level. Therefore, the control strategy should also take care of variation in basal insulin based on the glycaemia value above or below the target BG. This variation in basal is successfully implemented and tested in the open source artificial pancreatic system (openAPS) and the same strategy will be employed in this case.

Based on the established 5 states space model (1) and the state feedback (SF) control strategy with gains that ensures the hypo-free BG regulation, an observer with SF is implemented and tested on the UVA-Padova simulator for different meal scenario in open and closed loop condition. The comparison analysis is also carried out between a simulator model and the discussed 5 state model. The results of simulator with state feedback control strategy are analysed for different meal scenarios and time periods. The results which align with the requirements of clinical trials will lead to the development of control algorithm on openAPS application for prototype development. This application will be utilised for clinical trials in the future to substantiate the effectiveness of discussed control strategy. During the course of this research, an observer with known and unknown inputs is discussed, however an observer with known input is implemented and tested on simulator for the hybrid control where announcement of meal (or any other disturbance) is necessary for an effective control. The suitable unknown input observer (UIO) is suggested and checked for its efficiency for this application using 5 states space model (plant model) with the known meal intake.

Another aspect of this thesis is the study and observation of time delay models for an artificial pancreatic system. The implemented time delay models with 3 states is analysed for its efficiency, stability and resemblance with physiological response time under disturbances.

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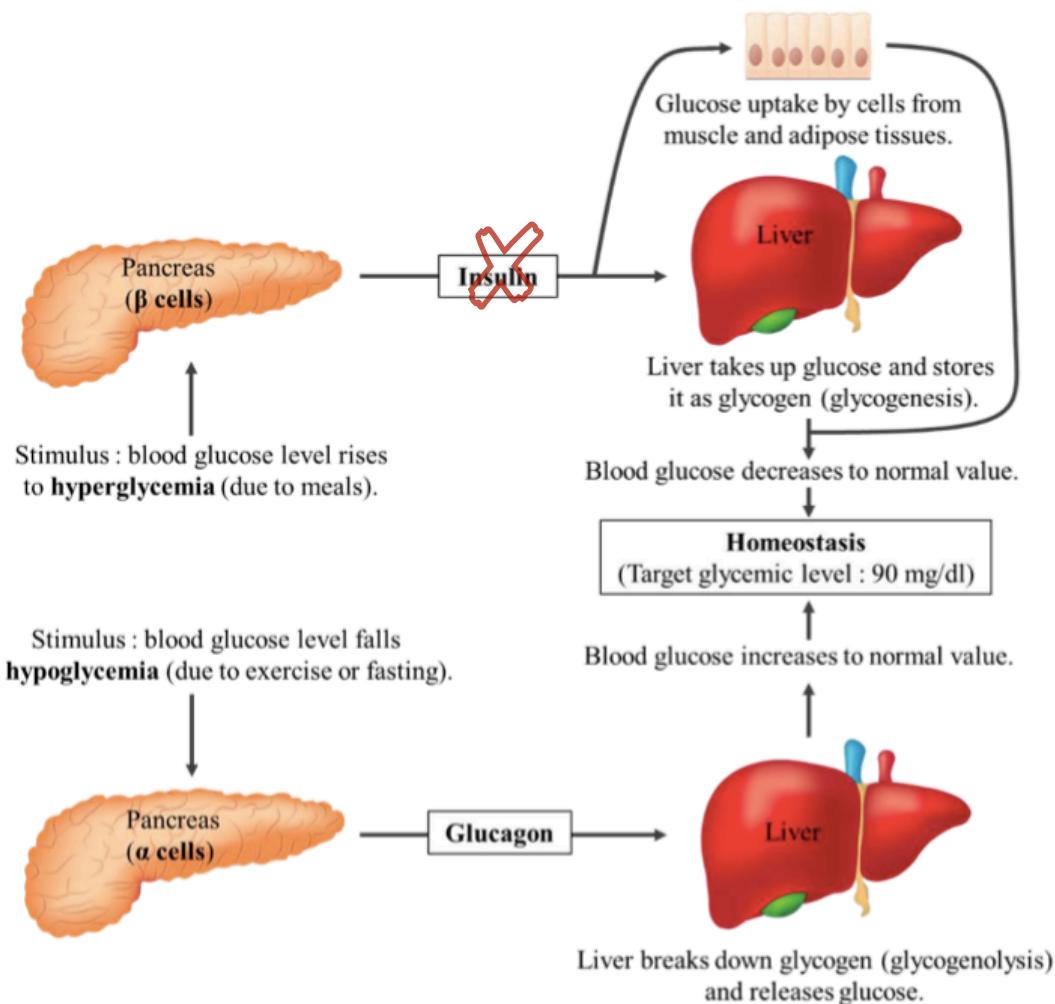
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Chapter : 1

TYPE 1 DIABETES AND CONTROL TREATMENTS

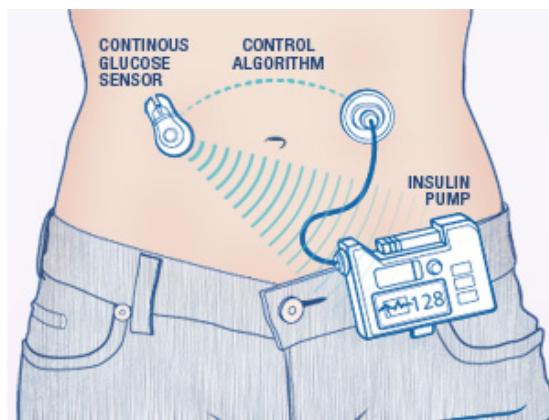
The goal of this project is to develop the fully automated solution with state feedback (SF) control strategy to carry out clinical trials for insulin infusion treatment to regulate blood glucose (BG) in **patients with Type 1 Diabetes**. The aim of this project is to design, analyse and implement the fully automatic glucose regulation system such that hypoglycaemic episodes (glucose level below 70 mg / dl) are reduced to zero. Therefore, study and analysis of effectiveness of established state feedback control strategy as per (1), design and implementation of observer for glucose-insulin dynamics, test and validation of control strategy on FDA approved simulator. Based on the results from simulator, diagnosis of prototype development including control algorithm development have been carried out to accomplish the goal of prototype development.

Type - 1 diabetes is a chronic disease where natural mechanism of glucose regulation in the plasma is dysfunctional. The destruction of pancreatic-cells lead to the insulinopenia (disappearance of insulin secretion) which makes body incapable of maintaining the blood glucose level. The chronic uncontrolled blood glucose level leads to severe problems like kidney failure, blindness , etc. Fortunately, with insulin discovery, treatments through insulin injection or infusion through subcutaneous compartment is readily available for the patients for glucose regulation.



Fig(1.1) : Type 1 Diabetes Pathophysiology

Artificial pancreatic system (APS) is an automated solution for glucose regulation in type-1 patients with diabetes. The system consists of continuous glucose monitoring (CGM) as a sensor, insulin pump as an actuator and a controller for calculating the amount of required insulin units. In recent developments towards the automation of glucose regulation, technologies from Dexcom, Medtronic , etc., have proven themselves in providing continuous measurements of subcutaneous glucose concentration and feedback control law (20). The control algorithm of existing APS technologies varies from simple PID algorithm to advanced algorithm like artificial intelligence. However, all these solutions are hybrid and still lack full autonomy i.e. patients need to announce meal, exercise or other disturbance scenarios for effective glucose regulation. The **hybrid control** in this project refers to the control which needs meal or other disturbances to be announced. This infers that hybrid control lacks full autonomy in the absence of knowledge of any introduced disturbance. This project underlines the importance of fully automated solution, therefore state feedback with an observer is designed and implemented with CGM as a measurement to estimate the meal and insulin states. Therefore, even if the patient doesn't announce the meal, state feedback control will effectively control the glucose using state estimator. Another important criterion for the control strategy is to reduce hypoglycaemia episodes which is taken care by choosing feedback gains as FIT (Functional Insulin Therapy) parameters such that closed loop system respects the positive constraints.



Fig(1.2) : Components of Artificial Pancreatic System (29)

One of the important therapies for the treatment of type 1 diabetes patients is flexible insulin therapy (FIT) which decides the quantity of insulin on daily basis based on the patient specific clinical parameters. This therapy stands on four pillars and employs following measurements to maintain glucose in the range of 70-180 mg / dl :

1. Basal Rate : Insulin infusion rate that maintains glucose at a constant level during fasting. Average Insulin required at basal level (Sleeping or resting or minimal activities or no food intake) is $0.3 \times \text{weight} \text{ (in kg)}$ of person insulin units required every 24 hrs.
2. ISF : **Insulin Sensitivity factor** is the glycemic drop for every extra unit of injected insulin while basal rate is correctly set. It differs with the person weight, height and age group. More is the weight of person, lesser is the sensitivity. It means a fat person consumes more insulin compared to normal weight person to reduce same amount of glucose in blood. The behaviour of sensitivity is non-linear outside the normal range of glycemia.
3. Raise : Increase in BG when 15-g carbohydrate (CHO) is digested while basal is correctly set.
4. CIR : **Carbohydrate to Insulin ratio** is used to identify the amount of carbs covered by a unit of Insulin. This ratio differs in every person, and a person's own ratio may vary over the time or even from meal to meal. For e.g. CIR depends on a glycemic index and is found to be considerably lower during the breakfast than any other meal.

However, these tools of FIT aren't enough to compute the correct amount of injected insulin. It fails to address the various disturbances (for e.g. physical exercises, stress and other activities) and incorrect

estimates of CHO intake. Therefore continuous monitoring and control i.e. fully automated solution is required to avoid both hypo-glycemic ($BG < 70$ mg/dl) and hyper-glycemic ($BG > 180$ mg/dl) condition. These continuous measurements not only help in statistical analysis but also enable the efficient control of BG to prevent the morbidity in diabetes.

The dynamics of a pancreatic system is implemented using physical and engineering science to study and evaluate the optimum control strategies along with time-series analysis. The mathematical model of dynamics of human glucose-insulin pave the way towards data intensive studies and comparison analysis which utilises the FIT data from non-diabetic and diabetic patients.

Organisation of Thesis :

In **chapter-2**, the mathematical model of dynamics of human glucose-insulin (2) is discussed and detailed with respective parameters which is further utilised for validating the control strategy discussed in **chapter 3**. The condition of hypoglycaemia is severe and cause stupor or seizure for type 1 diabetes patients as they are impaired with the natural mechanism of glucose restoration in blood. This condition is responsible for death of 4% of diabetic patients as per (7). In general, a PID algorithm which is simple in design is utilised for regulating the BG in artificial pancreatic system. However, it's inability to comply with positive constraints couldn't help in avoiding hypoglycaemia. Therefore, a control algorithm which stresses on avoiding the condition of hypoglycaemia will be studied in **chapter-3**. The model with control strategy is implemented on MATLAB and analysed for BG regulation and positive constraint ($bolus \geq 0$, insulin injection ≥ 0) under disturbance (such as meal introduction) for Type - 1 Diabetic patients. This research focuses on the state feedback control that respects positive constraints with established positivity gains as discussed in (1) and ensures that BG doesn't enter into hypoglycaemic condition. After obtaining the desired response from testing model, an observer is implemented to estimate the states including glucose, insulin and CHO (meal intake). The further objectives of this research include the observer design and implementation, testing and validation of control strategy on UVA Padova simulator and implementation of control algorithm for an open source artificial pancreatic system (openaps).

Time delay models are discussed in **chapter 4** and response analysis of state feedback control law with gain tuning is carried out to understand the behaviour of system dynamics with delays under positive constraints. Finally performance of state feedback control law is assessed using UVA Padova simulator with an observer based on the 5 state dynamic model in **chapter 5** to draw conclusions and results. In the end, a control algorithm will be developed based on the results from chapter 5 for openaps application. In **chapter 6**, openaps development and associated technologies will be detailed, and potential of product development using the open software will be explored.

Chapter : 2

GLUCOSE-INSULIN MODEL

The mathematical models of the glucose-insulin dynamics have been developed to study the diabetes and to conduct the experiments for various closed loop control strategies. These models are employed in the data intensive studies for further analysis on sensor accuracy, prediction and various control laws.

The first glucose-insulin model was developed by Bolie (8) who computed the normal blood regulation coefficients for the healthy subjects. Further development in model, computation and estimation of parameters is lead by Bergman (9) in 1979. He implemented the minimal non-linear model which later modified by De Gaetano (10) to incorporate the system delays by employing differential delay equations (DDE) in the non-linear model. Drozdov and Khanina (11) in 1995 proposed a model that uses a single explicit time delay for glucose production. Another time delay model is proposed by Li et al (12) in 2006 which discussed the dynamics with the two explicit delays; insulin transport delay (until insulin becomes remote insulin) and the delay in change in hepatic glucose production. In 2011, five states and four parameters linear model was developed which also went through clinical trials (3). This dynamic model is defined in terms of three state variables: BG Level, Insulin Infusion and Dextrose infusion (chemical identical of blood glucose) when euglycemia is maintained. The rate of change of BG with time is described by non-linear differential equation where BG level was positively affected by dextrose infusion, and negative effect on BG level by insulin injections such that behaviour of BG dynamics is similar to an inverse response system.

However, traditional minimal models couldn't prove long term stability and consistency. These models might fit with FIT parameters but suffer from lack of positive linear dynamics which is a necessity between glucose-insulin relation i.e. glucose concentration can never become negative. If glucose reduces to zero, then insulin must reduce to zero. In this chapter, we will explore and implement the model focusing on patients with Type-1 diabetes which also lead to positive non-linear dynamics. Later, glucose-insulin dynamics will also be assessed using mathematical model of delay differential equations with two discrete time delay associated with transport delay of insulin (subcutaneous to plasma) and delay in plasma glucose production after CHO intake.

Glucose - Insulin Dynamics Model (2)

Diabetic model comprises of glucose-insulin dynamics which study and quantify the following state and input variables :

1. x_g = Glucose concentration in blood plasma
2. x_{ip} = Insulin concentration in blood plasma
3. x_{is} = Insulin concentration in subcutaneous compartment
4. x_s = CHO content transferred to duodenum from stomach
5. x_d = CHO content transferred to plasma from duodenum
6. u_i = Injected insulin rate
7. u_m = CHO from the Meal

Glucose dynamics:

$$\dot{x}_g = -f_m(x_g, x_{ip}) - f_b(x_g) + F_l(x_g, x_{ip}) + \theta_4 x_d \quad (2.1)$$

Such that f_m is glucose consumption by muscles under the effect of insulin, f_b is glucose consumption by brain which is insulin independent, F_l is glucose storage or delivery by the liver and θ_4 is a constant for glucose release from CHO digestion.

In actual human body, glucose-dynamics is governed by GLUT transporters at cellular level.

Glucose consumption by muscle cells :

$$f_m(x_g, x_{ip}) = \epsilon x_g + \theta_2(1 - \exp(\frac{-x_g}{x_{gc}}))x_{ip} \quad (2.2)$$

Where x_{gc} is a critical glucose value and ϵx_g is an insulin independent term such that $0 \leq \epsilon < 1$. The independent term refers to the glucose consumption by muscles due to osmosis.

Glucose consumption by brain:

$$f_b(x_g) = \theta_b(1 - \exp(\frac{-x_g}{x_{gc}})) \quad (2.3)$$

Where θ_b is a constant for glucose consumption by brain which has to become zero in case of plasma glucose concentration becomes zero.

On putting equations (2.2) and (2.3) in equation (2.1),

$$\dot{x}_g = -\epsilon x_g - \theta_2(1 - \exp(\frac{-x_g}{x_{gc}}))x_{ip} - \theta_b(1 - \exp(\frac{-x_g}{x_{gc}})) + F_l(x_g, x_{ip}) + \theta_4 x_d \quad (2.4)$$

Where $F_l(x_g, x_{ip}) = \frac{2\theta_1}{1 + \exp(\frac{x_{ip}}{x_{ic}})} - C_0[\frac{\exp(x_g/x_{gc}) - 1}{\exp(x_g/x_{gc}) + 1}]$ such that 1st term induces an increase in plasma glucose concentration and x_{ic} is critical insulin concentration above which raise in BG vanishes (after some meal). The second term induces the decrease in BG as liver stores the excess glucose in the form of glycogen and fatty acids. Here C_0 is a constant.

when fasting is considered, $x_d = 0$ and

$$\begin{aligned} \theta_1 &= -\epsilon x_g - \theta_b(1 - \exp(\frac{-x_g}{x_{gc}})) + F_l(x_g, x_{ip}) \\ \dot{x}_g &= \theta_1 - \theta_2(1 - \exp(\frac{-x_g}{x_{gc}}))x_{ip} \end{aligned} \quad (2.5)$$

Insulin dynamics:

The dynamics of insulin in both plasma and subcutaneous compartment is described by following differential equations when no transport delay is considered.

$$\begin{aligned} \dot{x}_{ip} &= -\frac{1}{\theta_3}x_{ip} + \frac{1}{\theta_3}x_{is} \\ \dot{x}_{is} &= -\frac{1}{\theta_3}x_{is} + \frac{1}{\theta_3}u_i \end{aligned} \quad (2.6)$$

Where θ_3 is the response time for insulin dynamics.

