MODEL BASED CONTROL OF BLOOD GLUCOSE FOR TYPE 1 DIABETIC PATIENTS USING ARTIFICIAL PANCREAS

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DECLARATION

I hereby certify that the work which is presented in dissertation entitled, **"Model-based control of blood glucose for Type 1 diabetic patients using artificial pancreas"**, in partial fulfilment of the requirements for the award of the degree of Master of Engineering in Electronic Instrumentation and Control Engineering, Department of Thapar Institute of Engineering & Technology (Deemed to be University) is an authentic record of my own work carried under the supervision of Dr. Sahaj Saxena. It refers others researcher's work which are duly listed in the reference section. The matter contained in this dissertation has not been submitted, neither in part nor in full to any other degree to any other university or institute except as reported in text and references.

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(Sakshi Bhonsle)

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List of Abbreviations

AP	Artificial pancreas
APS	Artificial pancreas system
BG	Blood glucose
BMM	Bergman minimal model
CGM	Continuous glucose monitor
DM	Diabetes mellitus
FLC	Fuzzy logic controller
FO-PI	Fractional order-proportional integral controller
IMC	Internal model control
IP	Interperitoneal
IV	Intravenous
IVGTT	Intravenous glucose tolerance test
MPC	Model predictive control
P	Proportional
PM	Phase Margin
PI	Proportional-integral
PID	Proportional integral-derivative
SC	Subcutaneous
T1DM	Type 1 diabetes mellitus
US FDA	United states food and drug administration

List of Symbols

α	Alpha cells
β	Beta cells
ζ	Damping constant
ω_c	Gain cross-over frequency
τ_c	Time constant

ABSTRACT

Diabetes Mellitus is a chronic disease affecting millions of people around the world. Most common practise to treat this disease is taking insulin shots or injections that are taken prior to meals. However, this method of taking the drug manually does not necessarily provide required blood glucose control in the body and hence may lead to various other life threatening diseases. With automation in medical technology, an alternate solution is coming into development called artificial pancreas to automatically measure blood glucose in the body and deliver insulin accordingly and therefore maintain tight glucose control. To study this problem, a brief introduction is provided as to justify how this biomedical problem serves to be control system problem. For that various mathematical models and control algorithms are were studied. The aim of this thesis is to design controller for regulation of blood glucose for Type 1 diabetic patients through automated insulin delivery done in-silico using Bergman minimal model. Two controllers are designed for analysis namely, internal model control based PI controller and fractional order controller are designed and exploited in this field in order to maintain normal blood sugar in the following of meal (disturbance).

Chapter 1

Introduction

Diabetes Mellitus is a condition that occurs when glucoregulatory system of the body is not able to regulate blood glucose (BG) level within a normal range of 70-110 mg/dL [1]. The glucoregulatory system consists of organs that release a number of hormones such as insulin, glucagon, cortisol and several other metabolic enzymes that work together to maintain an optimum range of glucose in the body during and after digestion [2]. Maintaining blood sugar at a normal range is a challenging task for diabetic patients. Despite taking various measures to control BG, patients fail to achieve the desired glycaemic control. *Artificial Pancreas System* (APS) is one such innovation in medical technology that aims to maintain normal BG in diabetic patients. Before proceeding to the literature review, it is necessary to understand the cause of diabetes, its types and the way in which this problem is sought through automation in medical field.

1.1 Diabetes and its treatment

The human digestion process can be described as: when a person eats food, carbohydrates in the food get converted to glucose to produce energy in the body. This glucose is released in the blood stream and the BG level rises. This rise is sensed by β-cells in pancreas which releases insulin to help uptake of glucose by

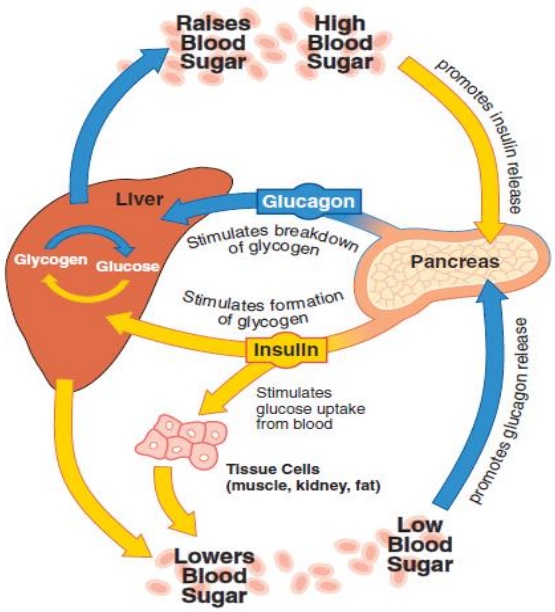

Fig. 1 Blood glucose is management in the body. [3]

cells in the body to convert it into energy. Insulin also helps to store extra glucose in liver as glycogen. This brings BG levels to a normal range. This is shown in Fig. 1.

During exercise and other strenuous activities, the BG level in the body may fall below the normal range. It is then followed by release of a hormone called glucagon from α-cells in the pancreas to stimulate the liver in breaking down of glycogen to glucose, thereby raising the BG level.

In a diabetic patient, an impaired function of insulin response causes BG to remain elevated, i.e., above 200 mg/dl. 2 h after meal (post prandial, that is, after meals) or fasting BG above 126 mg/dl. An elevated BG level in the body above 200 mg/dl is called *hyperglycaemia* whereas decreased BG level in the body, i.e., below 60 mg/dl is called *hypoglycaemia*. A high BG level for longer periods of time causes an increased risk of cardiovascular, eye and kidney diseases among others.

Diabetes Mellitus is mainly categorized into two types [4]: (i) Type 1 (T1DM), where pancreas are not able to produce enough insulin. This type occurs when pancreatic β-cells are killed by the autoimmune system of the body [5] (also called insulin-dependent diabetes); (ii) Type 2 (T2DM), where body's cells are not able to utilize glucose for energy with the help of insulin, i.e., the body becomes insulin-resistant (also called insulin independent diabetes). This type mainly occurs due to factors such as obesity and sedentary lifestyle. T2DM patients can be treated with the help of medicines, weight reduction and making lifestyle changes [6], whereas T1DM patients rely completely on external insulin to keep BG level in the body within the normal range. External insulin can be given either through insulin pumps or continuous subcutaneous insulin injections. Majority of T1DM patients use glucose meters or continuous glucose monitoring (CGM) devices to measure BG level at regular intervals of time. This may include checking BG level prior to meals, either before or after exercise or as desired by the patient. On an average a T1DM patient should check his BG levels upto 6 to 10 times daily [7] and this may hamper day to day activities of a person. It is obvious that if people are left to manage BG on their own, chaotic results of BG levels may be observed due to lack of precise and timely dose of insulin.

1.2 History in the development of artificial pancreas

Advancements in technology has led to the development of systems that can automatically calculate and deliver insulin based upon measured glucose levels. Systems for optimal delivery of insulin to maintain BG level within normal range are in development for several years and

could be seen as a control system problem in which insulin delivery rate is the control signal and BG concentration is the output to be regulated. Earlier systems for control of BG levels were essentially open-loop control systems that required insulin shots or injections prior to meal(s) [8] depending upon the amount of carbohydrates to be consumed, thereby calculating insulin dosage. In 1980's, with the advent of CGM device, patients were provided with algorithms to adjust their insulin dosage [9]. Later, with the help of advanced control strategies, closed-loop artificial pancreas systems were introduced which consists of a CGM sensor, an insulin pump and a control algorithm that calculates the insulin dosage. A control relevant schematic of APS is shown in Fig. 2 in which a glucose sensor is used to measure.

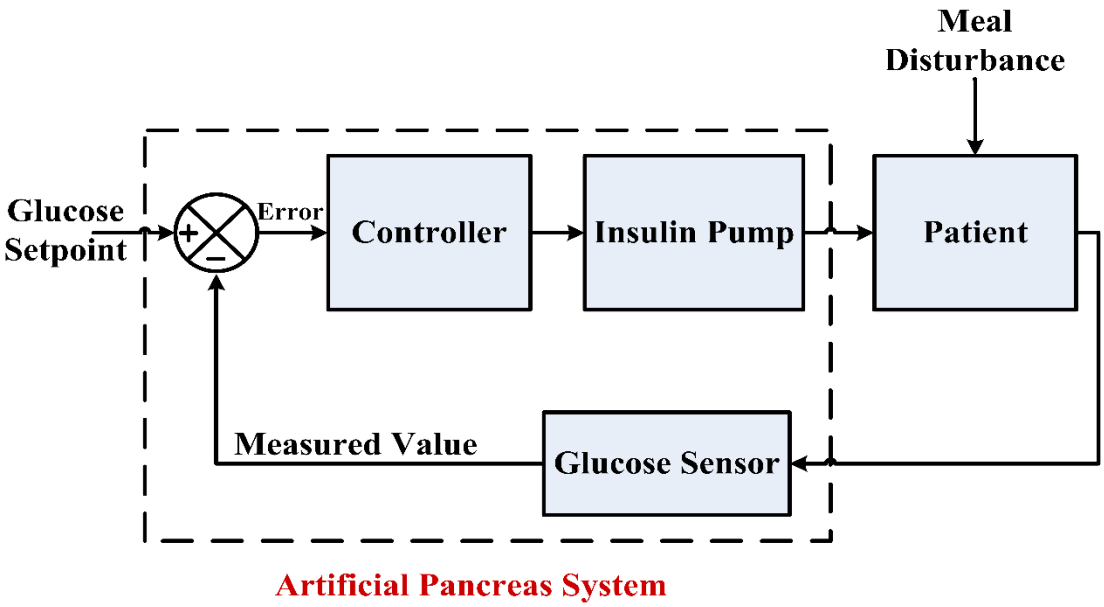

Fig. 2 Block diagram of an APS.