Digestion dynamics:

The digestion dynamics consists of two compartments, stomach and duodenum. The stomach compartment is fed by input u_m (meal/carbs). The two compartment digestion subsystem is modelled as follows where θ_5 is time constant for digestion dynamics.

$$\begin{aligned} \dot{x}_d &= -\frac{1}{\theta_5}x_d + \frac{1}{\theta_5}x_s \\ \dot{x}_s &= -\frac{1}{\theta_5}x_s + \frac{1}{\theta_5}u_m \end{aligned} \quad (2.7)$$

On simplifying the equation (2.4), (2.6) and (2.7), following model is observed which is consistent with the FIT parameters. The model is derived for moderate range of BG such that θ_2 remains a constant and ϵ is considered negligible such that ($x_1 = x_g$, $x_2 = x_{ip}$, $x_3 = x_{is}$, $x_4 = x_d$ & $x_5 = x_s$) which is given as below:

Glycemic dynamics : $\dot{x}_1 = \theta_1 - \theta_2 x_2 + \theta_4 x_4$

$$\begin{aligned} \text{Inulin dynamics} : \quad \dot{x}_2 &= \frac{-1}{\theta_3} x_2 + \frac{1}{\theta_3} x_3 \\ \dot{x}_3 &= \frac{-1}{\theta_3} x_3 + \frac{-1}{\theta_3} u_i \end{aligned} \tag{2.8}$$

$$\begin{aligned} \text{Meal digestion} : \quad \dot{x}_4 &= \frac{-1}{\theta_5} x_4 + \frac{1}{\theta_5} x_5 \\ \dot{x}_5 &= \frac{-1}{\theta_5} x_5 + \frac{1}{\theta_5} u_m \end{aligned}$$

This diabetic state space model is consistent with the positive constraints and also in-line with the medical practice i.e. flexible insulin therapy. **State space model based on the equation (2.8) is employed in chapter 2 to implement the estimator and analysis of state feedback control strategy. The above model will be called as 5 state model or pancreatic model in later chapters.**

Chapter : 3

Full State Feedback Control With Observer

(3.1) State Feedback Control :

State feedback is an effective tool and perform better than PID to control the dynamics of an entire system when mathematical model of a system is available. PID control is an efficient and simple control algorithm in case of Single Input Single Output (SISO) system. However, state feedback along with an observer helps in achieving the full control over the dynamics and closed loop poles of the Multiple Input, Multiple Output (MIMO) system, thereby reducing the effects of large variation, pole perturbation, and unmodelled dynamics. Observer is employed with plant model to estimate the physical states of a system that cannot be measured otherwise.

In this research thesis, the glucose-insulin model will be implemented on MATLAB simulator with full state feedback control which helps in controlling the dynamics of glycemic model under disturbances but also ensure the positivity constraint at the system's input. The dynamics of a MIMO system/plant could be stabilised and controlled by placing closed loop poles in desirable location in the s-plane. The full state feedback control is a method employed to achieve the right pole placement and the location of poles corresponds to the eigenvalues of the characteristic equation of a system and it is also responsible for the control of the system's dynamics.

In general, a state space equation with an output of a MIMO system is as follows:

$$\begin{aligned}\dot{x}(t) &= Ax(t) + Bu(t) \\ y(t) &= Cx(t) + Du(t)\end{aligned}\tag{3.1}$$

Therefore, poles of the above the system are given by roots of the characteristic equation as follows:

$$|sI - A| = 0$$

Full State Feedback :

$$u(t) = Fx(t)$$

Where F is the static feedback gain, x denotes the states of a system, A is a state matrix, B & D are input matrices, C is an output matrix.

$$\dot{x} = (A + BF)x$$

In this case, $D = 0$ such that,

$$y = Cx.$$

The poles of a system with the state feedback are the roots of following characteristic equation:

$$|sI - (A + BF)| = 0$$

The values of F are calculated from an above equation with desired stable closed loop poles in s-plane. The state feedback system is freely assignable only if system is controllable, i.e., rank of controllability matrix must be full.

The state space model based on the glucose-insulin dynamic equations (2.8) is developed and state feedback gains are calculated under positive constraints based on the aforementioned general theory on the state space model.

In this case, the state space model comprises of 5 states (x_1 =Glucose concentration in the blood plasma, x_2 =Insulin concentration in the blood plasma, x_3 = Insulin concentration in the subcutaneous compartment, x_4 =CHO content transferred to duodenum from the stomach, x_5 =CHO content transferred to the plasma from duodenum), 2 inputs (u_i = Insulin Injection and u_m = Meal Input) and 1 output (y = glucose measurement). The obtained state space system is non-linear due to the constant term θ_1 (glucose consumption by brain) in glucose equation. Besides, ISF/ θ_2 is also non-linear in nature when glucose value is out of bound or normal range (70-180 mg / dl). In this study, θ_2 is considered constant for preliminary study.

Equation (3.3) explains the implementation of the 5 state model on MATLAB for further analysis. This model is linearised to calculate the gains which stabilise the dynamics while respecting the positive constraints.

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \dot{x}_5 \end{bmatrix} = \begin{bmatrix} 0 & -\theta_2 & 0 & \theta_4 & 0 \\ 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} & 0 & 0 \\ 0 & 0 & \frac{-1}{\theta_3} & 0 & 0 \\ 0 & 0 & 0 & \frac{-1}{\theta_5} & \frac{1}{\theta_5} \\ 0 & 0 & 0 & 0 & \frac{-1}{\theta_5} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ \frac{1}{\theta_3} & 0 \\ 0 & 0 \\ 0 & \frac{1}{\theta_5} \end{bmatrix} \begin{bmatrix} u_i \\ u_m \end{bmatrix} + \begin{bmatrix} \theta_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (3.3)$$

$$y = [1 \ 0 \ 0 \ 0 \ 0] \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{bmatrix}$$

Control Law for Hypo-Free Glycaemia System (1) :

Insulin bolus calculation is dependent on patient's Blood Glucose (BG) level, BG target, insulin sensitivity function (ISF or CF), carbs intake, carbohydrate to insulin ratio (CIR) and insulin on board (IOB). Therefore, the total insulin dose recommendation is formulated as follows where basal insulin is the amount of insulin to be provided during the period of fasting such that BG is at its target level.

$$U = U_{BG} + U_{Carb} + U_{basal} - IOB \quad (3.4)$$

where $U_{BG} = \frac{BG_{level} - BG_{target}}{CF}$, $U_{Carb} = \frac{CHO}{CIR}$ and $U_{basal} = \frac{\theta_1}{\theta_2}$ such that $U_{bol} = U_{BG} + U_{Carb}$

U_{BG} is an insulin input requirement for blood glucose variation from target BG, U_{Carb} is an insulin input requirement for carbs intake and U_{basal} is an insulin input requirement at BG target/equilibrium level.

IOB is the amount of insulin that is still active in the body (insulin in the subcutaneous and plasma compartment) from previous boluses. IOB could be computed through insulin dynamics model suggested in equation (2.8). Since insulin injection comprises of parts of bolus and basal insulin, therefore states corresponding to the insulin dynamics can be written as :

$$\begin{aligned} x_2 &= x_{2bas} + x_{2bol} = x_{2bas} + \tilde{x}_2 \\ x_3 &= x_{3bas} + x_{3bol} = x_{3bas} + \tilde{x}_3 \end{aligned} \quad (3.5)$$

Such that : $x_{2bas} = x_{3bas} = \frac{\theta_1}{\theta_2} = U_{basal}$

By definition, $IOB = \int_0^t (u_{bol}(\tau) - \tilde{x}_2(\tau)) d\tau$

On putting equation from (3.5) in the insulin dynamic equation (2.8), following relation is observed:

$$\begin{aligned} \theta_3(\dot{x}_3 + \tilde{x}_2) &= u_{bol} - \tilde{x}_2 \\ IOB(t) &= \theta_3 \int_0^t (\dot{x}_3(\tau) + \tilde{x}_2(\tau)) d\tau \end{aligned}$$

On integrating, $\text{IOB}(t) = \theta_3(\tilde{x}_3(t) + \tilde{x}_2(t))$ (3.6)

Using equation (3.6) and the definition of U_{BG} and U_{carb} , total amount of injected insulin as per equation (3.4) is as follows:

$$U = U_{basal} + k\left(\frac{\tilde{x}_1}{\theta_2} - \theta_3(\tilde{x}_3(t) + \tilde{x}_2(t)) + \frac{\theta_4\theta_5}{\theta_2}x_4(t) + \frac{\theta_4\theta_5}{\theta_2}x_5(t)\right) \quad (3.7)$$

Here $\tilde{x}_1 = x_1(t) - x_{ref}$ and k allows stretching of trajectories such that greater the value of k ($k > 0$), faster the injection of insulin bolus for the same amount of administered insulin.

Therefore full state feedback gains,

$$F = k\left(\frac{1}{\theta_2}, -\theta_3, -\theta_3, \frac{\theta_4\theta_5}{\theta_2}, \frac{\theta_4\theta_5}{\theta_2}\right) \quad (3.8)$$

(3.2) Positivity of Closed Loop Trajectories :

As described in book (18), a continuous linear time system is said to be positive if and only if for every nonnegative initial state and for every nonnegative input, its states and outputs are nonnegative. The positivity of such system (A, B, C^T) exists, if and only if the matrix A is a Metzler matrix, that is, its non-diagonal elements are nonnegative [$a_{ij} > 0, \forall (i, j), i \neq j$] and $B \geq 0, C^T \geq 0^T$.

Many systems such as storage systems, accumulation phenomenon in human body and stochastic models have state variables which are non-negative. Glucose-Insulin dynamics in human body is an example of positive system where all the concerned state variables are positive. Therefore, an objective of the above stated model and control law is to ensure that the value of BG change is always positive when given input is non-negative in order to avoid the occurrence of hypoglycaemia. In PID algorithm, the risk of hypoglycaemia is reduced by introducing integral windup (or saturation blocks) and MPC (Model Predictive Control) does the same function by incorporating the necessary cost functions. In the research paper (1), author provided the proof of input/state positivity with the state feedback control by employing the gains mentioned in equation (3.8).

Linearised state space model with state feedback based on the equations (3.5) and (3.8) under no meal condition is as follows:

$$\begin{bmatrix} \dot{\tilde{x}}_1 \\ \dot{\tilde{x}}_2 \\ \dot{\tilde{x}}_3 \end{bmatrix} = \begin{bmatrix} 0 & -\theta_2 & 0 \\ 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} \\ \frac{k}{\theta_2\theta_3} & -k & -k - \frac{1}{\theta_3} \end{bmatrix} \begin{bmatrix} \tilde{x}_1 \\ \tilde{x}_2 \\ \tilde{x}_3 \end{bmatrix} \quad (3.9)$$

Where $\dot{\tilde{x}}(t) = (A + BF)\tilde{x}(t) = \tilde{A}\tilde{x}(t)$ such that the eigenvalues of \tilde{A} are computed as $(-k, -\frac{1}{\theta_3}, -\frac{1}{\theta_3})$. The above matrix (3.9) is not Metzler matrix as non-diagonal element is negative.

Therefore, goal is to compute the largest positive invariant set i.e. Metzler matrix for the closed loop system described in equation (3.9). In order to prove the positivity of the system, the largest polyhedral positively invariant set of this system is obtained utilising the conditions of the positivity system where set $M_1 = \{\tilde{x} \in R^3 | \tilde{x} \geq 0\}$, and $M_2 = \{\tilde{x} \in R^3 | k(\frac{1}{\theta_2})\tilde{x}_1 - \theta_3(\tilde{x}_2 + \tilde{x}_3) \geq 0\}$ such that $M = M_1 \cap M_2$:

$$G = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ \frac{k}{\theta_2} & -k\theta_3 & -k\theta_3 \end{bmatrix} \quad \& M(G) \text{ denotes the polyhedron, } M(G) = \{x \in R^3 | Gx \geq 0\}$$

This polyhedral set $M(G)$ is a positive invariant set, if only if there exist a Metzler matrix $H \in R^{r \times r}$, i.e. $h_{ij} \geq 0$ for $i \neq j$ such that

$$G\tilde{A} - HG = 0 \quad (3.10)$$

Using the above equation (3.10), $H = \begin{bmatrix} \frac{-1}{\theta_3} & 0 & \theta_2 & \frac{\theta_2}{k\theta_3} \\ 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} & 0 \\ 0 & 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} \\ 0 & 0 & 0 & -k \end{bmatrix}$

This ensures the positivity of the states and output of the glucose-insulin dynamics if started inside the polyhedron. Any trajectory starting within this polyhedron is ensured to remain in it even if disturbance like meal is introduced. Since meal is a positive disturbance, therefore insulin input will raise as glucose increases with the digestion of CHO.

(3.3) Full State Observer or Estimator:

State feedback control law established in previous chapter assumes that all the states of a plant are available to be quantified whereas in practice not all the states can be measured easily. Hence, observers are employed to estimate the values of such states. Observer is an approximation of the actual plant to estimate the states of the system with the help of available measurements, plant input and, the knowledge of mathematical model and initial conditions. The available measurements and other parameters help in rectifying the states such that error between the actual plant and an estimator model goes to zero. However, a system model has to be observable to place the poles of a system arbitrarily or at desired locations to estimate the system's states. In this case, the **system complies with the observability conditions and the rank of observability matrix (A, C) is found to be full**.

Observer approximation quality depends on the accuracy of measurements (more the noise, less is the confidence in measurement), system dynamics and knowledge of initial condition of the plant.

$$\begin{array}{lll} \text{Actual Plant} & : & \dot{x} = Ax + Bu \\ \text{Observer} & : & \dot{\hat{x}} = A\hat{x} + Bu + L(y - \hat{y}) \\ \text{State estimation error} & : & \dot{\tilde{x}} = (A - LC)\tilde{x} \end{array} \quad (3.11)$$

Such that $e(t) = \tilde{x} = x(t) - \hat{x}(t)$, $\dot{e}(t) = (A - LC)e(t)$ and satisfies that eigenvalues of $(A - LC)$ can be placed at the desired location, if the pair (A, C) is observable. The dynamics of an estimation error are fixed by the eigenvalues of $(A - LC)$ such that an estimation error vanishes asymptotically if and only if $(A - LC)$ is asymptotically stable.

Luenberger Observer as per equation (3.3) corrects the estimation of states with the gain (L) applied to the estimation error between the measured output (y) and an estimate of respective state (\hat{y}).

$$\begin{bmatrix} \dot{\hat{x}}_1 \\ \dot{\hat{x}}_2 \\ \dot{\hat{x}}_3 \\ \dot{\hat{x}}_4 \\ \dot{\hat{x}}_5 \end{bmatrix} = \begin{bmatrix} 0 & -\theta_2 & 0 & \theta_4 & 0 \\ 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} & 0 & 0 \\ 0 & 0 & \frac{-1}{\theta_3} & 0 & 0 \\ 0 & 0 & 0 & \frac{-1}{\theta_5} & \frac{1}{\theta_5} \\ 0 & 0 & 0 & 0 & \frac{-1}{\theta_5} \end{bmatrix} \begin{bmatrix} \hat{x}_1 \\ \hat{x}_2 \\ \hat{x}_3 \\ \hat{x}_4 \\ \hat{x}_5 \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ \frac{1}{\theta_3} & 0 \\ 0 & 0 \\ 0 & \frac{1}{\theta_5} \end{bmatrix} \begin{bmatrix} u_i \\ u_m \end{bmatrix} + \begin{bmatrix} \theta_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} L_1 \\ L_2 \\ L_3 \\ L_4 \\ L_5 \end{bmatrix} (y - \hat{y}) \quad (3.12)$$

The eigenvalues of $(A - LC)$ are placed in a LHP for the observer as computed by the state feedback control law because observer has duality with the state feedback and, eigenvalues of transpose systems are same. For simplicity, we will consider 3-state model where a system is considered in the absence of meal.

Therefore, $\lambda I - (A - LC) < 0$ such that $\lambda_1 = -k (k > 0)$, $\lambda_2 = \lambda_3 = \frac{-1}{\theta_3}$ where $(-k, -\frac{1}{\theta_3}, -\frac{1}{\theta_3})$ are eigenvalues of the system.

$$\begin{bmatrix} \lambda_1 + L_1 & \theta_2 & 0 \\ L_2 & \lambda_2 + \frac{1}{\theta_3} & \frac{-1}{\theta_3} \\ L_3 & 0 & \lambda_3 + \frac{1}{\theta_3} \end{bmatrix} = (\lambda_1 + k)(\lambda_2 + \frac{1}{\theta_3})(\lambda_3 + \frac{1}{\theta_3}) \quad (3.13)$$

Hence, gains of Luenberger observer calculated using aforementioned eigenvalues for 3-state model are $[k \ 0 \ 0]$. When state feedback is combined with an observer, then poles of such system are the poles from state feedback combined with the poles from observer design.

$$\begin{aligned} |\lambda I - (A + BF)| &= 0 \\ |\lambda I - (A - LC)| &= 0 \end{aligned}$$

The characteristic polynomial of this extended system :

$$\det(sI - A + BF) \times \det(sI - A - LC)$$

Using equation (3.12) and calculated observer gains as per equation (3.13), following state space model of Luenberger observer is implemented on MATLAB when meal input is introduced by patients and supposed to be known.

$$\begin{bmatrix} \dot{\hat{x}}_1 \\ \dot{\hat{x}}_2 \\ \dot{\hat{x}}_3 \\ \dot{\hat{x}}_4 \\ \dot{\hat{x}}_5 \end{bmatrix} = \begin{bmatrix} -k & -\theta_2 & 0 & \theta_4 & 0 \\ 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} & 0 & 0 \\ 0 & 0 & \frac{-1}{\theta_3} & 0 & 0 \\ 0 & 0 & 0 & \frac{-1}{\theta_5} & \frac{1}{\theta_5} \\ 0 & 0 & 0 & 0 & \frac{-1}{\theta_5} \end{bmatrix} \begin{bmatrix} \hat{x}_1 \\ \hat{x}_2 \\ \hat{x}_3 \\ \hat{x}_4 \\ \hat{x}_5 \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ \frac{1}{\theta_3} & 0 \\ 0 & 0 \\ 0 & \frac{1}{\theta_5} \end{bmatrix} \begin{bmatrix} u_i \\ u_m \end{bmatrix} + \begin{bmatrix} \theta_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} k \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} y \quad (3.14)$$

Here, $k = L_1 > 0$ is an observer gain. The established continuous time luenberger observer with the observer gain, $L = [k \ 0 \ 0 \ 0 \ 0]^T$ and state feedback gain, $F = k(\frac{1}{\theta_2}, -\theta_3, -\theta_3, \frac{\theta_4\theta_5}{\theta_2}, \frac{\theta_4\theta_5}{\theta_2})$ will be implemented on MATLAB after discretisation.

This model of state feedback observer with the dynamic measurement feedback is stable because separately designed observer and the control are stable and the eigenvalues of such system can be obtained directly from individual systems which is based on separation and linearity principle. The observer gain can be increased to any value since there is no saturation problem, however measurements could be noisy. Therefore, observers gains are chosen such that observer poles are 5-10 times faster than the closed loop poles to reduce estimation error before control. Another criterion is noise sensitivity, which emphasise on choosing low or high bandwidth gain based on the measurements noise and estimation efficiency respectively. In this case, set of gains of state feedback observer should guarantee that assigned eigenvalues falls in the desired region of controller. Therefore, both L & k will be tuned in the next section to achieve the desired responses such that L is always greater than k to ensure the faster convergence of estimation error before control of system but slow enough to get the dominant eigenvalues of state feedback remains in the control region.

In the next section, discussed observer (3.14), plant model (3.3) along with state feedback controller (3.8) will be implemented on MATLAB after discretisation and response analysis will be carried out to get the desired responses. The pancreatic observer model (or 5 state observer model) with state feedback control will also be analysed with and without known meal input to draw conclusions and shortcoming of the implemented luenberger observer in the absence of input.

(3.4) Discrete Model for Artificial Pancreatic System Observer with State Feedback Control :

The real physical systems like chemical process, storage system, etc., are continuous in nature. However, controllers which implement the control of such processes are discrete in nature. Therefore,

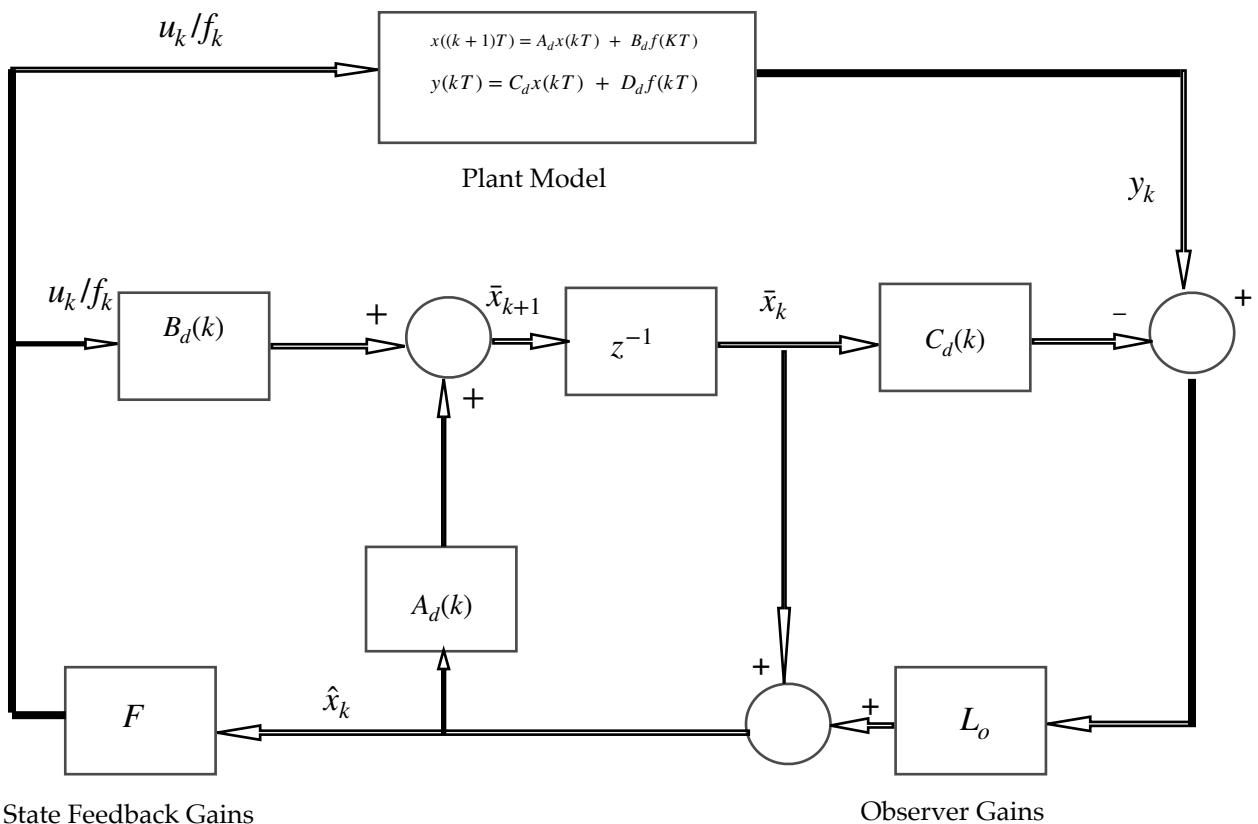
discrete time models of such process are sometimes preferred and may be needed for better control efficiency. The discrete system of such continuous models is obtained by sampling. The mathematical model of state space discrete time system is written as follows in terms of recursive formula by using linear matrix difference equations :

$$\begin{aligned} x((k+1)T) &= A_d x(kT) + B_d f(KT) \\ y(kT) &= C_d x(kT) + D_d f(kT) \end{aligned} \quad (3.16)$$

Here, T represents the constant sampling interval time.

There are various methods which help in obtaining the discrete time state space models from continuous system models. One of the method is zero order hold (ZOH) where a zero-order input with updates at intervals T ensures that the response of the discrete-time system in Eq. (3.16) will be identical to the continuous plant of Eq. (3.1) at the sampling time. The following discrete model of an estimator along with the state feedback control was developed from continuous model on MATLAB platform using ZOH conversion method.

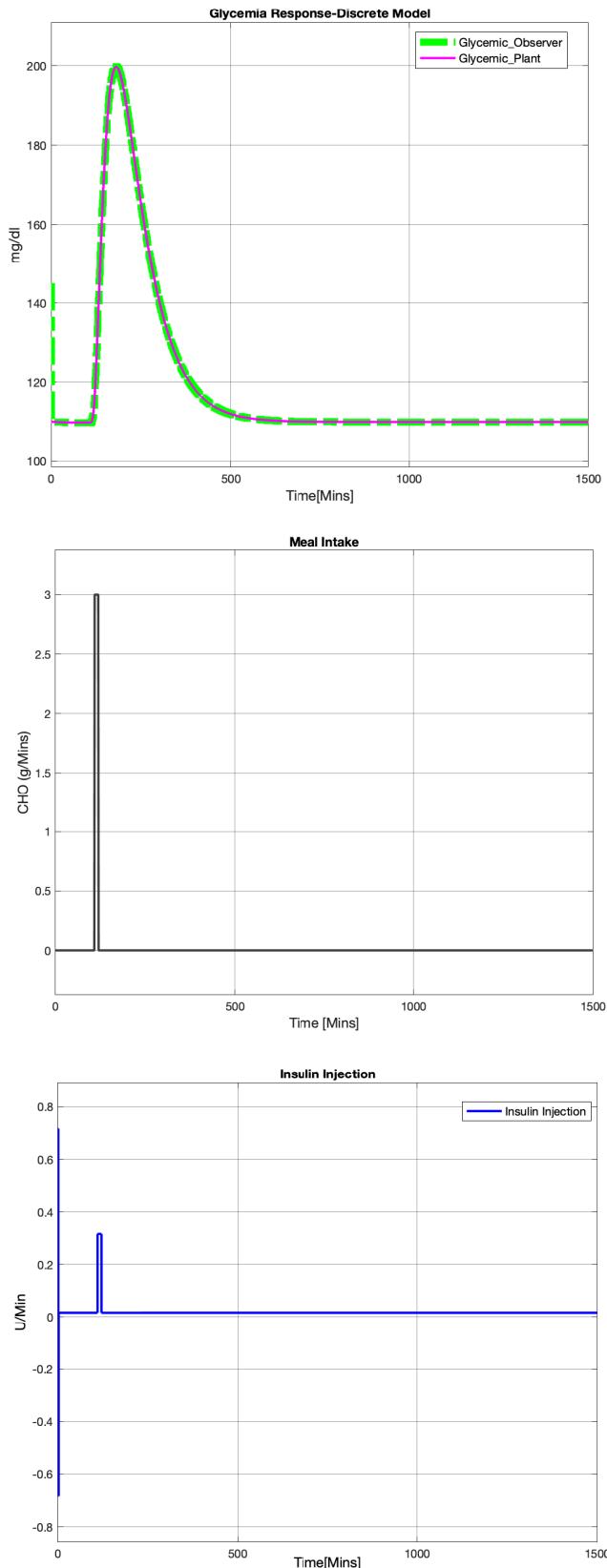
MATLAB - c2d function with Zero Order Hold conversion with sampling time, $T_s = 1$ mins such that $A_d = e^{AT_s}$, $B_d = (A_d - I)A^{-1}B$, $C_d = C$ & $D_d = D$ where A, B, C and D are continuous time state space matrices detailed in equation (3.3).



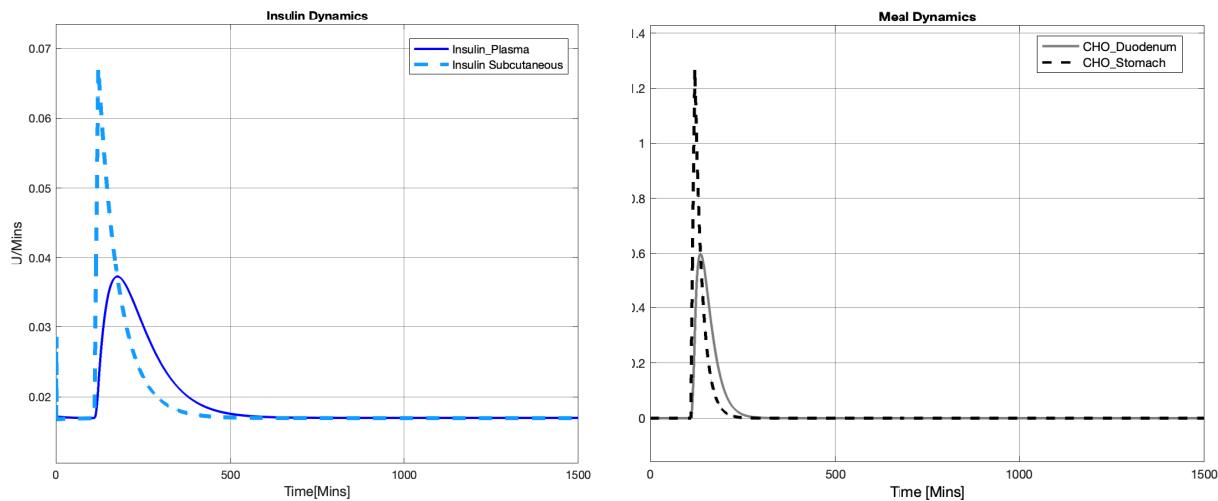
Fig(3.1) : Discrete Model of observer with state feedback control

The discrete model of an artificial pancreatic model is tested with an observer gain, $L = [1 \ 0 \ 0 \ 0 \ 0]^T$, state feedback gain, $F = k(\frac{1}{\theta_2}, -\theta_3, -\theta_3, \frac{\theta_4\theta_5}{\theta_2}, \frac{\theta_4\theta_5}{\theta_2})$ and the sampling rate of 1 mins. The dynamic

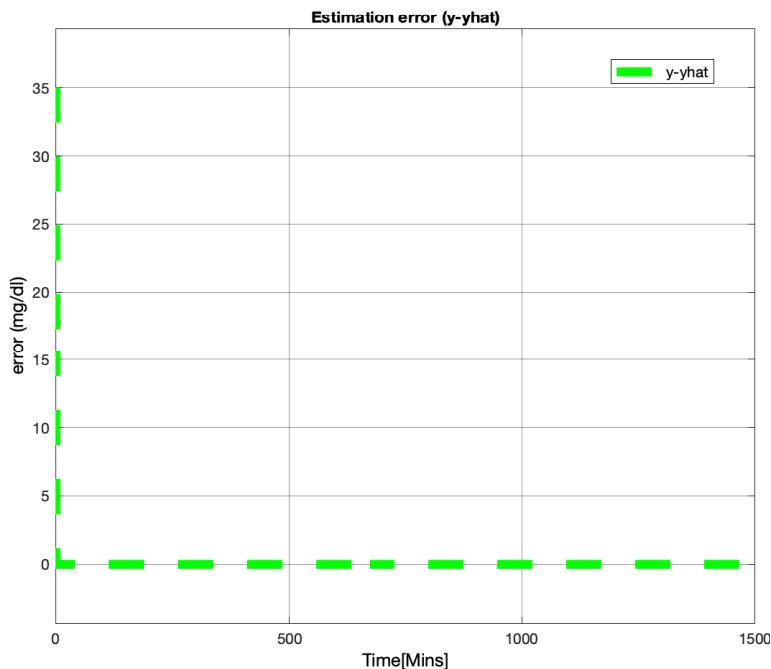
responses of the above system are as follows with observer's initial state values as $[145; \frac{\theta_1}{\theta_2}; \frac{\theta_1}{\theta_2}; 0; 0]$ and plant's initial condition as $[110; \frac{\theta_1}{\theta_2}; \frac{\theta_1}{\theta_2}; 0; 0]$:



Fig(3.2) : Response of Glucose, CHO (Meal Intake) & Insulin Injection of APS discrete model



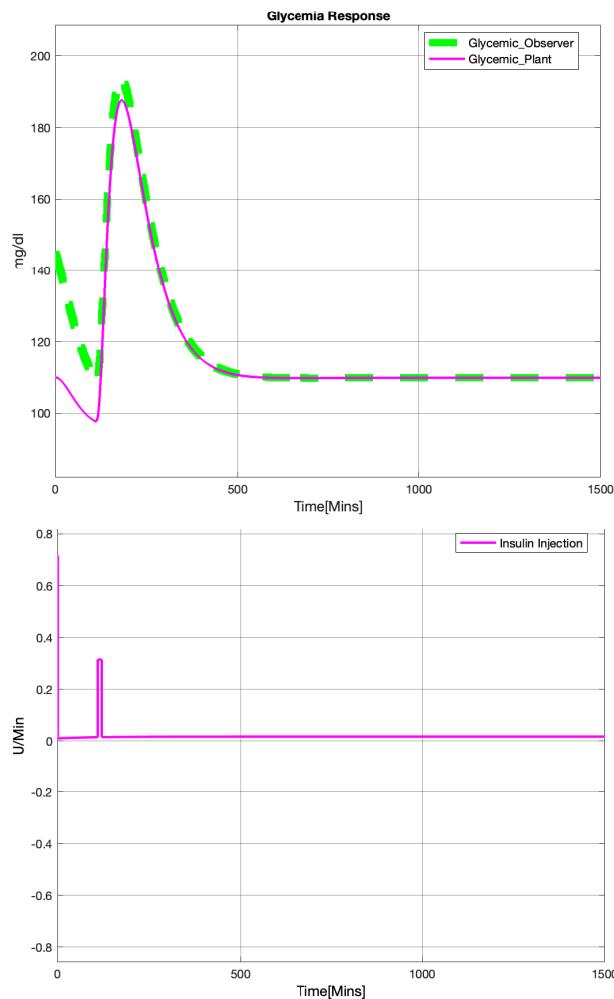
Fig(3.3) - Insulin & CHO dynamics response of observer



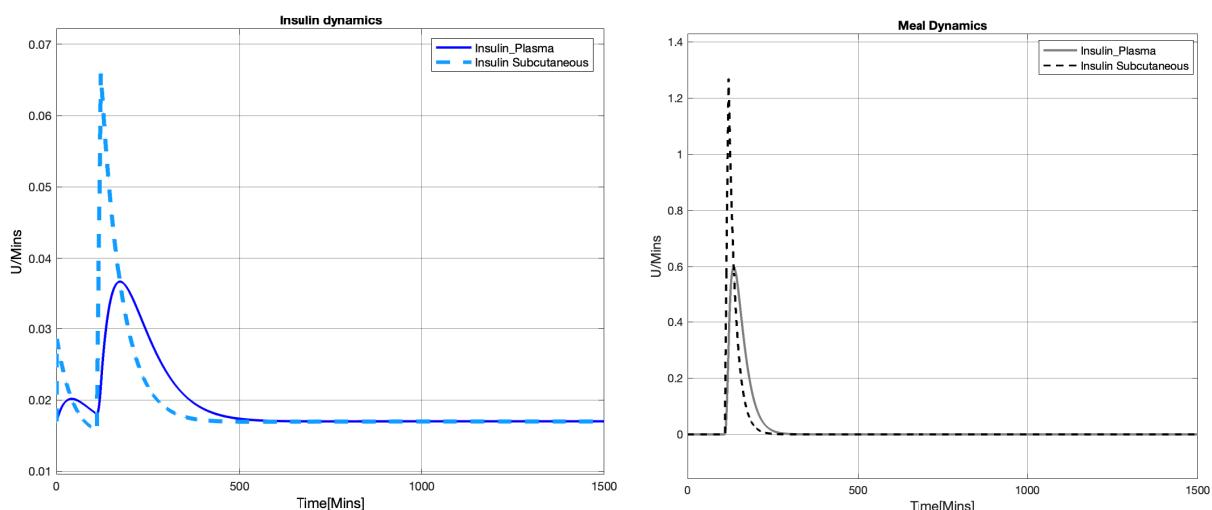
Fig(3.4) - Estimate error ($e = y - \hat{y}$)

The important observation from Fig(3.2) is the negative value of insulin at the beginning which doesn't comply with the control law (3.8) mentioned earlier in this chapter. When observer based state feedback system is employed, then closed-loop eigenvalues of such system are union of eigenvalues from state feedback and eigenvalues from observer design $\{\text{eig}(A - BK)\} \cup \{\text{eig}(A - LC)\}$. Therefore, eigen value of the overall system will be different from the eigen value required for positive closed loop system such that lesser the value of observer gains, closer is the system's eigenvalues with the state feedback eigenvalues. In this case, large value of observer gain is selected to ensure the faster convergence of estimation error as shown in Fig(3.4). When L is reduced significantly such that system's eigenvalues remain closer to state feedback, rate of error convergence slows down but system remains positive i.e. insulin input remains positive. The same result could be achieved by reducing k (tuning parameter of state feedback) keeping observer gain, $L_1 = 1$ which ensures the faster convergence but slower settling time for glucose after disturbance as eigen value corresponding to estimation error vanishes when error converges to zero.