BG level in the body and this measured glucose value is compared with a preset desired value of BG level. The error magnitude is fed to the controller which then outputs appropriate control signal to deliver insulin dosage required to bring the error to zero.

In view of this, several mathematical models (which will be discussed in next section) have been developed to understand and study the glucoregulatory system of the body, from simple models [10], [11] to complex models [12], [13]. However, no model can completely imitate body's function because various other factors that affect BG like exercise and stress are hard to model. On other hand, several control algorithms have been developed so far starting from trivial on-off controller [14] to advanced control schemes such as event-triggered model predictive control [15] ,[16], adaptive control [17], [18], robust proportional-integral-derivative

control [19], to name a few. In this context, one can refer [20], [21] to review some related work.

One of the major risks involved in APS is a case of hypoglycaemia which is characterized by dizziness, unconsciousness, hunger, sweating, etc. In order to reduce such events, a second hormone called glucagon is introduced in some studies [22]. The glucagon works opposite to insulin, i.e., increasing the BG level in the body. Hence, the APS are classified into two types: (i) single hormone APS (insulin delivery), and (ii) dual hormone APS (insulin and glucagon delivery, also called bi-hormonal). Introducing a second hormone adds complexity to the system, and there has been a debate whether to include it or not in the APS. However, a study [23] has shown that there is a minor difference in performance of both the APSs to achieve glycaemic control and therefore in the present study we have included only single hormone APS.

1.3 Thesis Structure

According to a report by World Health Organisation [24], nearly 422 million people are affected by the disease globally in 2014 and about 2.2 million deaths were caused due to increased BG level in the body in 2012. Therefore, it is necessary to understand this problem and to search its remedy. With this objective the thesis comprises of the following chapters: Chapter 1 provides an introduction to the diabetes and its related terms and technology, Chapter 2 discusses literature which describes the various control-relevant mathematical models present in the literature to describe the glucose-insulin dynamics. There are various models present albeit only those relevant to control system modelling and present in most of the papers are reviewed and studied. Second part of chapter 2 various control algorithms present in the literature. Chapter 3 presents research objectives and problem statement. Chapter 4 discusses the methodology that has been applied in to design the controller. Chapter 5 presents simulation results for controller design using internal model control (IMC) based PI and IMC based fractional order PI (FOPI) for the BMM model in the presence of external meal disturbance. Chapter 6 concludes the thesis with conclusion and future prospects.

Chapter 2

Literature Survey

In order to understand the closed loop relationship of the glucose, the pancreatic insulin and its action in the body, several mathematical models have been developed. Based on these mathematical models, control algorithms are formulated. This chapter is divided into two sections; the first part presents the various gluco-regulatory mathematical models and the second part presents the control algorithms that have been used to control blood sugar in T1DM patients.

2.1 Mathematical Models

Most of the mathematical models are based upon the compartmental modelling that assumes the whole body's glucose and insulin to be present in their respective compartments. The insulin is assumed to be released from one compartment to another (containing glucose) to reduce the rise in glucose concentration. One basic model that mathematically described the gluco-regulatory system was introduced by Bolie [10] in 1960.

As the model becomes more complex, more compartments are added to introduce effect of other factors such as hepatic release, fats, etc. Some control relevant models are discussed below.

2.1.1 Bergman Minimal Model

Bergman minimal model (BMM) is a low order model proposed by Bergman in 1980 [11]. The model was developed using the data obtained from the intravenous glucose tolerance test (IVGTT). Most widely used model for control purpose and to understand the pancreatic insulin release and insulin sensitivity in the body. The model consists of the following equations.

a) Glucose dynamics equations

The following equations demonstrates the rate of change of plasma concentration G, upon being excited by the insulin I from the remote compartment X and the meal glucose. Table I can be referred for nomenclature.

TABLE I
PARAMETER DESCRIPTION OF BMM MODEL

Parameters	**Description**	**Value**
G_b	Basal Glucose	mg/dL
I_b	Basal Insulin	$\mu U/L$
p_1	Insulin disappearance time constant	min^{-1}
p_2	Glucose effectiveness	min^{-1}
p_3	Fractional rate of insulin appearance	min^{-1}
n	Fractional rate of insulin clearance	min^{-1}

$$\frac{d}{dt}G(t) = -(p_1 + X(t))G(t) + p_1 G_b \tag{2.1}$$

$$\frac{d}{dt}X(t) = -p_2 X(t) + p_3(I(t) - I_b) \tag{2.2}$$

The insulin sensitivity index S_I, is given as $S_I = -p_3/p_2$.

a) Insulin dynamics equations

$$\frac{d}{dt}I(t) = -n(I(t) - I_b) + \gamma(G_p(t) - h)^+ t \tag{2.3}$$

The initial conditions for the equations are $G(0) = G_b$, $X(0) = 0$ and $I(0) = I_b$.

Suffix b denotes he basal value. The term $\gamma(G_p(t) - h)$ mimics the pancreas ability to produce insulin, which is usually taken zero for T1DM patients. The '+' sign in (2.3) means that the term is to be taken into considerations only if the plasma glucose concentration is above a threshold level of h. Different models have been proposed to describe the exogenous meal disturbance structure in the body. One such model was proposed by Fischer [25] in 1991 called the Fischer meal disturbance model given as

$$D(t) = B\exp(-dt) \tag{2.4}$$

where $D(t)$ (mg/dL/min) is the rate of exogenous glucose infusion, d is the rate of glucose decay in the body and B characterizes the amount of food taken. Later, many complex meal

absorption models were purposed such as Lehman and Deutsch meal model, which describes the oral meal as a trapezoidal function [26] and other oral glucose absorption models as in [27]. Over the years, modifications have been done in the original BMM model to include the effect of free fatty acids [28] and exercise [29].

2.1.2 Dalla Man's Model

This mathematical model of glucose-insulin dynamics occurring during meals was developed by Dalla Man and co-workers to effectively demonstrate the various physiological events occurring during the digestion process, i.e., from ingested food to its absorption. The model was initially developed for normal and T2DM patients [12]. And in order to simulate for T1DM patients, a subcutaneous (SC) insulin infusion module was used to substitute insulin secretion module [30]. A simulation software [31] was developed in 2009 to study the gluco-regulatory system of the body. The model consists of the glucose and insulin sub-systems and their relationship between the various glucose fluxes as given in the following equations. The description of the various parameters and variables can be referred from Table II.

a) **The insulin subsystem**

The insulin kinetic equations [12] are described using the two-compartment model, that contain the masses in the liver and the plasma compartments, respectively, as

$$\frac{d}{dt} I_l(t) = -(m_1 + m_3(t)) I_l(t) + m_2 I_p(t) + S(t) \tag{2.4}$$

$$\frac{d}{dt} I_p(t) = -(m_2 + m_4) I_p(t) + m_1 I_l(t) \tag{2.5}$$

$$I(t) = \frac{I_p}{V_I} \tag{2.6}$$

The initial conditions in the above equations are $I_l(0) = I_{lb}$, $I_p(0) = I_{pb}$ and $I(0) = I_b$ and S is the insulin secretion linked with the hepatic extraction (*HE)* defined as

$$HE(t) = -m_5 S(t) + m_6 \tag{2.7}$$

$$m_3(t) = \frac{HE(t) m_1}{1 - HE(t)} \tag{2.8}$$

b) The glucose subsystem

The glucose subsystem describes the glucose kinetics equations using the two-compartment model as

$$\frac{d}{dt}G_p(t) = EGP(t) + R_a(t) - U_{ii}(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \tag{2.9}$$

$$\frac{d}{dt}G_t(t) = -U_{ii}(t) + k_1 G_p(t) - k_2(t) G_t(t) \tag{2.10}$$

$$G(t) = \frac{G_p}{V_G} \tag{2.11}$$

TABLE II
PARAMETER DESCRIPTION FOR DALLA MAN MODEL

Parameters	**Description**	**Units**
G_p&G_t	Glucose mass in plasma and tissues resp.	mg/kg
G	Blood glucose concentration	mg/dL
E	Basal glucose concentration	mg/dL
EGP	Renal extraction rate	$mg/dL/min$
I_p	Insulin mass in plasma	$pmol/kg$
I_l	Insulin mass in liver	$pmol/kg$
I	Insulin plasma concentration	$pmol/L$
k_1&k_2	Rate parameters	min^{-1}
$m_{i=1,2\ldots}$	Rate parameters	min^{-1}
R_a	Rate of glucose appearance	$mg/kg/min$
S	Insulin Secretion	$pmol/kg/min$
U_{ii}	Insulin independent glucose utilization	$mg/kg/min$
U_{id}	Insulin dependent glucose utilization	$mg/kg/min$
V_G	Distribution volume of glucose	dL/kg
V_I	Insulin distribution volume	min^{-1}

The initial condition in the above equations are $G_p(0)$, $G_t(0) = G_{tb}$ and $G(0) = G_b$. The subscript b denotes the basal value of the respective variables.