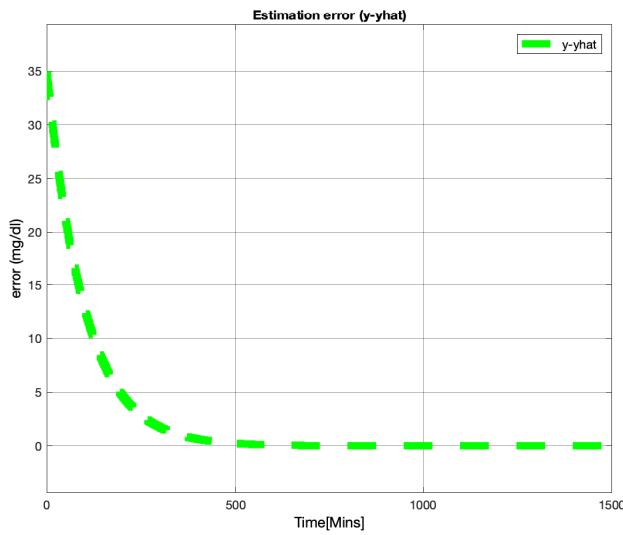
The dynamic responses of same state feedback system with an observer gain, $L = [0.01 \ 0 \ 0 \ 0 \ 0]^T$, same initial conditions and meal scenario are as follows:



Fig(3.5) - Response of Glucose & Insulin Injection of APS discrete model ($L_1 = 0.01$)

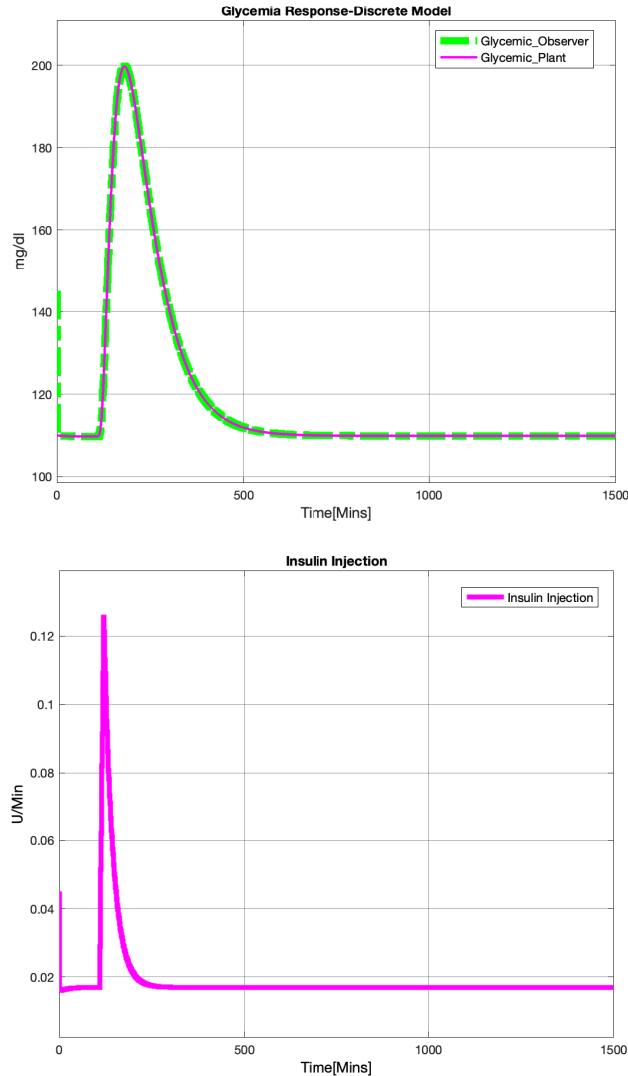


Fig(3.6) - Insulin & CHO dynamics response of observer



Fig(3.7) - Estimate error ($e = y - \hat{y}$)

The desired response for observer based SF control is obtained when k is reduced to 0.02 and observer gain, L is chosen such that estimation is at least 5-10 times faster than the control. In this case, we chose $L_1 = 0.2$ & $k = 0.02$



Fig(3.8) - Response of Glucose & Insulin Injection of APS discrete model ($L_1 = 0.2$ & $k = 0.02$)

(3.5) Unavailability of Meal Input - Unknown Input Estimation :

Luenberger observer is a simple and an efficient estimator when a model is defined accurately. However, in case of model uncertainty or unknown inputs, Luenberger observer is unable to estimate all the states of a system along with the unknown inputs. In the case of unknown meal input or absence of a meal input, current estimation of x_4 and x_5 (states of meal dynamics) couldn't be achieved using simple luenberger observer for its inability to reconstruct the initial states of meal dynamics model.

In this case, measuring the meal input is not possible and could be expensive to find the exact CHO content. But knowledge of this unknown input and associating states is necessary for robust control especially in state feedback control strategy. The study of observers which can estimate unknown input or uncertainty in model is initiated by (13) in 1988. They estimated the unknown input by differentiating the output measurements. Since differentiating output becomes a difficulty in case of noisy measurements, a combined state/input estimator which does not require differentiation of the measured outputs is proposed by (14) in (1998) which can asymptotically estimate the unknown inputs to any degree of accuracy. Other Unknown Input Observer (UIO) includes Proportional-Integral (PI) observer, invertible UIO, UIO with algebraic approach, etc. The unknown input decoupled functional observer (UIDFO) is one of the input estimators (or extension of UIO) which built upon a state functional observer where the estimation error is decoupled from unknown inputs.

In order to accomplish the full estimation of meal dynamics along with glucose-insulin dynamics states and its implementation on discrete system to employ state feedback control strategy, adaptive observer based on full order Luenberger observer concept will be explored. In 2003, authors of paper (15) introduced an estimator for unknown input inspired by adaptive diagnostic observer proposed by Wang and Daley (16). This observer employs estimation error along with learning rate variable to construct the unknown input as follows:

$$\begin{aligned}\hat{x} &= A\hat{x} + Bu + G\hat{d} + L(y - C\hat{x}) \\ \hat{d} &= \rho K(y - C\hat{x})\end{aligned}\quad (3.17)$$

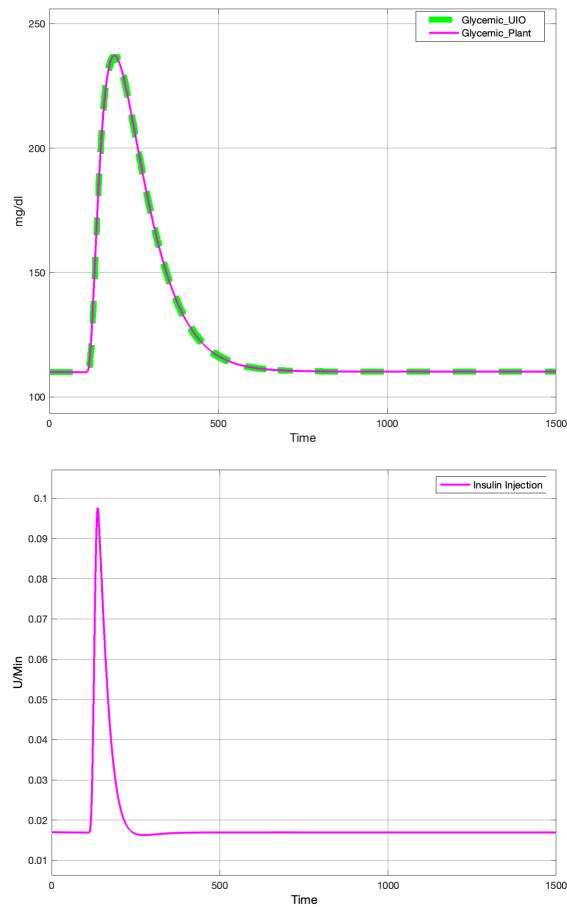
Where A,B, C & G are known and constant matrices of appropriate dimensions. The \hat{d} is an unknown input or disturbance. This observer can asymptotically observe states and inputs to any desired accuracy level, if it satisfies the following two conditions proposed by Corless and Tu (13):

$$\begin{aligned}P(A - LC) + (A - LC)^T P &= -Q \\ G^T P &= KC\end{aligned}\quad (3.18)$$

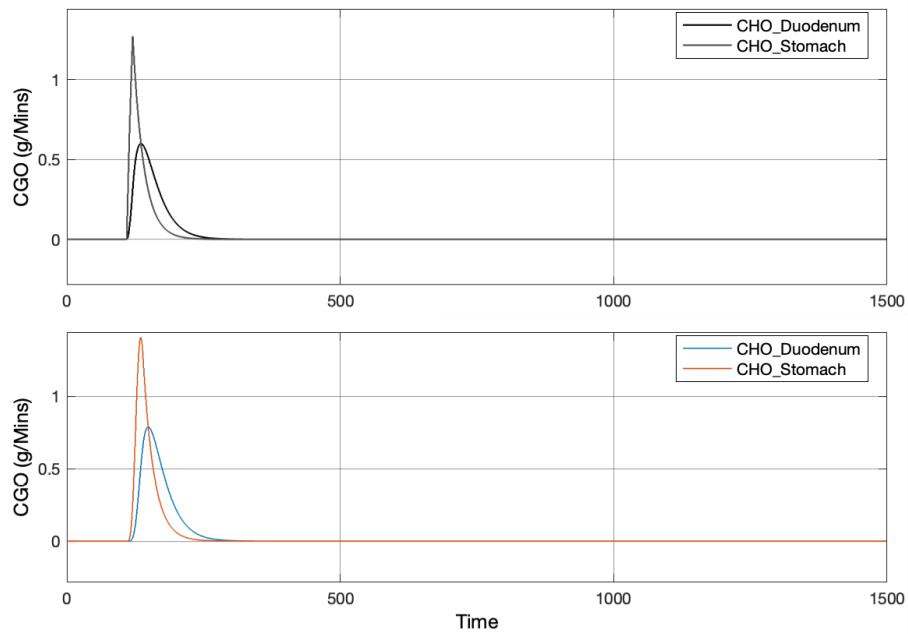
Where, L & K matrices exist such that P & Q are symmetric positive definite (SPD) matrices. As a prerequisite, 5 state model is checked for observability condition and rank (CG) = rank(G) = r which ensures the availability of measurements according to the number of unknown estimates. Another condition is that rank of $\begin{bmatrix} A - LC & G \\ C & 0 \end{bmatrix}$ = n+r where rank of matrix (A-LC) is n. However, discussed model couldn't fulfil these pre requisite conditions until C is considered as full measurement matrix. Therefore, C will nee considered as identity matrix for solving the conditions as per equation (3.18) with known Q and L to calculate values of K and P. In order to estimate the meal dynamics, Luenberger observer will be extended by implementing the above adaptive observer ($K = 0.952$) as per equation (3.17) where learning rate, $\rho = 0.84$. The learning rate could be modified whenever input is available which in this case is meal intake by patients. The proof for above method is pending and need to be addressed for further assessment of UIO. The discussed observer converge the estimation error to zero even though pre-requisites of Corless and Tu are not fulfilled. This UIO is easier to implement in discrete system programming along with the update of learning rate variable if the initial parameters and the matrices are calculated in prior by implementing and testing the same observer on MATLAB platform. Another important point is observer suitability with the meal input which perfectly aligns with the requirement of constant or slowly varying inputs.

The discussed UIO couldn't be tested on UVA Padova because of unavailability of licence. However, its response is satisfactory when tested with the plant (5 state model) model with defined meal input. The comparison of meal dynamics between plant model and UIO observer is shown in Fig (3.10). The resulted control output from UIO with state feedback along with glucose response is depicted in Fig (3.9). Due to the oscillating behaviour of state relating to stomach compartment of meal dynamics of UIO, State Feedback control output is found to be different from the control output response of observer with

the known input as per the Fig (3.8). The responses given below are satisfactory but need further improvement for better estimation.



Fig(3.9) : Response of Glucose & Insulin Injection of APS discrete model with UIO



Fig(3.10) : Meal Dynamics - Top : Plant Model and Bottom : UIO Observer

Chapter : 4

TIME DELAY MODEL AND CONTROL

Time delays are intrinsic part of many real processes and control systems. Delay differential equations helps in building the time delay infinite-dimensional model which represent the mathematical definition of system more closer to its real process. These equations help in reducing the order of a model and also incorporate the delays of control hardwares. Therefore, besides actual delays, time lags can be utilised in simplifying high order models. However, incorporation of time delays complicate the system's model. The time delay system has infinite eigenvalues which makes it difficult to stabilise the system by eigenvalues placement method as its almost impossible to find all the eigenvalues of such system through its characteristic equation.

The motivation behind the implementation of time delay system is to study, analyse and compare the dynamics of TDS with the dynamics of 5 state model under disturbances for long term stability. Another important criterion is response time of insulin activity in case of time delay system which is found to be more relatable to actual physiological response.

In order to reduce the order of glucose-insulin model discussed in chapter 1 (as per equation 2.8) and to achieve the resemblance of glucose-insulin model to real process (which include measurement delay) for better dynamic performance, time delay model is implemented and tested. The delays for model reduction from 2nd order to 1st order system for insulin and meal dynamics are based on physiological processes like digestion, blood-tissue fluid transmission. If actual system of the diabetic patient is considered with an exogenous insulin delivery system, the insulin input is observed in plasma after some transport delay (approx. 15 mins) from subcutaneous compartment. Similarly, food digestion and glucose build up in plasma accounts for approximately 30-40 mins delay after meal is being consumed (stomach compartment). Initially, 5 state observer model (3.3) is implemented with measurement delay of 5 mins and responses are analysed for stability and error convergence. The state feedback gains are similar to equation (3.8) with $k = 0.02$ and observer gain $L_1 = 0.5$. The system came out to be stable and responses are found to be similar as shown in fig (3.11).

In second step, discrete time delay model of pancreatic system is implemented on MATLAB as state space model (4.1) such that 2nd order model (2.8) of insulin and meal dynamics is reduced to 1st order system.

$$\begin{bmatrix} x_1(k+1)T \\ x_2(k+1)T \\ x_3(k+1)T \end{bmatrix} = \begin{bmatrix} 0 & -\theta_2 & \theta_4 \\ 0 & \frac{-1}{\theta_3} & 0 \\ 0 & 0 & \frac{-1}{\theta_3} \end{bmatrix} \begin{bmatrix} x_1(kT) \\ x_2(kT) \\ x_3(kT) \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ \frac{1}{\theta_3} & 0 \\ 0 & \frac{1}{\theta_5} \end{bmatrix} \begin{bmatrix} u_i(kT - \tau_1) \\ u_m(kT - \tau_2) \end{bmatrix} + \begin{bmatrix} \theta_1 \\ 0 \\ 0 \end{bmatrix}$$

(4.1)

$$y = [1 \ 0 \ 0] \begin{bmatrix} x_1(kT - \tau_3) \\ x_2(kT) \\ x_3(kT) \end{bmatrix}$$

Where T is a sampling period, τ_1 is a transport delay for the insulin input to appear in plasma compartment, τ_2 is a delay introduced for the meal digestion and τ_3 is a measurement delay. The open loop response of system (4.1) without any disturbance is analysed and found to be stable. The same scenario is tested with state feedback but the response of system is found to be highly unstable. The effect of time delay in closed loop system is similar to the effects of lowering the sampling frequency. The time delay pancreatic model as per equation (2.9) resembles the first order time delay system for insulin and meal dynamics. The frequency analysis of such systems establishes the fact that time delay introduces the phase lag in the system which makes the system unstable as ω increases. This results in reduction of gain margin so that system remains in region of stability. For e.g. gain margin of insulin model is reduced to 16.8 db when time delay is introduced. The same model used to have infinity gain margin without delay. As mentioned in (5), DDEs are known to possess the so-called stability switches which implies that when there is an increment in time delay from

zero, a steady state may go from a stable regime to an instability via a Hopf bifurcation, and then return to the stable regime again. In fact, for some critical delay time, the steady state will never regain its stability after becoming unstable. Also, DDEs are transcendental, i.e. time delay systems usually have infinite roots which makes it difficult to find the closed loop eigenvalues of linearisation. However, when system's dimension is comparatively low (one or two), complete characterisation of stability is possible along with the conditions for Hopf bifurcation.

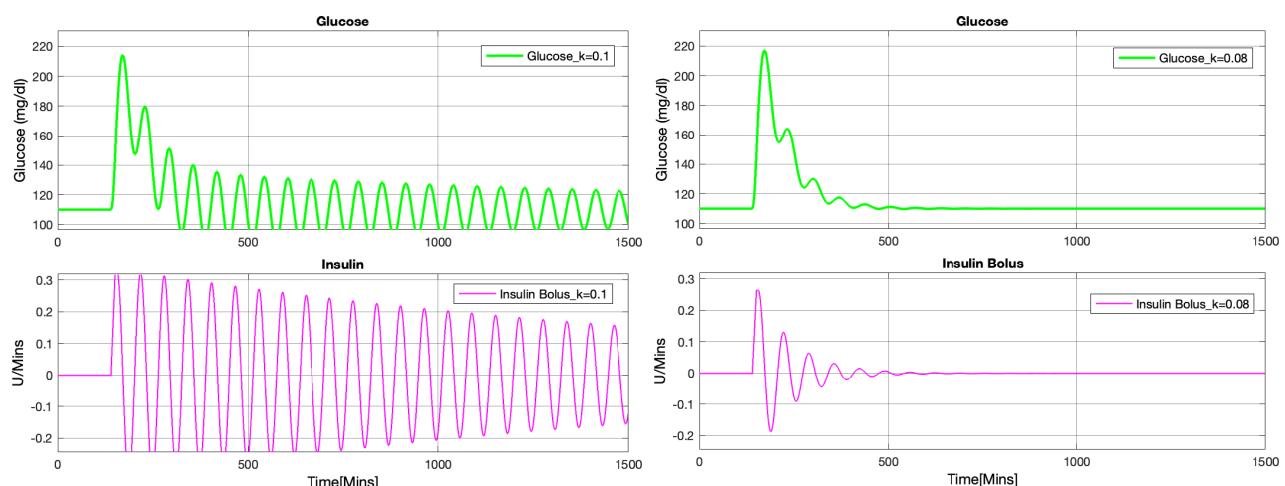
Another obstacle in handling delays in design is that the delay cannot be expressed as a rational polynomial. There are some approximations like Skogetsky method, Taylor and Padé approximation which are being used in solving the characteristic equation for eigenvalues but its the z-domain transformation which is able to preserve the rational polynomial nature of transfer functions.

According to (4), a sufficiently large delay de-stabilises the system because the rate of change toward the equilibrium set-point remains too high when that rate depends on a past value of the system state. The value of feedback gain decides the convergence rate toward the set-point which when multiplied with the lagged error may not accurately reflect the true system's error at that particular time. Therefore, one can stabilise the feedback system by reducing the gain which is already established by frequency analysis of first order time delay system. This analysis is further substantiated by Routh who provided the stability criteria for gains of time delay system such as gain lies in the range : $-1 < k < 2\frac{\tau}{\tau_d} + 1$

Using above equation, range of k is calculated for the pancreatic system which is found to be 0 to 1.044 (as k has to be greater than zero for positive system). Initially, k could be any value above zero for feedback gains defined in equation (3.8) but now, it is constrained between 0 to 1.044 on introduction of time delays in the system. Since z-transformation preserve the rational polynomial nature therefore, z transform of (2.9) is implemented on MATLAB without meal dynamics and frequency analysis is carried out for following transfer function:

$$G(s) = \frac{x_1}{u_i} = z^{-15} \frac{-0.8264z - 2.753e^{-16}}{z^2 - 1.983z + 0.9835} \quad (4.2)$$

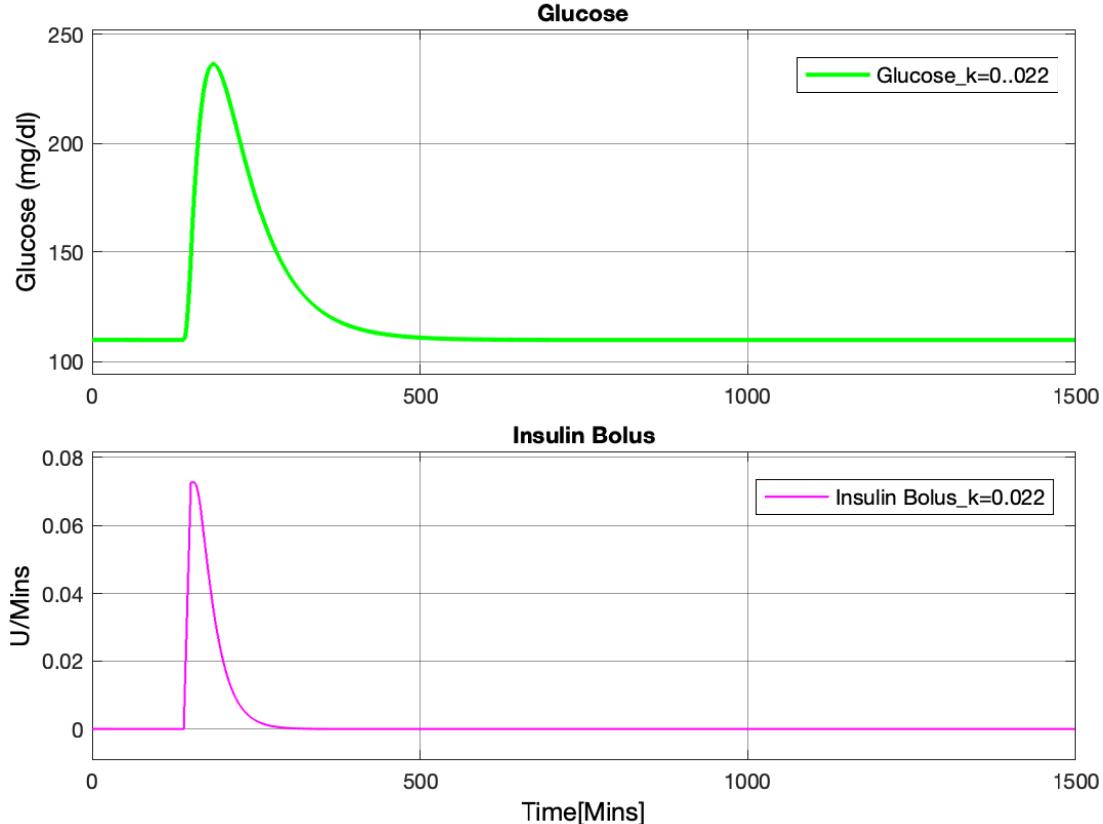
The gain margin of above system is reduced from infinity to 1.31 db when delay of 15 mins is introduced in the system since time delay adds the phase lag to the system. Meal intake act as a disturbance in the glycemic dynamics which further creates a delay of 30 mins for insulin to take action in order to compensate the increase in plasma glucose. Hence, the same system (4.2) is implemented with 45 mins delay and analysed for gain margin. As expected, gain margin further reduced to 0.98 db and phase margin is negative which implies that open loop system becomes unstable with disturbance. All these theories establish that tuning gain k which decides the convergence rate for SF control needs to obey the gain margin whereas state feedback gains which direct the system towards desired eigenvalues could be same. In this case, it's the value of k which need to be tuned to synchronise the convergence rate of glycemic with the rate of change in glucose based on its past value.



Fig(4.1) - SF responses of pancreatic time delay system (Left : $k = 0.1$ & Right : $k = 0.08$)

In first case, system is tested with $k = 1$ and analysed for desired glycemic response and control input. As mentioned earlier, the state feedback system was already found to be unstable with this value of k which also aligns with required phase margin during meal intake. Therefore, smaller values of k within the range ($0 < k < 1$) are tested to get the desired response of both glucose and control output (insulin input) for desired eigenvalues for positive system.

The responses of above figures clearly show the stable but oscillatory nature of system (4.1) with state feedback for mentioned values of k . But responses of fig(4.1) are not the desired responses as oscillations are still observed in control output (insulin input) and glucose dynamics. On further reducing the value of k , desired response is achieved at $k = 0.022$ where system is positive and glucose settles down in required time period.



Fig(4.2) - SF responses of pancreatic time delay system ($k = 0.022$)

The chosen value of k ensures the closed loop system convergence in the stable region. The time delay pancreatic model with selected gain ($k = 0.022$) is also tested with increased delay (+5 mins) to analyse the system's robustness and stability in the region of desired eigenvalues. The result is found to be stable and desired response was obtained as shown in fig(4.2). The system is tested on simulator platform but detailed analysis is pending. Therefore, time delay model and its control strategy test on simulator model will not be discussed in next chapter. Initially, control strategy test on simulator will focus on the observer based on 5 state model which will be analysed in detail in next chapter.

Chapter : 5

UVA PADOVA SIMULATOR

(5.1) Introduction

The UVA Padova (University of Virginia and Padova) type 1 simulator (6) is a first software model to be approved by FDA (Food and Drug Administration) for pre-clinical trials of insulin treatments including *in silico* trials for testing and validating the measurements, controllers and the actuator designs. This lead to the revolutionary change in the development of an artificial pancreatic control algorithms and *in-silico* testings in a cost effective environment. The first model is introduced in 2008 which included 300 *in silico* subjects (100 virtual adults, 100 adolescents and 100 children) for emulating model parameter database such as FIT parameters. The model is revised in 2013 which not only incorporates the non-linearities of insulin action during hypoglycaemia in glucose kinematics model but also included new rules in determining insulin to carb ratio (CR) and the correction factor (CF). More than 32 research groups and 63 publications have been recorded to publish their results extracted from this simulator to establish their theories. The UVA Padova simulator is based on the model of (8) discussed in the reference paper (6) in detail. The S2013 is implemented on the MATLAB software with user interface to define the testing scenario. One can modify the meal parameters (includes number and schedule of meals, CHO quantity, etc.), select the subjects and hardware (includes sensors and pumps) based on the test requirements. It also provides the options for outcome analysis including glucose traces, risk graph, individual Poincaré plots of glucose dynamics, etc.

The model parameters including basal rate, CIR and CF are categorised based on their age group which is detailed as per below table (5.1). This distribution very well represents the parameters observed in real patients. The distribution of parameters in children and adolescent age group were obtained from T1DM adults by incorporating some changes in the average parameter vector. For e.g. insulin sensitivity (CF) is higher in children compared to the adults and adolescents.

Parameters	Child Average	Adolescent Average	Adult Average
Basal/hr	0.4038	0.804	1.18
Insulin Sensitivity (CF)	110	56	43
Carb ratio (CIR)	24	18	16
Fasting BG	119.84	119.22	119.58
Avg. Body Weight	29.97	48.76	69.70

Table (5.1) - FIT Parameters of different section of populations

The CIR for the simulation is calculated as the ratio of ingested CHO quantity and optimal insulin bolus based on the theoretical definitions developed in recent days:

$$CIR = \frac{CHO}{insulin\ bolus}$$

Insulin sensitivity, CF is calculated using total daily insulin (TDI) which is determined for each virtual patient using optimal CIR and basal infusion rate considering respective average diets. This parameter is determined using “1700 rule” as follows:

$$CF = \frac{1700}{TDI}$$

(5.2) Test of control algorithm on Simulator

Initially, 5-state observer model of glucose-insulin dynamics with the state feedback is implemented with positivity gains established in chapter 3 with safety tuning parameter, $k = 1$. All the states are estimated using Luenberger observer with known meal input and state feedback control is employed and tested with both glucose measurement and as well as observer estimate of measurement along with other estimated states (which includes plasma and subcutaneous insulin, duodenum and stomach CHO).

The target and initial value of glucose in simulator is subject specific as given in table (5.1). However, inbuilt noise in simulator sensor always introduces some errors in glucose reading which approximately ranges between (2-25 mg/dl). This introduces an estimate error in the very beginning as observer is initialised at subject specific fasting BG. In order to test and validate the implemented state feedback control strategy with gains that ensures positivity constraints, following tests have been carried out in given sequence to understand the dynamics of the simulator and analysing its responses under the state feedback control strategy with positivity gains (3.8) :

(1) Open loop response:

Open loop of the 5 state estimator (3.14) is compared and analysed with the open loop responses of the UVA Padova simulator model with and without a meal. This analysis will help in understanding the difference between developed model and UVA Padova model. The response of both simulator model and an estimator shows no difference when injected with open loop basal under no disturbance. Therefore, comparison analysis will be detailed for both the model under meal scenario.

(2) Test for dynamic response of UVA Padova Simulator model:

UVA Padova Simulator will be tested with open loop basal insulin input above and below the actual basal insulin under no disturbance. This test is carried out to understand the impact of insulin on the equilibrium state of the simulator model. This will further helps in defining the basal insulin for simulator model. The tests for studying model dynamic of simulator will provide the insight into the response time of glucose dynamics under disturbance with or without bolus. This analysis can be utilised for comparing the insulin fixed bolus (open loop) with insulin calculated from control feedback.

- I. Test with insulin above and below the actual basal insulin
- II. One meal with no bolus
- III. No meal with a bolus
- IV. One meal with a bolus

(3) UVA Padova Simulator response with state feedback control strategy under one meal (30g) scenario introduced at 110 mins. This experiment will be carried out for all age groups with their respective parameters as discussed in table (5.1).

(4) Test of state feedback control strategy for 1 day (5 meal) scenario for all the subjects.

(5) Test of state feedback control strategy for 1 week (5 meal) scenario for all the subjects. These tests are carried out to observe and analyse long term response of glycemic under disturbances although multiple meal scenario is not validated by FDA.

(1) Open Loop Response :

Both simulator and estimator are introduced with 1 meal scenario (3g/min for next 10 mins) at 110 mins with subject specific basal insulin as open loop input.

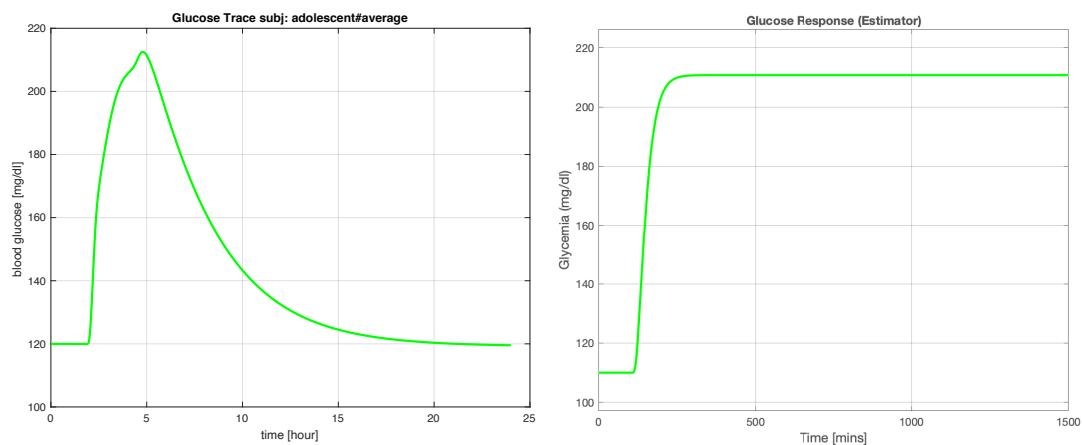


Fig (5.1) : Left : UVA Padova Simulator Response & Right : Luenberger Observer

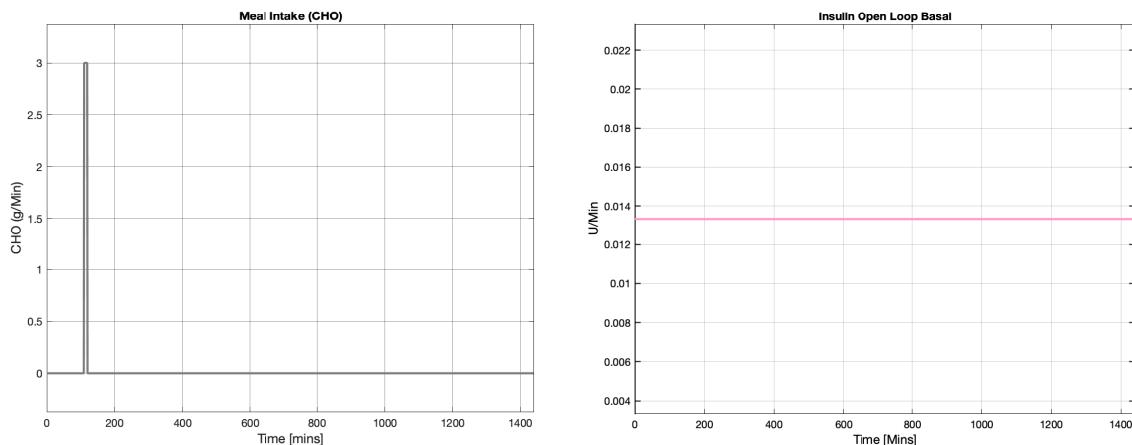
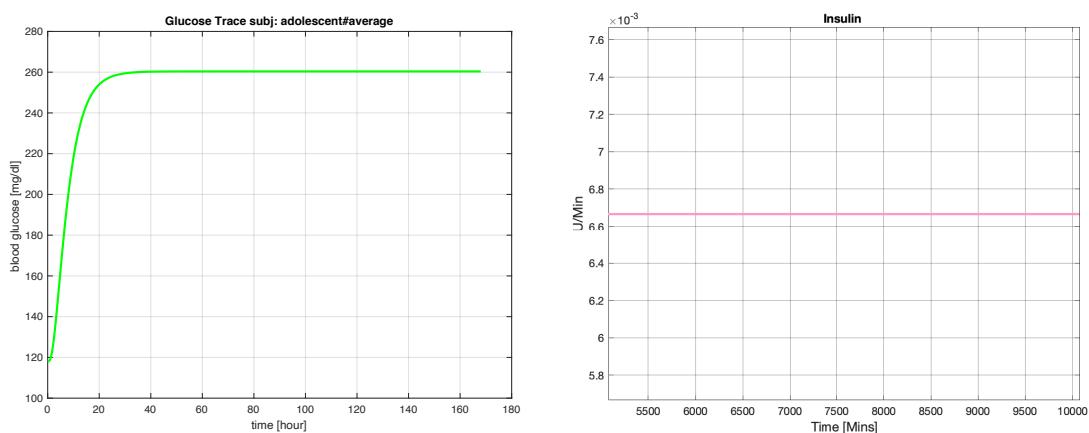