The model consists of four unit process models that describe other processes that take place in the glucose and insulin subsystems and have been identified using forcing function strategy. The first unit model describes endogenous glucose production in the body which is body which is both insulin dependent (uptake by tissues) and insulin independent (uptake by brain) and the fourth unit model is insulin secretion that describes pancreatic response to

glucose in the body. The whole model consists of 24 non-linear differential equations having 35 parameters. The detailed explanations of the model can be found in [12]. Due to accuracy of this model, it has been incorporated in the UVA/Padova Simulator which has been approved by the United States Food and Drug Administration (US FDA) to replace animal trials. The simulator is considered to be a virtual patient [31] and contains data for 300 virtual patients; 100 each for adolescent, adults and children, augmented with CGM sensor related pertubations to mimic the real-time scenario and an in-silico insulin pump.

2.1.3 Hovorka Model

A non-linear model was proposed by Hovorka et al. [32] for T1DM patients is based upon the model predictive control strategy. The model describes the relation between the subcutaneous insulin delivery and the intravenous (IV) glucose absorption using two subsystems as discussed below. The detailed model can be referred from [32] for model constants and parameters values. The description for various parameters of the Hovorka model are mentioned in Table III.

a) Glucose subsystem: The glucose subsystem equations are given by

$$\frac{d}{dt}C(t)=\left(\frac{F_{01}^{c}}{V_G G(t)}+x_1(t)\right)C_1(t)+k_{12}C_2(t)-F_R+U_G(t)+EGP_0(1-x_3(t)) \qquad (2.12)$$

$$\frac{d}{dt}C_2(t)=x_1(t)C_1(t)-(k_{12}+x_2(t))C_2(t)\,y(t)G(t)=\frac{C_1(t)}{V_G} \qquad (2.13)$$

where C_1 and C_2 are the masses in accessible and non-accessible compartments, respectively. x_1 , x_2 and x_3 represents the remote action on the distribution, disposal and production of glucose and G is the glucose concentration, respectively. The term F_{01}^{c} is the insulin independent glucose flux, given by

$$F_{01}^{c}=\begin{cases}F_{01}\\ \dfrac{F_{01}G}{4.5}\end{cases} \qquad (2.14)$$

and F_R is the renal glucose clearance, given by

$$F_R=\begin{cases}0.003(G-9)V_G\\ 0\end{cases} \qquad (2.15)$$

TABLE III
PARAMETER DESCRIPTION FOR HOVORKA MODEL

Symbols	Description	Units
A_G	Carbohydrate bioavailablity	-
EGP_o	Endogenous glucose production extrapolated to zero insulin concentration	$mmol$ / kg / min
F_{01}	Non-insulin dependent glucose flux	$mmol$ / kg / min
k_e	Rate of insulin removal from plasma	$\min^{-1}$
k_{12}	Rate of transfer of glucose from IP to SC	$\min^{-1}$
$t_{m,Ip}$	Maximum possible time to absorb the SC insulin	min
t_{mG}	Maximum time taken for glucose appearance rate	min
V_G	Distribution volume of glucose	L / kg
V_i	Distribution volume of insulin	L / kg

and U_G is the rate at which glucose is absorbed in the intestine, is defined as

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{mG}}}{t_{mG}^2} \ . \tag{2.16}$$

b) The Insulin subsystem: The equations describing the absorption of SC delivered insulin are

$$\frac{d}{dt} S_1(t) = U(t) - \frac{S_1(t)}{t_{m,Ip}} \tag{2.17}$$

$$\frac{d}{dt} S_2(t) = \frac{S_1(t)}{t_{m,I_p}} - \frac{S_2(t)}{t_{m,I_p}}. \tag{2.18}$$

Here S_1 and S_2 are the chain of compartments that depict the absorption of subcutaneously infused insulin. $U(t)$ is the sum of bolus insulin and infused insulin. The insulin infusion rate, $U_I(t)$ and insulin concentration in the plasma I_p are described as

$$U_I(t) = \frac{S_2(t)}{t_{m,I_p}} \tag{2.19}$$

$$\frac{d}{dt} I_p(t) = \frac{U_I(t)}{V_i} - k_e I_p(t) \tag{2.20}$$

2.1.5 Fabietti model

A mathematical model was developed by Fabeitti et al. to describe SC glucose and IV insulin kinetics in the T1DM patient. Similar to original BMM model, it consists of 2 sub-systems (glucose and insulin) as discussed earlier. However, the glucose dynamics equation includes various terms that affect glucose concentration from hepatic glucose output, renal clearance

rate E_R and a term E_b for differentiate of glucose absorption from mixed meal. The description of symbols used in model are in Table IV and detailed model can be studied from [33].

a) **The glucose subsystems:** The first equations represents the concentration of glucose in the plasma compartment G and the second equation describes the amount of glucose in SC compartment Y.

$$\frac{d}{dt}G(t) = -\frac{G(t)}{T_{yg}} + \frac{Y(t)}{T_{gy}} - E_R + \frac{1}{V_g}(-M_i + E_b + E_g + G_{iv}) \tag{2.21}$$

$$\frac{d}{dt}Y(t) = K_{yg}\left(\frac{G(t)}{T_{yg}} - \frac{Y(t)}{T_{gy}}\right) - K_{is}P_{circ}X(t)Y(t) \tag{2.22}$$

TABLE IV
PARAMETER DESCRIPTION FOR FABIETTI MODEL

Symbols	**Description**	**Units**
E_R	Renal extraction rate	$mmol / h$
E_g	Rate of intestinal absorption of glucose	$mmol / h$
E_b	Rate of glucose absorption (hepatic release)	$mmol / h$
G	Glucose compartment	$mmol / L$
G_{iv}	Intravenous glucose absorption rate	$mmol / L$
I	Insulin Compartment	μ / h
K_{yg}	Glucose Volume distribution rate between blood and intersticial compartment respectively.	-
K_{is}	Coefficients of sensitivity for insulin dependent glucose uptake	mL / μ / min
P_{circ}	Circadium variation coefficient of insulin sensitivity	-
S	Rate of insulin flow from SC to plasma compartment	μ / h
t_{xi}, t_m, t_i	Insulin diffusion time constants	h
t_{yg}, t_{gy}	Glucose diffusion time constants	h
V_{iv}	Intravenous insulin infusion rate	μ / h
V_{sc}	Subcutaneous insulin infusion rate	μ / h
X	Remote compartment	μ / h

Y	Glucose concentration in interstitial compartment	$mmol/L$

b) **The insulin subsystem:** The following equations describe the insulin dynamics in the T1DM patient for both SC insulin delivery S and intravenous insulin delivery V_{iv},

$$\frac{d}{dt}I(t) = \frac{1}{T_{xi}}(I(t) + K_i(V_{iv} + S(t))) \tag{2.23}$$

$$\frac{d}{dt}X_i(t) = \frac{1}{T_m}(-X_i(t) + I(t)) \tag{2.24}$$

$$\frac{d}{dt}S(t) = \frac{1}{T_i}(-S(t) + V_{sc}) \tag{2.25}$$

2.2.5 Sorenson's model

A complex physiological model to describe glucose-insulin dynamics at organ and tissue level was proposed by Sorenson [13]. The model describes T1DM patient using 19 differential equations and 44 parameters, from which 11 equations represent glucose dynamics, 7 represent insulin dynamics and 1 equation is for glucagon secreted from the liver. The model consists of six sub-compartments that describe the uptake of glucose by brain, heart/lungs, kidney, periphery (tissues), and gut (stomach and intestine). The values of the parameters are constant in the model and can be referred from [13].

Based on the presented comprehensive description of the model, the model are effectively classified into lower-order models such as BMM model and higher order models in [12], [13] and [32]. It is important to note that all the models are developed for simulation purpose to study physiology in diabetic patients and assess some extreme conditions that are not practically and ethically possible to test.

2.2 Control Algorithms

Feedback control systems are in development for biomedical applications for several decades to provide optimal drug delivery to the patients [34]. Conventional methods to treat T1DM are insulin injections taken prior to meals. As mentioned earlier, these methods could be efficient in providing timely and precise amount of dosing required for patients hence account for various other disease besides the side effects caused to other parts of the body. It is important to design a proper closed-loop control system to fully automate the process to prevent hypoglycaemia and long term hyperglycaemia. Despite various robust control algorithms, the performance of a controller is often limited by the dynamics of the glucose sensor and insulin

delivery system [19]. After years of research practise, the US FDA has approved the first automated insulin delivery system in 2016 namely, the Medtronic's MiniMed 670G System for T1DM patients who are 14 years and above, which is based hybrid closed loop control [35],[36]. In 2018, the system was approved for the children between the age 7-14 years [37]. Some control algorithms employed on BG regulations through artificial pancreas have been discussed in the following subsections.