Fig (5.2) : Left : Meal Scenario & Right : Insulin open loop response

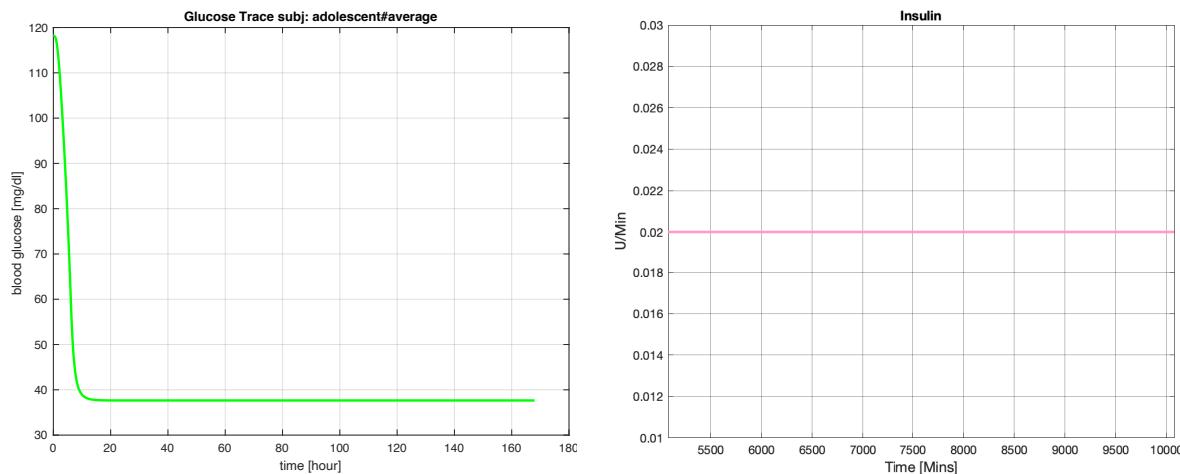
(2) Test for dynamic response of UVA Padova Simulator Model

I. Test with insulin above and below basal insulin

The dynamics of blood glucose is analysed with higher and lower basal insulin rate over 1 week to understand the relation between blood glucose and basal insulin of UVA Padova simulator model.

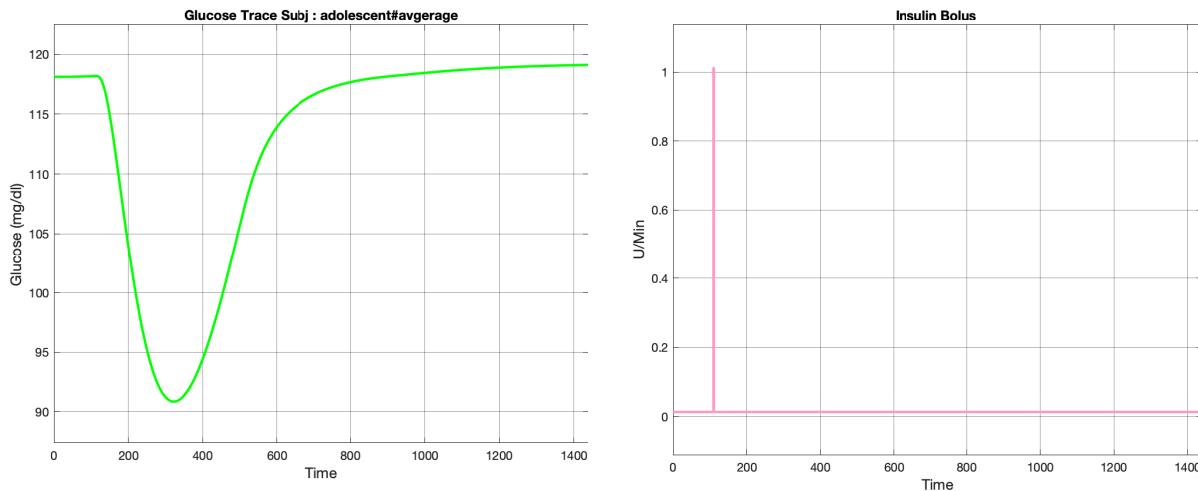


Fig(5.3) - Glucose response when basal insulin is reduced to 0.4 from 0.8U/hr (Actual Basal Insulin Rate)



Fig(5.4) - Glucose response when basal insulin is increased to 1.2 from 0.8U/hr (Actual Basal Insulin Rate)

II. Bolus without a meal

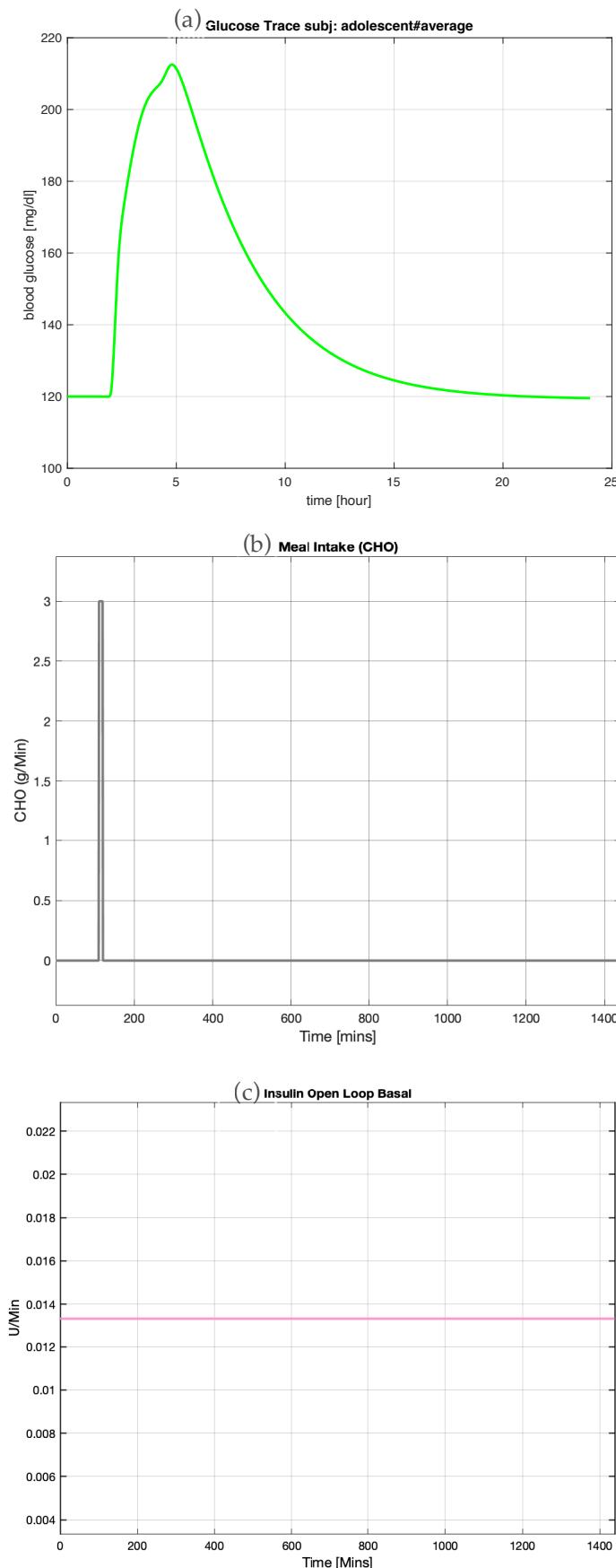


Fig(5.5) - Simulator response with a bolus unit under no meal condition

The difference observed for open loop response between simulator and observer model is due to the different definition used for the basal insulin. UVA Padova defines basal insulin as an amount of insulin to bring the glucose to target/equilibrium condition even after disturbance whereas basal insulin for the 5 state observer model is the amount of insulin when plasma glucose value is at the target value (fasting BG). Hence, the first three experiments establish the difference between simulator and our model with respect to the dynamics of glucose against the basal insulin and their resemblance to actual physiological response. The UVA Padova simulator has non-linear relation between insulin and glucose when the plasma glucose value is below threshold value. The insulin sensitivity reduces such that more insulin is needed to deplete the same amount of glucose content when glucose is below threshold value.

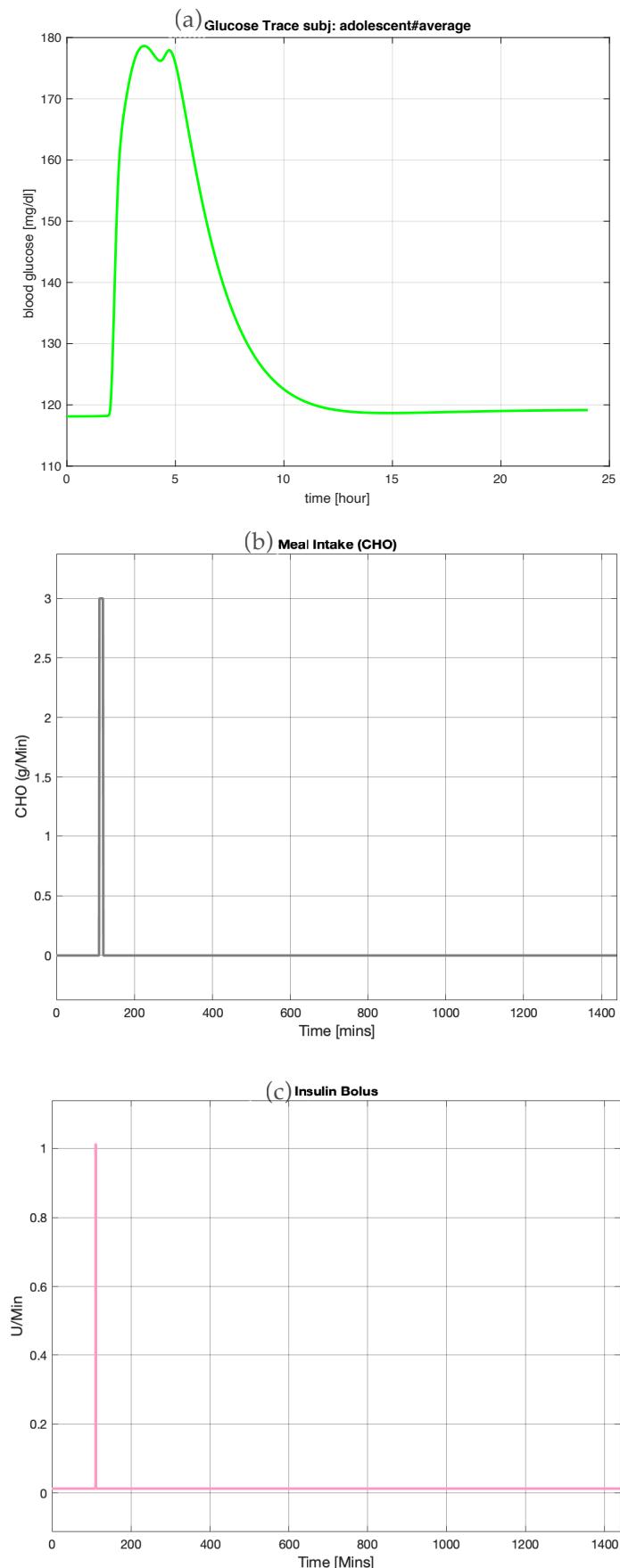
It is to be noted that simulator response doesn't replicate the physiological responses when meal is introduced in the system with no bolus. The simulator also fails to emulate the actual physiological responses when extra bolus is introduced under no disturbances i.e. body of T1DM patients can't recover from disturbances like meal or large amount of injected insulin without proper treatment. The system can't stabilise itself after being disturbed in open loop scenario. The concerned responses are shown in figure (5.5) and (5.6). However, 5 state model has linear relation with insulin, therefore positive disturbance like increase in CHO content will demand for more insulin to control the glucose level which resembles the physiological response of the T1DM patient.

III. Open loop response for one meal with no bolus



Fig(5.6) - Simulator response under one meal scenario with no bolus

IV. One meal with a bolus



Fig(5.7) - Open loop simulator response (a) Glucose response (b) Meal (c) Insulin Bolus

The glucose stabilises to its target value with a unit of bolus after meal consumption as shown in Fig(5.7). However, it takes more than 6 hours for glucose to settle down in its target range which is way more than the ideal time of 3 hrs.

3. UVA Padova Simulator response with state feedback control strategy - One meal (30g) scenario introduced at 110 mins for different age groups :

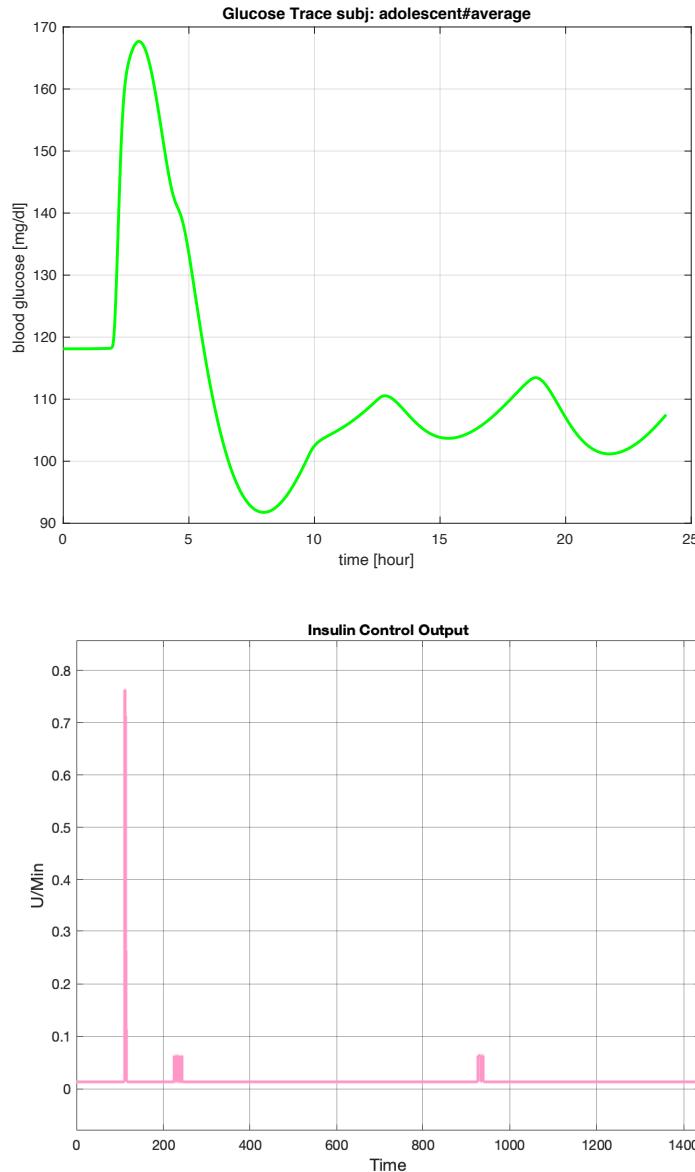


Fig (5.8) - Simulator response under one meal scenario with state feedback control strategy

UVA Padova Results for One day - One meal Scenario

Population Group	ID Mean BG	% Time < TGT-low (70 mg/dl)	% Time in target (70-180 mg/dl)	% Time > TGT-high (180 mg/dl)	BG Risk Index
Adolescent	112.04	0.00	100.00	0.00	0.68
Adult	107.40	0.00	100.00	0.00	0.47
Children	124.87	0.00	97.43	2.57	0.73

Table (5.2) : Result Analysis

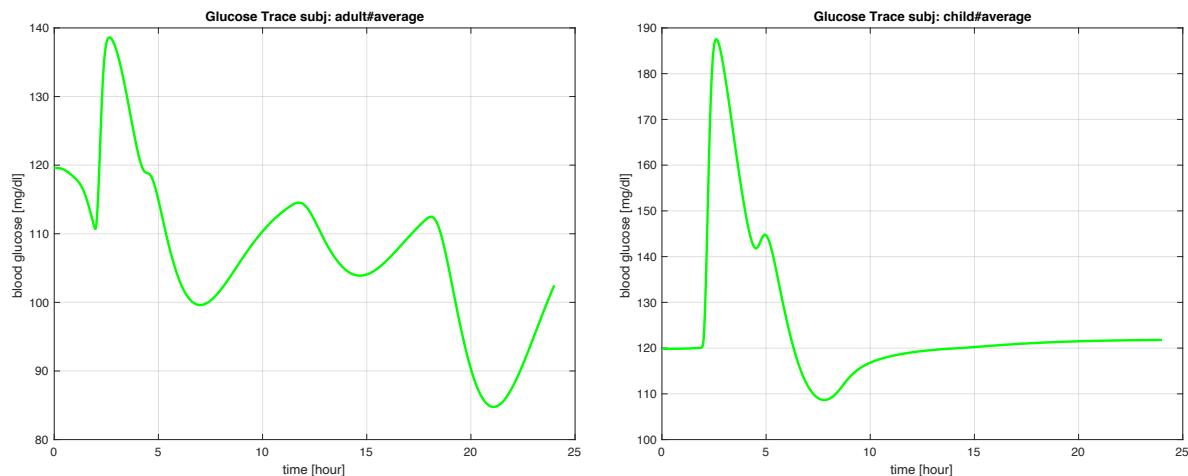


Fig (5.9) - Simulator response under one meal scenario with SF control
Left : Adult Average & Right : Children Average

The result analysis in table(5.2) further substantiate the achieved desired response where percentage time in target is above 95% which is considerably more than the required percentage as per the clinical requirements. According to clinical trials of hybrid artificial pancreatic system, percentage of time in target should be greater than 82% and percentage of time in hypoglycaemia should be below 3%. The above responses of experiment and result analysis fully comply with the desired results for clinical trials. Therefore, established state feedback control is able to achieve desired responses by avoiding hypoglycaemia. The noise in measurements means inaccurate estimation which leads to the substantial error in calculation of the control output that further decides the response of glycemic under disturbances. The impact of measurement noise and uncertainties in the system could be reduced by implementing Kalman filter. Besides, variation in glucose is larger in children and adolescents than in adults, reflecting that diabetes is more difficult to control in these cohorts. This could be explained with the fact that children receive more amount of CHO per kilogram of body weight compared to adults. According to (6), when children, adolescents, and adults received the same amount of carbs in proportion to their body weight (1g/kg), glucose concentration was found to be similar in the 3 groups.

FDA approved only one meal scenario for UVA Padova, however further experimentation with multiple meal scenario will be carried out in next section to observe and understand the long term responses of simulator with state feedback strategy.

(4) Test of state feedback control strategy for 1 day (5 meal) scenario for all the subjects

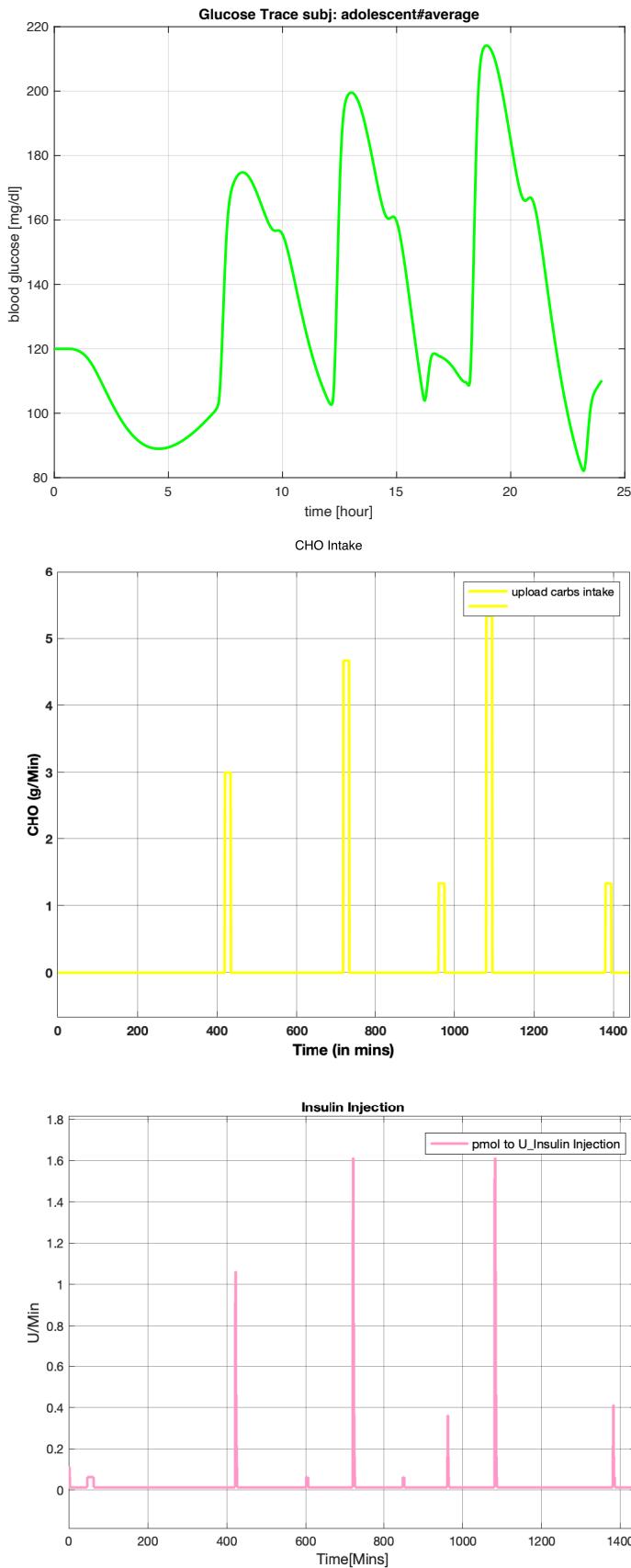


Fig (5.10) - Simulator response for 1 day 5 meals scenario with SF control (a) Glucose response (adolescent avg), (b) Meal Scenario & (c) Insulin Injection

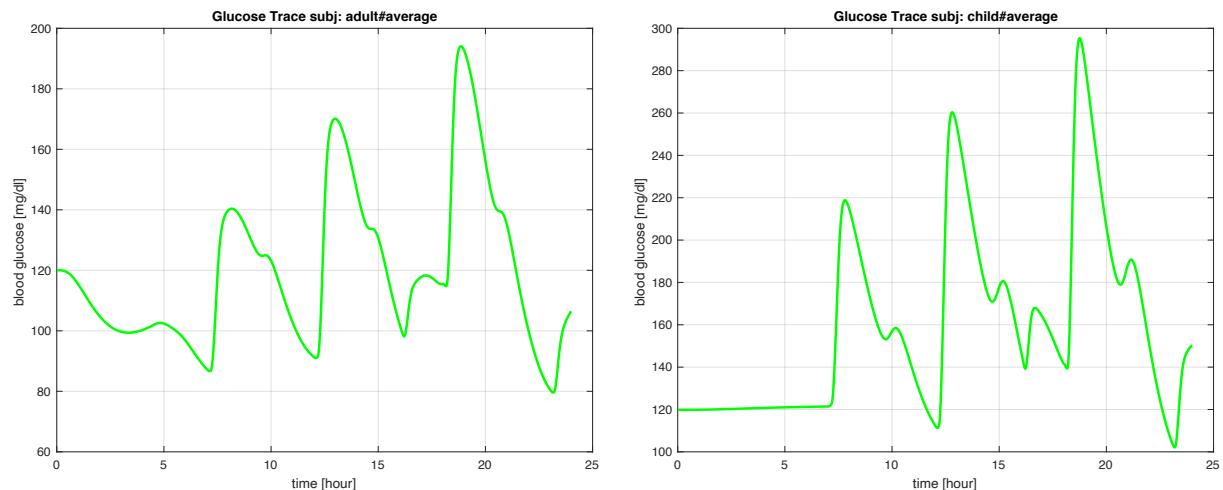


Fig (5.11) - Simulator response of glucose dynamics under 1 day 5 meals scenario with SF control
Left : Adult Average & Right : Children Average

(5) Test of state feedback control for 1 week (5 meal/day) scenario for all the subjects.

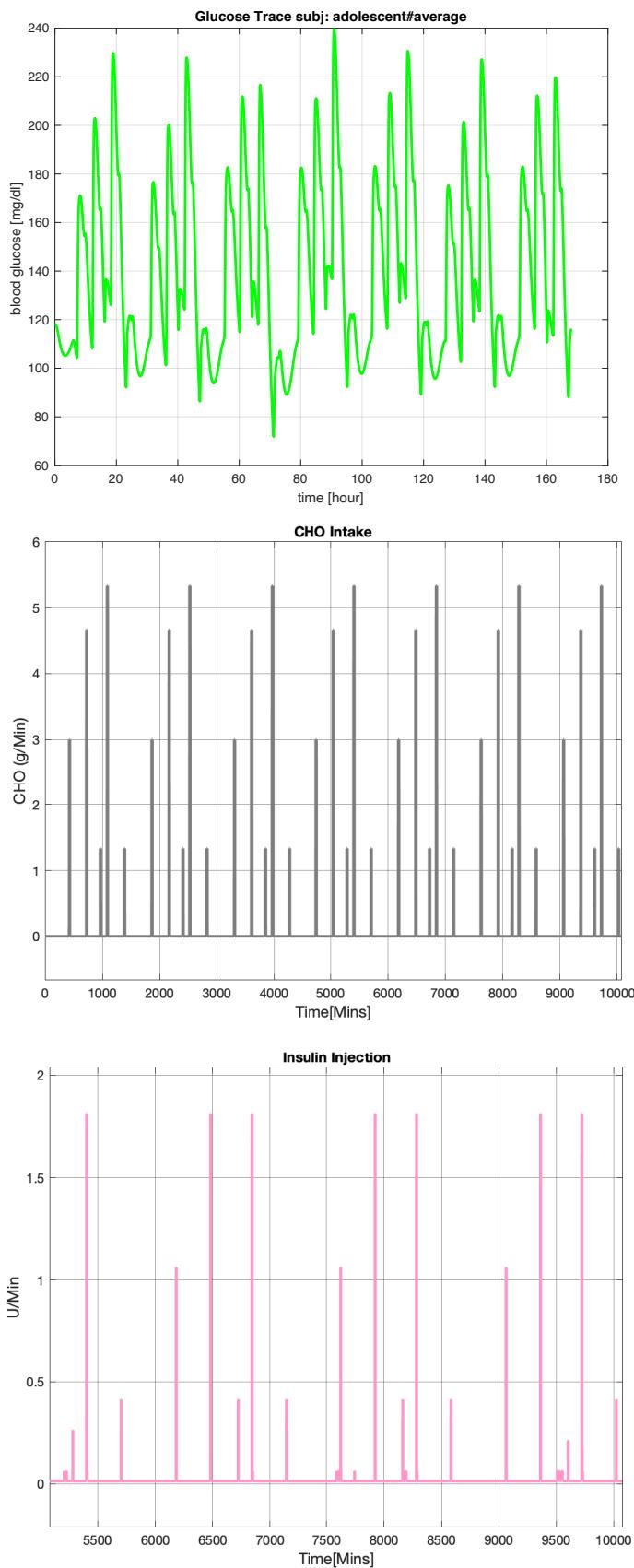


Fig (5.12) - Simulator response for 1 week (5 meals / day) scenario with SF control
 (a) Glucose response of adolescent avg, (b) Meal Scenario & (c) Insulin Injection

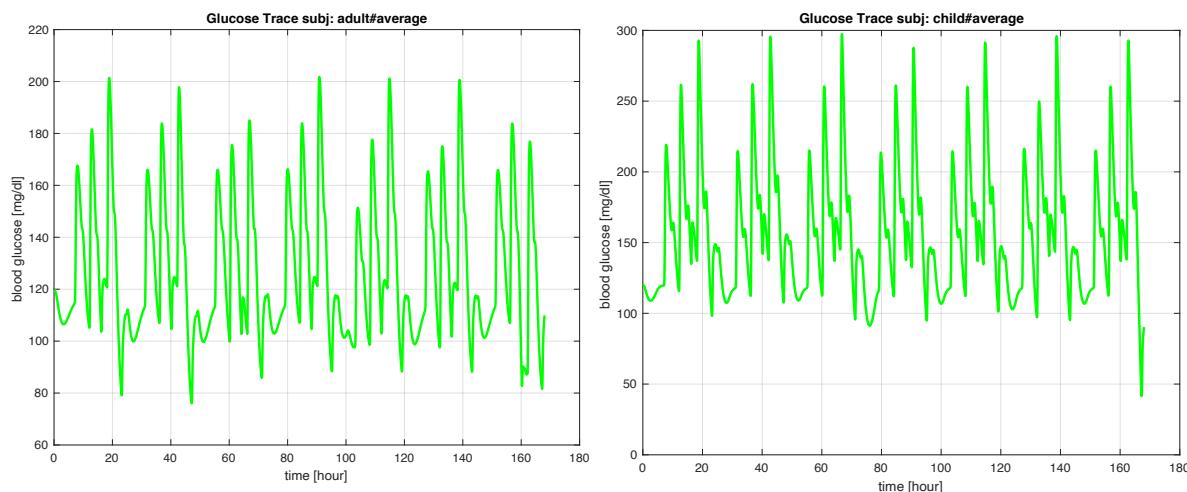


Fig (5.13) - Simulator response of glucose dynamics under 1 week (5 meals / day) with SF control
Left : Adult Average & Right : Children Average

UVA Padova Results for 1 Week Scenario

Adolescent Average :

Gain (k)	ID Mean BG	% Time < TGT-low (70 mg/dl)	% Time in target (70-180 mg/dl)	% Time > TGT-high (180 mg/dl)	BG Risk Index
1	137.78	0.00	85.75	14.25	3.00
0.90	140.97	0.00	82.82	17.18	3.32
0.80	142.20	0.00	80.85	19.15	3.16
0.75	142.13	0.33	80.27	19.40	3.75

Adult Average :

Gain (k)	ID Mean BG	% Time < TGT-low (70 mg/dl)	% Time in target (70-180 mg/dl)	% Time > TGT-high (180 mg/dl)	BG Risk Index
1	124.59	0.50	94.55	4.95	1.62
0.90	126.72	0.00	95.13	4.87	1.54
0.80	126.94	0.39	93.93	5.68	1.56
0.75	128.77	0.00	92.81	7.19	1.68

Child Average :

Gain (k)	ID Mean BG	% Time < TGT-low (70 mg/dl)	% Time in target (70-180 mg/dl)	% Time > TGT-high (180 mg/dl)	BG Risk Index
1	155.01	0.00	77.38	22.62	4.82
0.90	157.07	0.44	74.94	24.62	5.15
0.80	156.57	0.00	77.79	22.21	4.94
0.75	159.04	0.00	75.16	24.84	5.32

The results obtained for 1 day (5 meals) and 1 week (5 meals/day) scenario still found to be in line with the clinical practices for adult case. However, it is to be noted that desired results of percentage time in target ($\geq 82\%$) and percentage time in hypoglycaemia ($< 3\%$) as per clinical trials is only available for adult group. Therefore, simulator results of control strategy for children and adolescent group can't be analysed for their effectiveness. Based on the result analysis of adult group for one meal or multiple meal scenario for long term stability, the established state feedback control with the 5 state estimator could be employed for further clinical trials.

Chapter : 6

CONTROL ALGORITHM

Openaps is an open source platform for closed loop artificial pancreatic system development. The software algorithm is available on Github for open access and complete guide for implementing APS device along with mobile application is available on the website <https://openaps.readthedocs.io/en/latest/>. The main algorithm which calculates the required insulin for the patient is available on Github under oref0/lib folder called as **determine-basal**. The control algorithm is build in javaScript language and integrated in the same programming file with the existing parameter definitions and data files.