2.2.1 Proportional-Integral-Derivative control (PID)

One of the most widely used controller in the industrial application is the PID controller. The controller effectively imitates the β-cells's insulin secretion in the body in response to glucose and was called external physiological insulin delivery (e-PID) [38]. The insulin is rapidly secreted by the β-cells in the bolus form during the first phase in response to the increased blood glucose (proportional component) and in the second phase (integral-component), it is released slowly, called basal insulin, to account for insulin required in between the meals to keep blood glucose at a normal level [39], [40]. The controller signal *u(t)* or the insulin delivery rate is calculated as,

$$u(t) = K_p e(t) + K_i \int e(t)dt + K_d \frac{d}{dt} e(t) \tag{2.26}$$

Where $e(t) = G_m(t) - G_t(t)$ is the error and G_m and G_t denotes the measured BG and glucose setpoint respectively. The terms K_p, K_i and K_d denotes the proportional gain, integral gain and derivative gain, respectively. Initially in-vivo studies were conducted by Steil et al. [39] for subcutaneous insulin delivery and glucose sensing (SC-SC). In order to reduce hypoglycaemia cases, i.e., to reduce the over delivery of insulin, insulin feedback was included to make controller more robust [41]. Chee et al. developed a rule based PID controller [42] for critically ill-patients. Marchetti et al. developed switching PID controller using Hovorka model such that controller is turned on only after meals and is off before meal bolus [43]. Various schemes for tuning the hybrid-PID and PID controller parameters to obtain optimised results are developed using cuckoo search algorithm [44] and firefly algorithm [45]. In-silico experiments were conducted by Huyett et al. [41] for interperitoneal insulin delivery and interperitoneal glucose sensing (IP-IP) [46], for implantable artificial pancreas. Chakraborty et al. conducted the first in-vivo experiment for IP-IP sensing in dogs using canine model [47].

2.2.2 Model predictive control (MPC)

A model predictive strategy predicts future output, i.e., the blood glucose concentration based upon the effect of present and future control signal, i.e., insulin rate. This control strategy is

widely being used because of its capability to incorporate the changes occurring in the interpatient variability over the course of time. However, the performance of a model-based controller is based on how accurate a model imitates the actual system and system parameters tend to remain constant. One of the major advantage of MPC to use its constraint handling capability. Some of the earlier results were shown by Parker and co-authors [48] have shown results for MPC for intravenous sensing and intravenous insulin delivery using Sorenson model [13] and Bequette using BMM [15]. Magni [49] did comparision using PID and linear MPC using the Dalla Man model. First outpatient study using MPC algorithm was conducted by [50]. An event based MPC was proposed by [16], for low power consumption of the device. A Zone-MPC based control has been used to get an adaptive controller in [51].

2.2.3 Fuzzy logic controller (FLC)

A fuzzy logic controller does not demand any differential equation model of the glucose-insulin system. Rather, it requires a set of rules based upon the expert knowledge of the system or problem. Unlike PID controller which imitates the function of a β-cell [52]. FLC controller imitates the function of a potential caregiver [53]. The first fully closed-loop APS based on a physician's expertise were personalised tuning was provided using a personalisation factor, proportional to patient's total daily insulin dosage. A clinical study was conducted using Mamdani based FLC under controlled conditions [54]. BG control in BMM model using Takagi-Sugeno FLC was proposed in [55].

2.2.4 Neural network control

A neural network uses large amount of input and output data to train a network. The initial study using neural network approach were conducted by Trajnaoski and Wach [56], where system was identified by neural network and neural predictive control (using MPC) was developed. Phee et al. [57] developed an intelligent insulin system based on neural fuzzy controller using pseudo-outer product-Yager system. A controller using dynamic inversion based upon neuro-adaptive approach was developed in [58]. Artificial neural networks were developed in to predict future plasma glucose based on previous glucose-insulin data in [59], [69]. Ali and Padhi [18] developed a neural network based on single network adaptive critic synthesis using the BMM model.

2.2.5 Adaptive control

In an adaptive control scheme, the system model is embedded into the controller and the parameters of the controller are adjusted as per the changes in the system's behaviour. Various adaptive schemes are: (i) minimum variance control, (ii) self tuning regulator, (iii) linearized quadratic control and (iv) generalised predictive control. The adaptive control system does not

depends upon the initial value of the system, rather only present state is taken into consideration. A more exhaustive review of various adaptive techniques applied in the field of APS is discussed in [17].

2.2.6 Robust control techniques

The H_∞ controller takes into account uncertainity and errors present in the system and hence adds to robustness. An automatic, full observer state feedback controller was proposed in [60] for intravenous route of insulin delivery. Parker et al. [61] developed continuous time $H_\infty$where the 19^{th} order patient model [13] was reduced to 3^{rd} order model using linearization, and a meal disturbance model was added. The controller was applied on three models: (i) full order model, (ii) reduced order linear and (iii) non-linear model. A modified H_∞ control was proposed for switching insulin infusion rates [62]. These infusion rates were described as basic control vectors and the switching rule to switch from one control vector to another was calculated using Ricatti equation and discrete dynamic programming equations. Femat et al. [63] developed a H_∞controller where a transfer function of weighing restriction was added to account for healthy pancreas' frequency response. Morales-Contreras et al. [64] developed a robust controller using μ-synthesis technique.

A large number of control algorithms have been performed for APS. Among these only PID, MPC and Fuzzy have been studied experimentally in clinical studies. PID control algorithm can be individualised or made patient specific accordingly setting the PID tuning parameters. In MPC, the weighing function of the objective function or model is used for individual predictions [20] whereas adaptive controllers have been used in conjunction with other controllers such as FLC and PID to provide real time adjustment of parameters [65], [66]. It is relatively challenging to decide as to which control strategy is the best. In this context a comparative analysis of PID and MPC techniques is done in [67].

Chapter 3

Problem Statement

3.1 Identified Research gaps

- There is no exact mathematical model that can accurately present the glucose-insulin dynamics in the body. Higher order models that incorporate various others factors like exercise, consumption of fats, individual tissue glucose consumption etc., are difficult to analyse in simulations.
- Most of the control algorithms implemented for blood sugar regulation purpose are able to do bring it to normal range of 70-110 mg/dL, however they are accompanied by hypoglycaemia where blood sugar drops below 60 mg/dL.

3.2 Problem Statement

The purpose of this work is to design a controller that will imitate the function of a pancreas to control blood sugar in T1DM patients using a BMM model and reduce occurrence of hypoglycaemia cases along with maintaining normal BG level after meals. In order to reach this goal, various mathematical models that describe the glucose-insulin cause-effect relationship are studied. The BMM model has been used for purpose of this work. A proof-of-concept to implement integer order and fractional order PI controller using IMC technique is done. Since, most of the biomedical systems present in the literature are essentially non-linear systems and IMC technique is applied only on linear systems, the linear system of the plant needs to be generated, which is described in Chapter 4.

Chapter 4

Proposed Methodology

In order to control blood glucose for type 1 diabetes patient, a controller is designed to study the effect of glucose, insulin and meal in the body. An integer order and fractional order PI controller are designed. PID controller is still being used in industrial applications despite having various control algorithms because of its robustness, set-point tracking and effective disturbance. There are many methods to tune the PID gains such as Zeigler-Nicholas [68], Cohen-Coon [69], etc. In this study IMC based PID scheme is applied for the objective of tuning of PID gains and hence to control blood glucose in the body. For that internal model control (IMC) based tuning of proportional-integral (PI) gains is done. Since IMC tuning of PID is done only for linear systems, a linearized system is obtained of a non-linear BMM model. Section 4.1 discusses IMC technique and its modelling scheme. Section 4.2 discusses fractional order calculus and how a fractional order controller can be obtained using IMC technique. In Section 4.3 a simple technique is presented to linearize a non-linear system and this identified approximated system's transfer function is then used for controller design for real system.

4.1 IMC Technique

The internal model control is model-based technique developed by Morari and Zafiriou [70] is used with feedback controllers to directly yield controller parameters and is known to possess robustness in the presence of modelling uncertainties. This technique utilizes a single tuning parameter λ, to manually tune the PID gains. Rivera et al. [71] demonstrated how IMC control structure can be converted to a conventional feedback PID control structure.

4.1.1 Fundamentals

A block diagram depicting general IMC scheme and a general feedback controller is shown in Fig. 3. The output of the IMC controller $C_{IMC}(s)$ and the plant model $G_p(s)$, gives the model response, $Y_M(s)$. The difference between the model response and the actual plant response $Y(s)$ is fed back to the internal model controller as input. The IMC controller scheme can be converted to a conventional feedback controller scheme using the following relation

$$C(s) = \frac{C_{IMC}(s)}{1 + G_p(s) C_{IMC}(s)}. \tag{4.1}$$

For designing IMC based controller, the plant model $G_p(s)$ must be factorised into $G_p^-(s)$ and $G_p^+(s)$. The positive part $G_p^+(s)$ contains the delay term and right-half plane zeros, with a unity

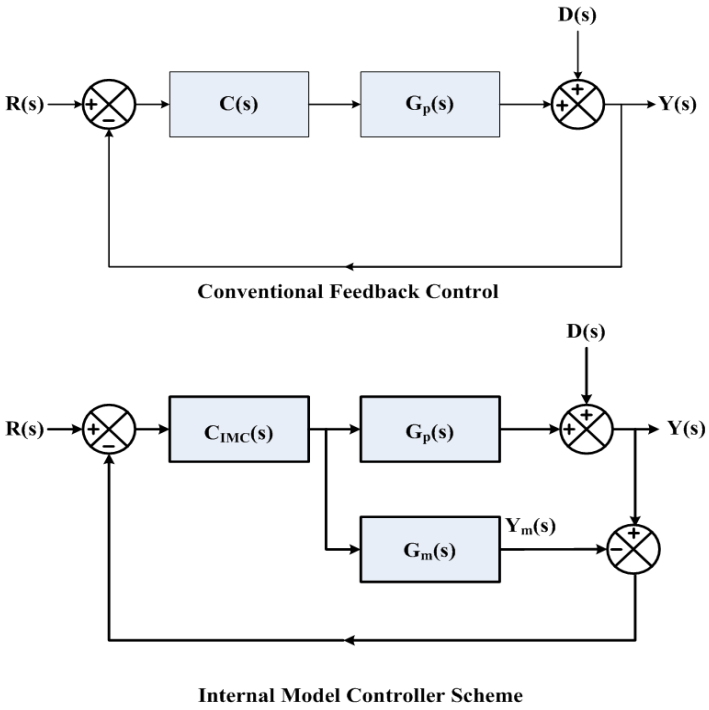

Fig. 3 Block diagram depicting both conventional feedback controller and IMC controller scheme.

steady state gain and the negative part $G_p^-(s)$ is employed for IMC design. Finally, the $C_{IMC}(s)$ is given as

$$C_{IMC}(s) = Q(s)F(s) \tag{4.2}$$

where $Q(s)$ is

$$Q(s) = \frac{1}{G_p(s)}, \tag{4.3}$$

and $F(s)$ is a low order filter defined as

$$F(s) = \frac{1}{(\lambda s + 1)^n} \tag{4.4}$$

The filter in Eqn. (4.4) is used to make the controller realizable (in the semi-proper or proper fraction form). The tuning parameter λ is desired loop time constant and n is always a positive integer.

4.1.2 Design procedure for IMC based PID

A general form of transfer function of the form of is

$$G(s) = \frac{K(s+z_1)(s+z_2).....(s+z_k)}{(s+p_1)(s+p_2).....(s+p_m)} \tag{4.5}$$

A plant model of the following form is considered,

$$G_p(s) = \frac{K}{\tau s+1} \tag{4.6}$$

where K is the gain of the system [72]. The internal model controller can be obtained using (4.2), (4.3) and (4.6) as

$$C_{IMC}(s) = \left(\frac{\tau s+1}{K}\right)\left(\frac{1}{\lambda s+1}\right) \tag{4.7}$$

where $n=1$ and $Q(s)$ is obtained as

$$Q(s) = \frac{\tau s+1}{K}. \tag{4.8}$$

The $C_{IMC}(s)$ can now be converted to the traditional feedback structure, $C(s)$, using Eqn. (4.1) and an IMC based PI controller of the following form is obtained.

$$C(s) = \frac{\tau s+1}{K\lambda s} = \frac{1}{\lambda}\left[\frac{\tau}{K}+\frac{1}{Ks}\right] = K_p + \frac{K_i}{s} \tag{4.9}$$

where proportional gain $K_p = \frac{\tau}{\lambda K}$ and integral gain $K_i = \frac{1}{\lambda s}$. It can be seen from Eqn. (4.9) that gains become the function of single tuning parameter λ.

4.2 Fractional-Order Calculus

Fractional order is in development since the start of regular calculus. However, it is in the recent years that various areas of science and technology have been found to use fractional order derivatives and calculus in applications to solve problems.

Podlubny [73] proposed a concept of fractional order controllers PI^{λ} and $PI^{\lambda}D^{\mu}$ controllers for conventional PI and PID controller. λ is the order of integration and μ is the order of derivation. The controller is said to provide better performance for a fractional order systems than a simple PID. There are four possible cases of system and controller,

(i) Controller and system both being integer order.

(ii) Integer order controller for a fractional order system.

(iii) Fractional order controller for a fractional order system.

(iv) Fractional order controller for an integer order system.

Most of the work done using fractional calculus is for the type (iv) category. One of the most important advantage of fractional order PID (FOPID) system is the choice to select five parameters instead of three as in conventional PID. Therefore, it provides more flexibility, adjustability in controller design. Several tuning methods have been used in past to tune FOPID parameters. Recently IMC based control PID was introduced to tune FOPID controller [74]. IMC structure provides simplicity, robustness and intuitive nature in design [75].

A fractional property is introduced in the controller with help of closed loop reference model given as

$$f(s) = \frac{1}{1+\tau_c s^{\alpha+1}}, \tag{4.10}$$

where α lies between 0 and 1. The controller can then be decomposed to two parts i.e., integer order controller and a simple fractional filter $1/s^{\alpha}$, also called fractional integrator. Here α is given as,

$$\alpha = \frac{\pi - PM}{\pi/2} - 1 \tag{4.11}$$

where PM is the phase margin and τ_c is the time constant given as,

$$\tau_c = \frac{1}{\omega_c^{\alpha+1}} \tag{4.12}$$

and ω_C is the gain crossover frequency.

4.2.1 Design procedure for IMC based FOPID

A conventional feedback as in Fig. 3 is considered. The integer order plant model

$G_p(s)$ is considered as in (4.4). The IMC controller can be obtained using Eqn. (4.2) as,

$$C_{IMC}(s) = G_p^{-1}(s) f(s) \tag{4.13}$$

A conventional fractional order controller is of the form of

$$C(s) = H(s) K_p \left(1 + \frac{1}{\tau_i s} + \tau_D s\right) \tag{4.14}$$

where $H(s)$ is the fractional part of the controller and rest is the integer part of controller. The IMC controller $C_{IMC}(s)$ is obtained using Eqn. (4.13) as

$$C_{IMC}(s) = \left(\frac{\tau s + 1}{K}\right)\left(\frac{1}{1 + \tau_c s^{\alpha+1}}\right) \tag{4.15}$$

The conventional feedback form is obtained as

$$C(s) = \frac{\tau s + 1}{K(\tau s + 1)(1 + \tau_c s^{\alpha+1}) - K(\tau s + 1)} \tag{4.16}$$

or,

$$C(s) = \frac{\tau s + 1}{K(\tau_c s^{\alpha+1})} \tag{4.17}$$

or,

$$C(s) = \frac{1}{K\tau_c s^{\alpha+1}}(\tau s + 1) = H(s)(K_P + K_D s) \tag{4.19}$$

From (4.19), it can be seen that fractional controlled can be decomposed into fractional part *H(s)* and integer order part. Eqn. (4.19) forms a fractional order proportional-derivative (PD) controller. After rearranging the terms a fractional order PI controller can be formed as,

$$C(s) = \frac{1}{\tau_c s^{\alpha}}\left(\frac{\tau}{K} + \frac{1}{Ks}\right) = H(s)\left(K_p + \frac{K_i}{s}\right) \tag{4.20}$$

4.3 System Identification

The BMM model is considered here. The terms $D(t)$ and $U(t)$ are added to Eqn. (2.1) and (2.3) respectively, to account for external meal glucose adopted from [25] and rate of externally infused insulin for T1DM patients and is also the controller output. The values of parameters are followed from [15] in Table V.

TABLE V

PARAMETERS VALUE FOR BMM MODEL

Parameters	Value	Units
p_1	0.028735	$\min^{-1}$
p_2	0.028344	$\min^{-1}$
p_3	5.035e-5	mU/L
V_I	12	L

n	5/54	min^{-1}
G_b	80	mg / dL
I_b	15	mU / L

The BMM model equations are re-written for simulation purpose as:

$$\frac{d}{dt}G(t) = -p_1 G(t) - X(t)G(t) - G_b) + D(t) \tag{4.21}$$

$$\frac{d}{dt}X(t) = -p_2 X(t) + p_3 I(t) \tag{4.22}$$

$$\frac{d}{dt}I(t) = -n(I(t) - I_b) + \frac{U(t)}{V_I} \tag{4.23}$$

In order to identify transfer function model, the non-linear BMM model is approximated to a linear low-order model for control purpose. For this, a unit-step input is provided to system to observe its response without any disturbance. (i.e., meal) in MATLAB.

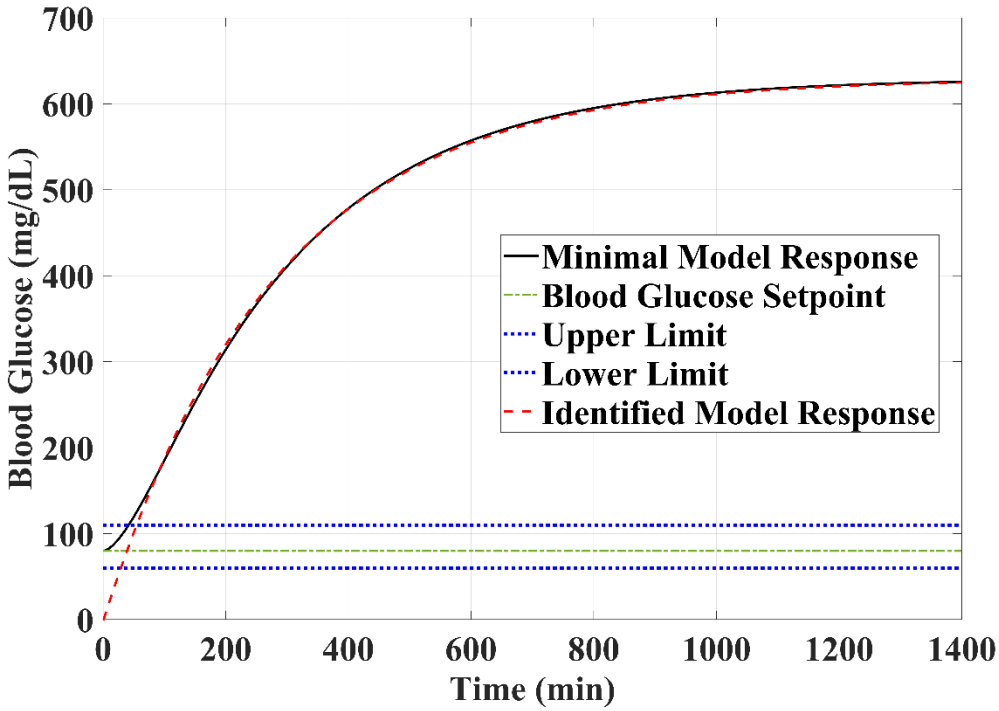

Fig. 4 Response of BMM and its identified model.