State Feedback Control Algorithm:

begin

Initialise parameters

```
x[n-1] ← x[0] % Glucose, Insulin & Meal states  
θi[n - 1] ← θi[0] % FIT parameters & time constants  
Ts ← 5 % sensor_update time  
ρ ← ρ[0] % learning rate
```

Read sensor, actuator & user inputs

```
s[n] ← glucose_status{} % Glucose CGM data  
y[n] or bg ← glucose_status.glucose % Glucose CGM value  
u[n-1] ← currenttemp.rate % Last pump rate  
x1[ref] ← target_BG % BG target value  
θ2 ← profile.sens  
CR ← profile.carb_ratio  
unit ← profile.out_units % Glucose unit  
basal ← profile.current_basal % Basal
```

Calculation of parameters

```
θ1 = basal * θ2 % Constant in Glucose dynamics equation
```

```
θ4 = θ2/CR
```

```
%% unit conversion
```

```
if unit = mg/dl then
```

```
    do nothing
```

```
else
```

```
    y[n] = y[n] /18 (mmol/l)
```

```
%% Glucose correction (x[n] = current value, x[n-1] = last value)
```

```
x1[n] ← x1[n - 1] + θ1 - θ2x2[n - 1] + θ4x4[n - 1] + L(y[n] - y[n - 1])
```

```
function SFControl1 (glucose_status{}, currenttemp.rate, profile, IOB.data, rT, x[n-1])
```

```
for (i=0; i=i+1; i<5)
```

```
x3[n] ← x3[n - 1](1 -  $\frac{1}{θ_3}$ ) +  $\frac{1}{θ_3}u_i[n - 1]$  % Insulin subcutaneous
```

```
x2[n] = x2[n - 1](1 -  $\frac{1}{θ_3}$ ) +  $\frac{1}{θ_3}x_3[n - 1]$  % Insulin Plasma
```

```
x5[n] = x5[n - 1](1 -  $\frac{1}{θ_5}$ ) +  $\frac{1}{θ_5}u_m[n - 1]$  % Meal Stomach
```

```
x4[n] = x4[n - 1](1 -  $\frac{1}{θ_5}$ ) +  $\frac{1}{θ_5}x_5[n - 1]$  % Meal Duodenum
```

```
x1[n] ← x1[n - 1] + θ1 - θ2x2[n - 1] + θ4x4[n - 1] % Plasma Glucose
```

```

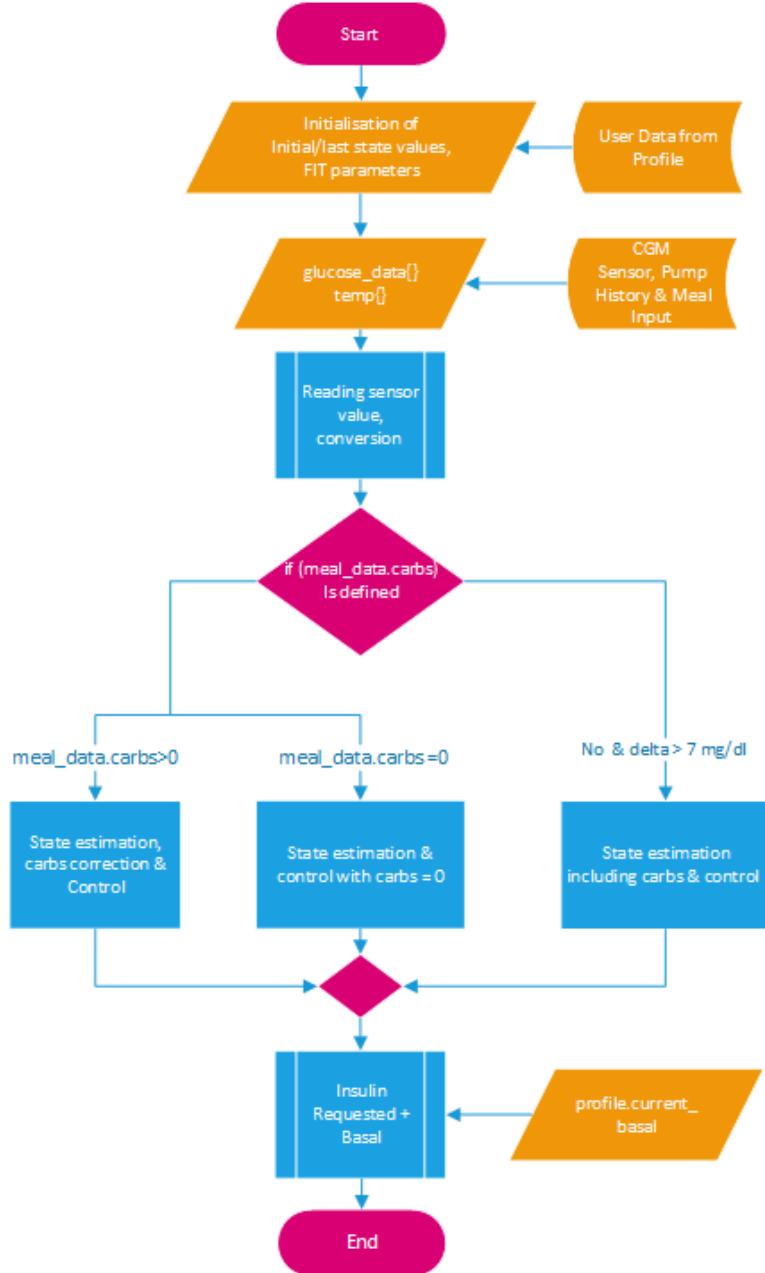
x5[n - 1] ← x5[n]
x4[n - 1] ← x4[n]
x3[n - 1] ← x3[n]
x2[n - 1] ← x2[n]
x1[n - 1] ← x1[n]
end
end

function SFControl2(glucose_status{ }, currenttemp.rate, profile, IOB.data, rT, x[n-1])
    for (i=0; i=i+1; i<5)
        um[n - 1] = Kρ(y[n] - y[n - 1]) % Meal estimate
        x3[n] ← x3[n - 1](1 -  $\frac{1}{\theta_3}$ ) +  $\frac{1}{\theta_3}u_i[n - 1]$ 
        x2[n] = x2[n - 1](1 -  $\frac{1}{\theta_3}$ ) +  $\frac{1}{\theta_3}x_3[n - 1]$ 

        x5[n] = x5[n - 1](1 -  $\frac{1}{\theta_5}$ ) +  $\frac{1}{\theta_5}u_m[n - 1]$ 
        x4[n] = x4[n - 1](1 -  $\frac{1}{\theta_5}$ ) +  $\frac{1}{\theta_5}x_5[n - 1]$ 
        x1[n] ← x1[n - 1] + θ1 - θ2x2[n - 1] + θ4x4[n - 1]
        x5[n - 1] ← x5[n]
        x4[n - 1] ← x4[n]
        x3[n - 1] ← x3[n]
        x2[n - 1] ← x2[n]
        x1[n - 1] ← x1[n]
    end
end

if (current time = sensor time) then
    if meal_input = defined then % defined carbs ≥ 0
        execute SFControl1
        U = k( $\frac{x_1[n] - x_1[ref]}{\theta_2}$  - θ3(x3[n] -  $\frac{\theta_1}{\theta_2}$  + x2[n] -  $\frac{\theta_1}{\theta_2}$ ) +  $\frac{\theta_4\theta_5}{\theta_2}x_4[n]$  +  $\frac{\theta_4\theta_5}{\theta_2}x_5[n]$ )
        insulinReq ← U
        rT.rate ← U + Basal
        y[n - 1] ← y[n]
    end
    if meal_input = Undefined & delta > 5 then
        execute SFControl2
        U = k( $\frac{x_1[n] - x_1[ref]}{\theta_2}$  - θ3(x3[n] -  $\frac{\theta_1}{\theta_2}$  + x2[n] -  $\frac{\theta_1}{\theta_2}$ ) +  $\frac{\theta_4\theta_5}{\theta_2}x_4[n]$  +  $\frac{\theta_4\theta_5}{\theta_2}x_5[n]$ )
        insulinReq ← U
        rT.rate ← U + Basal
        y[n - 1] ← y[n]
    end
    else
        print message (sensor value is old)
    end

```



Fig(6.1) : Flow chart for Control algorithm

CONCLUSION

Luenberger observer based on 5 state model along with state feedback control (3) performed well on UVA Padova simulator and desired responses as per fig (5.8) and (5.9) were achieved under known disturbances. The chosen gains of control strategy ensures the positive responses of the states and inputs of an artificial pancreatic system. The stated control strategy maintains that glucose response remains in target of range (70-180 mg / dl) and helps in avoiding the stage of hypoglycaemia (below 40 mg / dl). However, this observer model is incapable of estimating the unknown disturbances. In this case, unknown meal carbs couldn't be estimated if a patient fails to announce the meal. This observer is an efficient estimator for the hybrid control but unannounced meal or other disturbances couldn't be accounted for fully automatic control. Therefore, Unknown Input Observer is considered for unknown disturbance estimation to accomplish the goal of an efficient fully automatic control without the need of a patient intervention.

The implementation and testing of UIO (extended luenberger observer) on simulator is a subject for further analysis and couldn't be carried out due to the unavailability of simulator at later stage. However, control algorithm with unknown input estimation is tested with 5 states model (with known meal intake) and compared with desired responses as per Fig (3.9) and (3.10). Based on the results, UIO is also detailed and realised for further development.

The analysis of simulator model also raised few queries when open loop dynamics of simulator is tested under disturbances (like meal intake or high amount of injected insulin). These responses don't align with the physiological expectations which opened a door for further investigation and therefore, model of simulator need to be studied in detail.

Based on the results from simulator for single meal scenario for different subjects, proven state feedback control along with implemented observer model could be employed for further clinical trial to assess the performance of tested hybrid control system for long term stability. Therefore, established control algorithm as per Fig (6.1) is developed to be incorporated in the openAPS software program for prototype development. The hybrid state feedback control i.e. when meal input is known is tested on openAPS platform for functional check of algorithm. However, full fledged development of program and integration with openAPS for prototype development is still in progress.

The time delay model is implemented for the comparison analysis of the resemblance of mathematical model and its control with the actual physiological process. The introduction of time delays did complicate the pancreatic system and its stability by introducing infinite eigenvalues, but responses of stable time delay system were able to achieve the desired response time for glucose dynamics. The response time as per fig (4.2) was found to be lower compared to 5 states model and ensures the convergence of glucose at equilibrium position within 3 hrs. The responses of TDS on simulator was satisfactory but detail analysis for the observer based on time delay system is still pending and scope for further study.

In conclusion, luenberger observer based on 5 state model along with state feedback and positivity gains achieved an acceptable response on simulator for its implementation for an APS application for hybrid control. However, unknown meal input estimation is necessary for the implementation of fully automatic APS device. Therefore, further testimony of UIO on UVA Padova simulator is must for analysing its effectiveness for estimating the unknown disturbances/inputs. In the end, control algorithm is developed based on the luenberger observer with the proven state feedback control along with the unknown input estimation as an option as detailed in chapter 6.

REFERENCES

1. Magdelaine, N., Rivadeneira, P. S., Chaillous, L., Fournier-Guilloux, A. L., Krempf, M., Mohammadriddha, T., Ait-Ahmed, M., & Moog, C. H. (2020). Hypoglycaemia-Free Artificial Pancreas Project. *Iet Systems Biology*, 14(1), 16–23. <Https://Doi.Org/10.1049/Iet-Syb.2018.5069>
2. Nicolas Magdelaine, Lucy Chaillous, Isabelle Guilhem, Jean-Yves Poirier, Michel Krempf, Claude H. Moog, And Eric Le Carpentier (2015) A Long-Term Model Of The Glucose–Insulin Dynamics Of Type 1 Diabetes, *I Transactions On Biomedical Engineering*, Vol. 62, No. 6, June 2015
3. Claudia Califano, Emeric Scharbarg, Nicolas Magdelaine, Claude Moog. A Nonlinear Time-Delay Realization For Gastroparesis In Patients With Diabetes. *Annual Reviews In Control*, Elsevier, 2019, 48, Pp.233-241. <10.1016/J.Arcontrol.2019.07.005>. <Hal-02267973>
4. Frank S.A. (2018) Time Delays. In: Control Theory Tutorial. Springerbriefs In Applied Sciences And Technology. Springer, Cham. Https://Doi.Org/10.1007/978-3-319-91707-8_13
5. Kyrychko, Y. N., & Hogan, S. J. (2010). On The Use Of Delay Equations In Engineering Applications. *Jvc/ Journal Of Vibration And Control*, 16(7–8), 943–960. <Https://Doi.Org/10.1177/1077546309341100>
6. Dalla Man, C., Micheletto, F., Lv, D., Breton, M., Kovatchev, B., & Cobelli, C. (2014). The Uva/Padova Type 1 Diabetes Simulator: New Features. *Journal Of Diabetes Science And Technology*, 8(1), 26–34. <Https://Doi.Org/10.1177/1932296813514502>
7. Kovatchev, B. P., Farhy, L. S., Cox, D. J., Straume, M., Yankov, V. I., Gonder-Frederick, L. A., & Clarke, W. L. (1999). Modeling Insulin-Glucose Dynamics During Insulin Induced Hypoglycemia. Evaluation Of Glucose Counterregulation. *Journal Of Theoretical Medicine*, 1(4), 313–323. <Https://Doi.Org/10.1080/10273669908833028>
8. V. W. Bolie, Coefficients Of Normal Blood Glucose Regulation, *J. Appl. Physiol.*, 16 (1960), 783–788.
9. R. N. Bergman, Y. Z. Ider, C. R. Bowden And C. Cobelli, Quantitative Estimation Of Insulin Sensitivity, *Am. J. Physiol.*, 236 (1979), E667–E677.
10. A. De Gaetano, G. Mingrone And M. Castagneto, Nonmem Improves Group Parameter Estimation For The Minimal Model Of Glucose Kinetics, *Am. J. Physiol.*, 271 (1996), E932–E937.
11. Drozdov A, Khanina H. A Model For Ultradian Oscillations Of Insulin And Glucose. *Math Comput Model* 1995;22(2):23–38.
12. A. Makroglou, J. Li, Y. Kuang Mathematical Models And Software Tools For The Glucose–Insulin Regulatory System And Diabetes: An Overview *Appl. Numer. Math.*, 56 (2006), Pp. 559–573
13. Park, Y., & Stein, J. L. (1988). Closed-Loop State And Input Observer For Systems With Unknown Inputs. *International Journal Of Control*, 48(3), 1121–1136. <Https://Doi.Org/10.1080/00207178808906239>
14. Tang D., Chen L., & Hu E. (2014). A Novel Unknown-Input Estimator For Disturbance Estimation And Compensation. *Australasian Conference On Robotics And Automation*, Acra, 02-04-Dec, 2–4.
15. Xiong, Y., & Saif, M. (2003). Unknown Disturbance Inputs Estimation Based On A State Functional Observer Design. *Automatica*, 39(8), 1389–1398. [Https://Doi.Org/10.1016/S0005-1098\(03\)00087-6](Https://Doi.Org/10.1016/S0005-1098(03)00087-6)
16. H. Wang And S. Daley. Actuator Fault Diagnosis: An Adaptive Observer-Based Technique. *IEEE Transactions On Automatic Control*, Vol. 41, No. 1, July 1996
17. Mann, B. P., & Patel, B. R. (2010). Stability Of Delay Equations Written As State Space Models. *Jvc/ Journal Of Vibration And Control*, 16(7–8), 1067–1085. <Https://Doi.Org/10.1177/1077546309341111>
18. Bátkai, A., Fijavž, M. K., & Rhandi, A. (2017). Positive Linear Systems. In *Operator Theory: Advances And Applications* (Vol. 257). Https://Doi.Org/10.1007/978-3-319-42813-0_8
19. Léchappé, V., Moulay, E., & Plestan, F. (2018). Prediction-Based Control Of Lti Systems With Input And Output Time-Varying Delays. *Systems And Control Letters*, 112, 24–30. <Https://Doi.Org/10.1016/J.Sysconle.2017.12.006>
20. <Https://Www.Medtronicdiabetes.Com/Customer-Support/Minimed-670G-System-Support/About-Auto-Mode>
21. Galeani, S., Tarbouriech, S., Turner, M., & Zaccarian, L. (2014). A Tutorial On Modern Anti-Windup Design. *2009 European Control Conference*, Ecc 2009, 306–323. <Https://Doi.Org/10.23919/Ecc.2009.7074421>
22. Cardeliquio, C., Souza, M., Fioravanti, A., Cardeliquio, C., Souza, M., Fioravanti, A., Analysis, S., Cardeliquio, C. B., & Souza, M. (2018). Stability Analysis And Output-Feedback Control Design For

-
- Time-Delay Systems To Cite This Version : Hal Id : Hal-01679094 Stability Analysis And Output-Feedback Control Design For Time-Delay Systems
23. Łuczak, D., & Wójcik, A. (2016). DSP Implementation Of State Observers For Electrical Drive With Elastic Coupling, 92(5), 100–105. <Https://Doi.Org/10.15199/48.2016.05.19>
 24. West, B., Lewis, D., & Leibrand, S. (2016). Openaps Documentation.
 25. Toffanin, C., Kozak, M., Sumnik, Z., Cobelli, C., & Petruzelkova, L. (2020). In Silico Trials Of An Open-Source Android-Based Artificial Pancreas: A New Paradigm To Test Safety And Efficacy Of Do-It-Yourself Systems. Diabetes Technology And Therapeutics, 22(2), 112–120. <Https://Doi.Org/10.1089/Dia.2019.0375>
 26. Li, J., Kuang, Y., & Li, B. (2001). Analysis Of Ivgtt Glucose-Insulin Interaction Models With Time Delay. Discrete And Continuous Dynamical Systems - Series B, 1(1), 103–124. <Https://Doi.Org/10.3934/Dcdsb.2001.1.103>
 27. Kuroda, A., Taniguchi, S., Akehi, Y., Mori, H., Tamaki, M., Suzuki, R., Otsuka, Y., & Matsuhisa, M. (2017). Accuracy And Time Delay Of Glucose Measurements Of Continuous Glucose Monitoring And Bedside Artificial Pancreas During Hyperglycemic And Euglycemic Hyperinsulinemic Glucose Clamp Study. Journal Of Diabetes Science And Technology, 11(6), 1096–1100. <Https://Doi.Org/10.1177/1932296817735122>
 28. Mergner, S., & Senam, O. (2009). Modelling, Analysis And Control Of Linear Systems Using State Space Representations. Universitätsverlag Göttingen, February 2014, 1–235. Http://Www.Gipsa-Lab.Inpg.Fr/~O.Senam/Docs/Me_Auto.Pdf%0Ahttp://Webdoc.Sub.Gwdg.De/Univerlag/2009/Mergner.Pdf
 29. Components Of Artificial Pancreatic System <Https://Www.Howtorelief.Com/Artificial-Pancreas-Device-Cost-Advantages/>