The solid line in Fig.4 depicts the open-loop step response of the original BMM system which shows high magnitude of blood sugar level. The system can be seen (solid line Fig. 4) to resemble a step response of a second order system with damping constant $\zeta = 1$ (critically

damped) or $\zeta > 1$ (over damped). Though this gives a choice to set system parameters ζ and ω_n (natural frequency) so that variable pole locations are possible. However, this increases the complexity to design a controller especially for $\zeta > 1$ as one time constant tends to be larger than the other. Also, since oscillations are absent in the system, a first-order transfer as in (4.6) can be formulated where time constant τ is defined as time taken by the system response to reach 63.2% of the steady state value and K is the system gain.

Observing the value τ and K from Fig. 4, an approximated first order transfer function is obtained as:

$$G_p(s) = \frac{629}{280s + 1} \tag{4.34}$$

The step response of both the actual model and the identified linear transfer model in (4.22) are depicted in Fig. 4 which clearly shows that both models have similar time-domain characteristics and hence are in good agreement.

Chapter 5

Results and Discussions

5.1 IMC based PI controller

Having formulated the model, the IMC based PI controller and fractional order PI controller are designed to achieve the blood glucose level under normal range (i.e, 70-110 mg/dL) after meals. An unannounced meal disturbance is introduced into the system for three times a day. The meal disturbance similar to [25] is used for providing non-linear external disturbance and is simulated for a duration of 24 hours i.e., for breakfast (7:00 am), lunch (1:00 pm) and dinner (8:00 pm). The desired value of blood glucose is set as 80 mg/dL. Higher-order meal models are also available that describe the meal absorption precisely; the reason to choose this meal model is that it has faster dynamics [76] for control purpose. Now, using (4.9) and (4.34), IMC-PI controller is formulated as

$$C(s) = \frac{1}{\lambda}\left(\frac{280}{629} + \frac{1}{629s}\right) \tag{5.1}$$

It can be seen from (5.1) that the controller gains have now become function of a single tuning parameter λ and the values of K_p and K_I are obtained to be 0.44515 and 0.001589 respectively.

The model is simulated for various values of λ ranging from 0.1 to 3 to obtain an optimal controller. Fig. 5 shows the simulation results for meal disturbance rejections and set point tracking. The designed controller is also compared with previously designed conventional P and PD controller for BMM model using as shown in Fig. 5(e) and 5(f), respectively.

5.1.1 Simulation results for IMC-PI controller

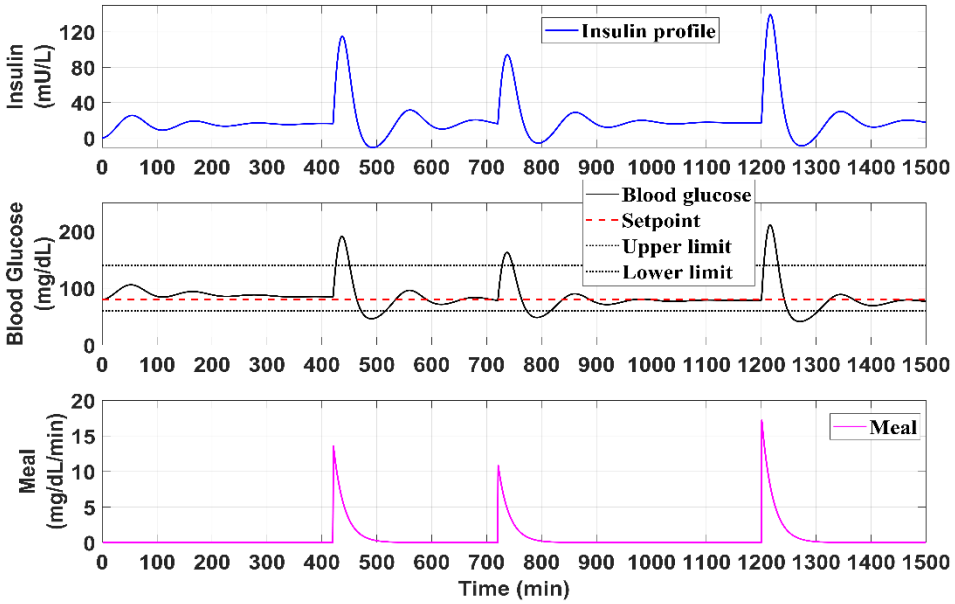

Fig. 5(a) Simulation results for λ=0.5.

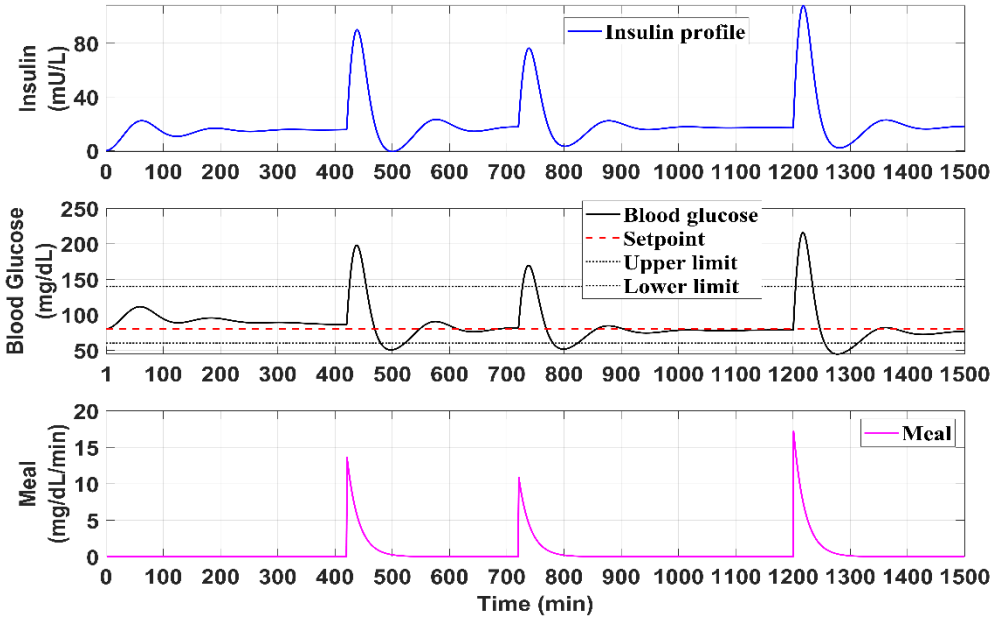

Fig. 5(b) Simulation result for λ=0.7

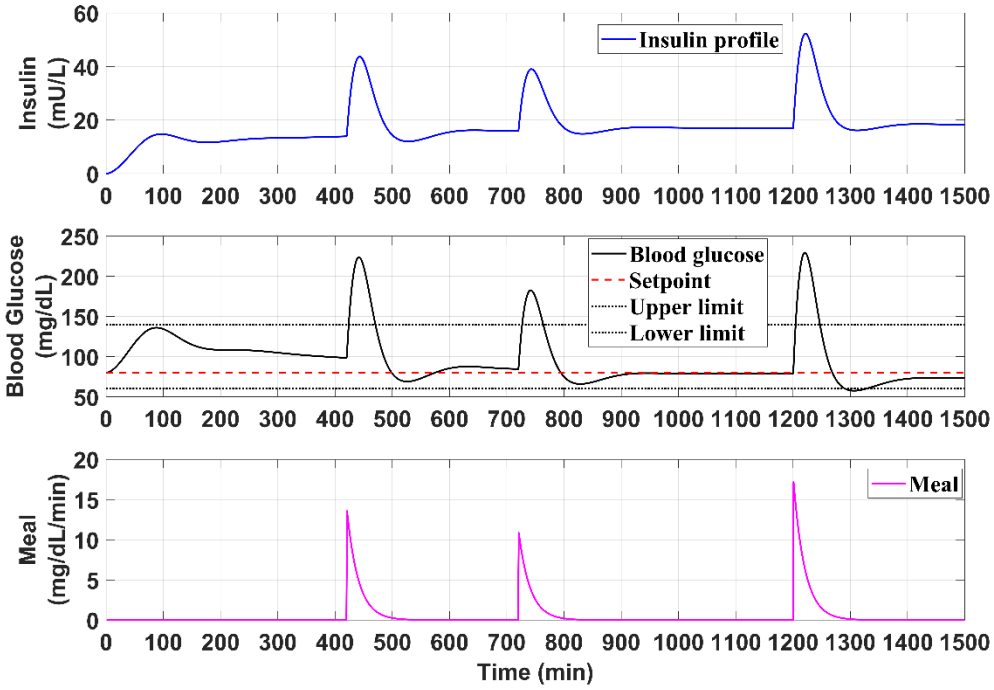

Fig. 5(c) Simulation results for λ = 1.7

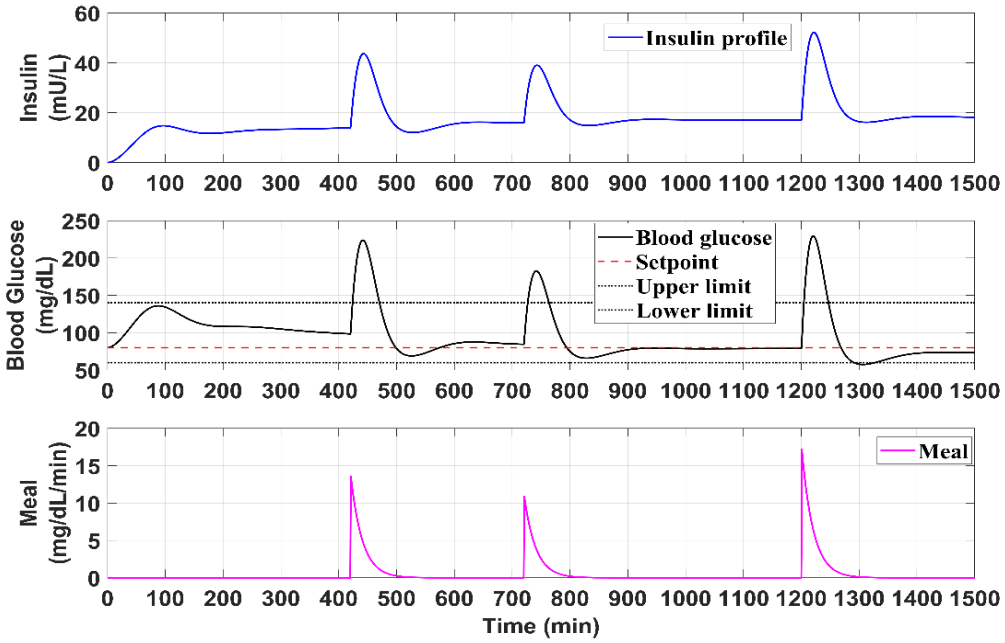

Fig. 5(d) Simulation results for λ = 2.0

5.1.2 Discussions

The results for four values of λ i.e., for = 0.5, 0.7, 1.7 and 2.0 are shown in Fig. 5 to observe the difference in controlled blood sugar levels (solid black line). After exhaustive simulations, the controller is found to exhibit improved results for λ=2.0 as can be seen in Fig. 5(d). For λ less than 1.7, cases of BG level going below 60 mg/dL (Lower limit, dotted black line) can be seen. However, in all the cases high magnitude of BG level were controlled effectively. As for controller output i.e., insulin, tends to decrease (solid blue line) as λ is increased and thereby controlling BG effectively.

5.2 Comparative analysis

A comparative analysis of the IMC technique is done with a previously designed proportional (P) and proportional-derivative (PD) controller [77] as shown in Fig. 5(e) In Fig. 5(e), it is observed that P-controller is not able to maintain BG at setpoint of 80 mg/dL and high magnitude of blood glucose peak is also observed after meals. A similar case is observed with PD controller in Fig. 5(f) where although a very high amount of insulin is released, it is not able to bring BG to a normal range. Thus it is clear that in both the cases IMC based PI controller is effectively able to maintain BG after meal disturbances.

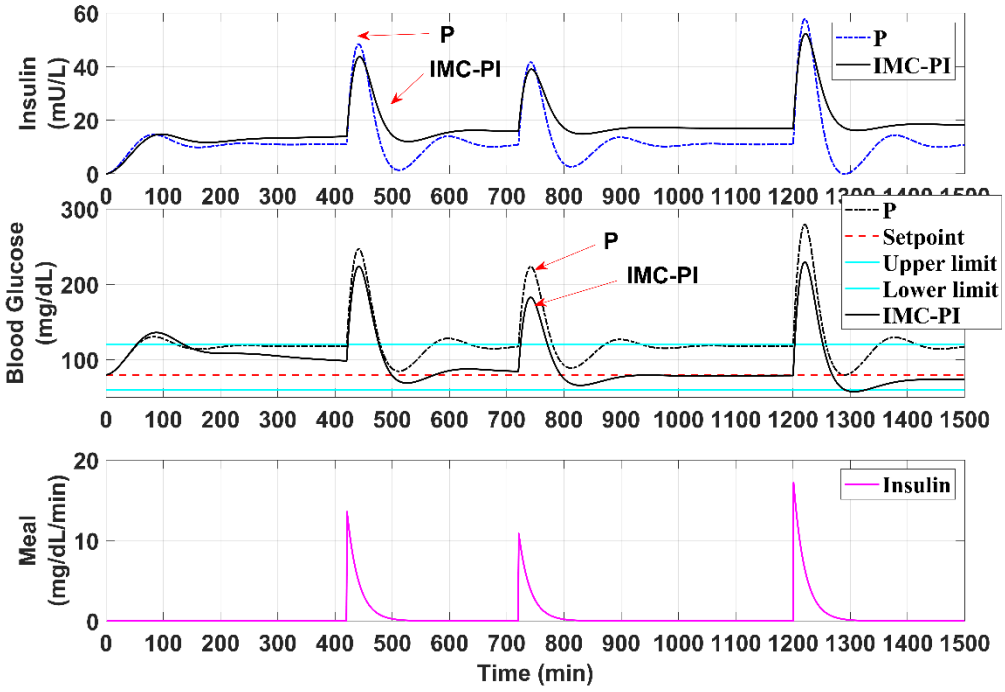

Fig. 5(e) Comparative analysis of P and IMC based PI controller.

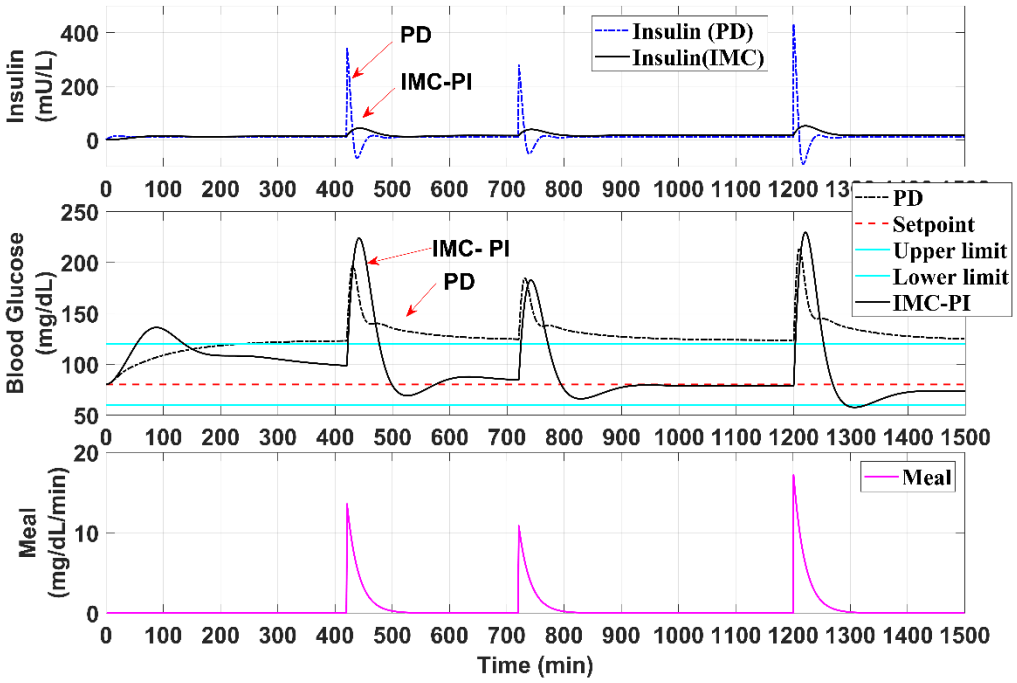

Fig. 5(f) Comparative analysis of P and IMC based PI controller.

5.3 IMC based fractional order PI Controller

Similarly, as a case study IMC based PI fractional order controller was obtained as

$$C(s) = \frac{1}{\tau_c s^{\alpha}}\left(\frac{280}{629} + \frac{1}{629s}\right) \tag{5.2}$$

The Fimcon toolbox of MATLAB has been used to exploit the fractional property of the controller. The value of phase margin is ranged from $45° - 60°$ and ω_c is also varied from 0.05 to 1.

5.3.1 Simulation results for phase margin =45°, different values of gain cross over frequency.

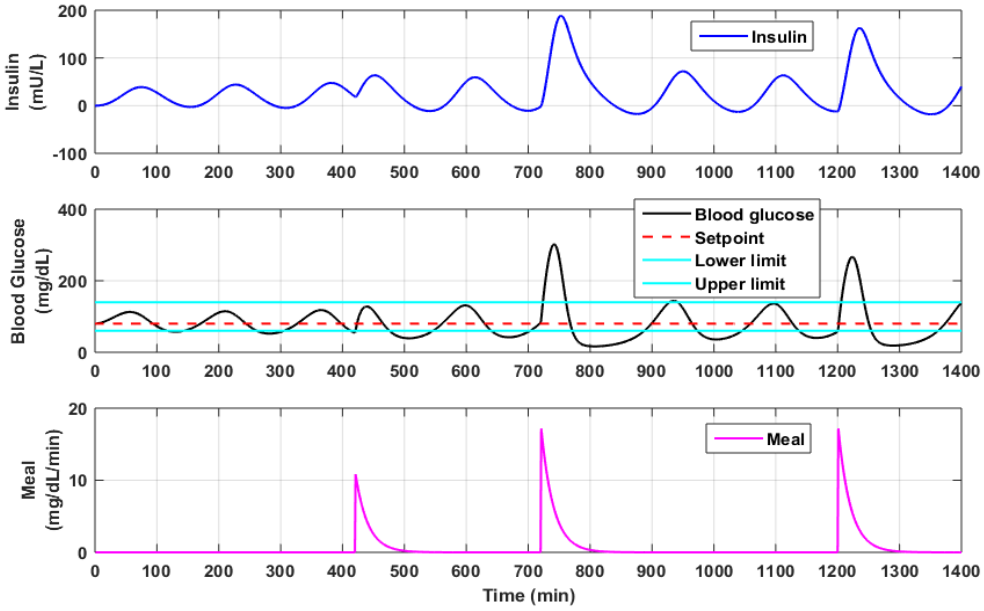

Fig 6 (a) Results for PM = 45° and ω_c = 0.5 rad/s.

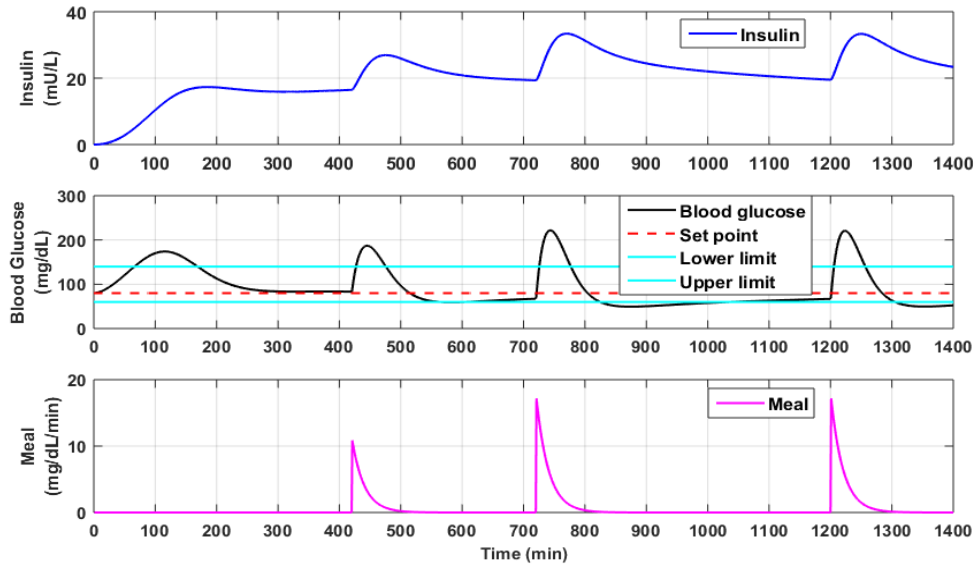

Fig 6 (b) Results for PM = 45° and ω_c = 0.1 rad/s

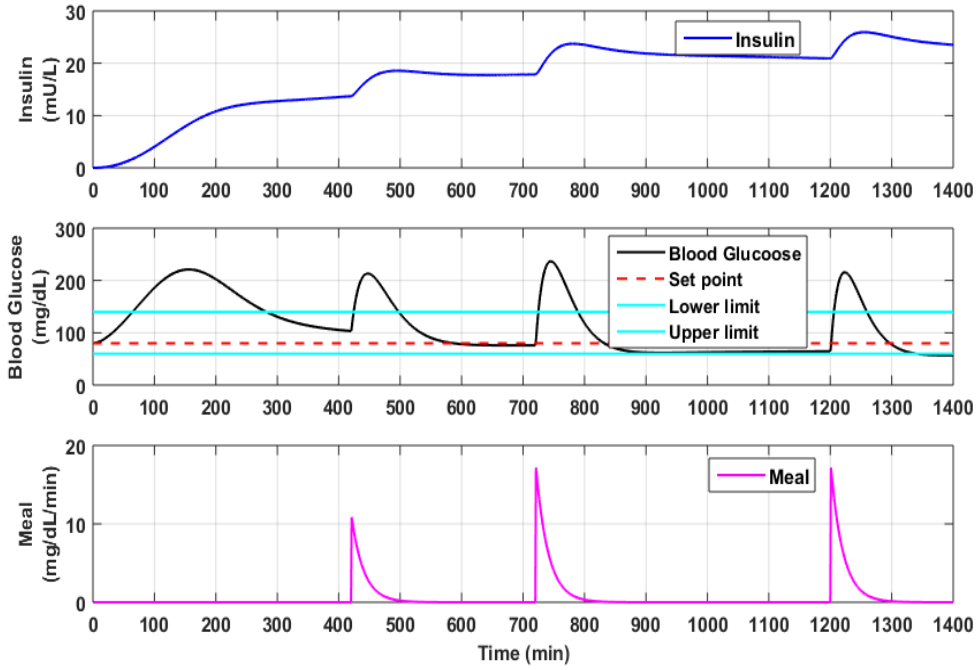

Fig 6(c) Results for PM = 45° and ω_c = 0.05 rad/s.

5.3.2 Simulation results for phase margin =60°, different values of gain cross over frequency.

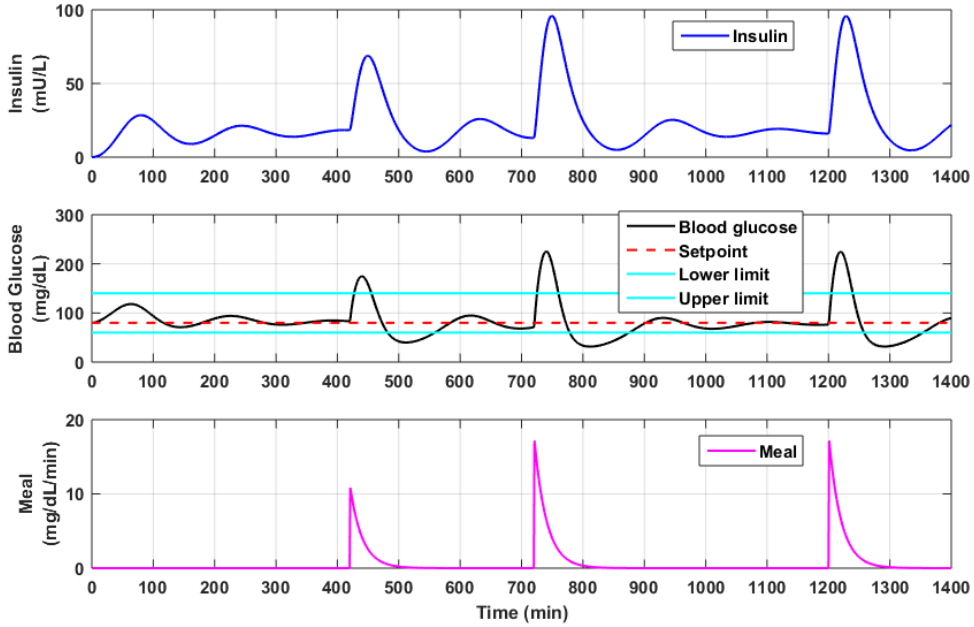

Fig 6(d) Results for PM = 60° and ω_c = 0.5 rad/s.

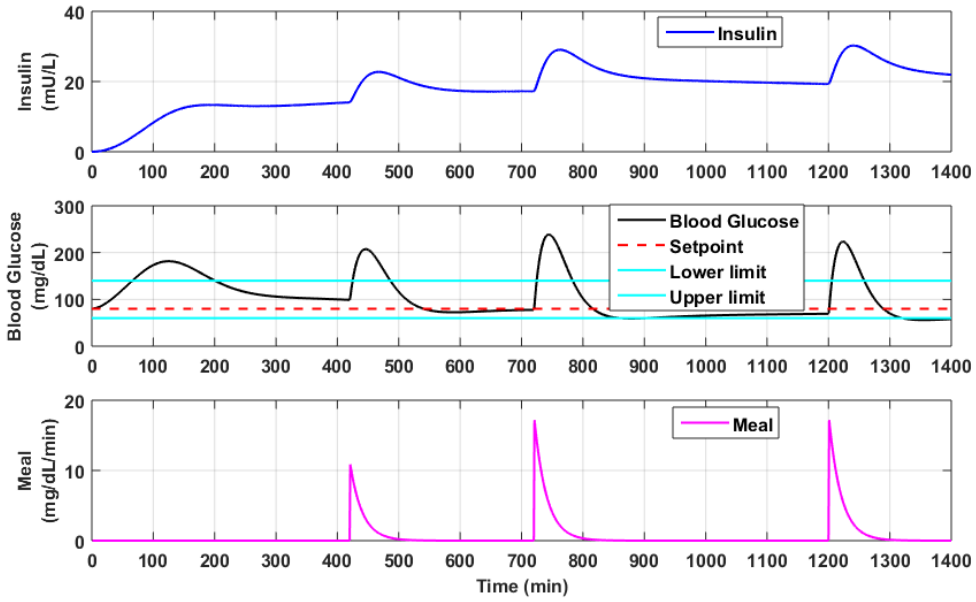

Fig 6 (f) Results for PM = 60° and ω_c = 0.1 rad/s.

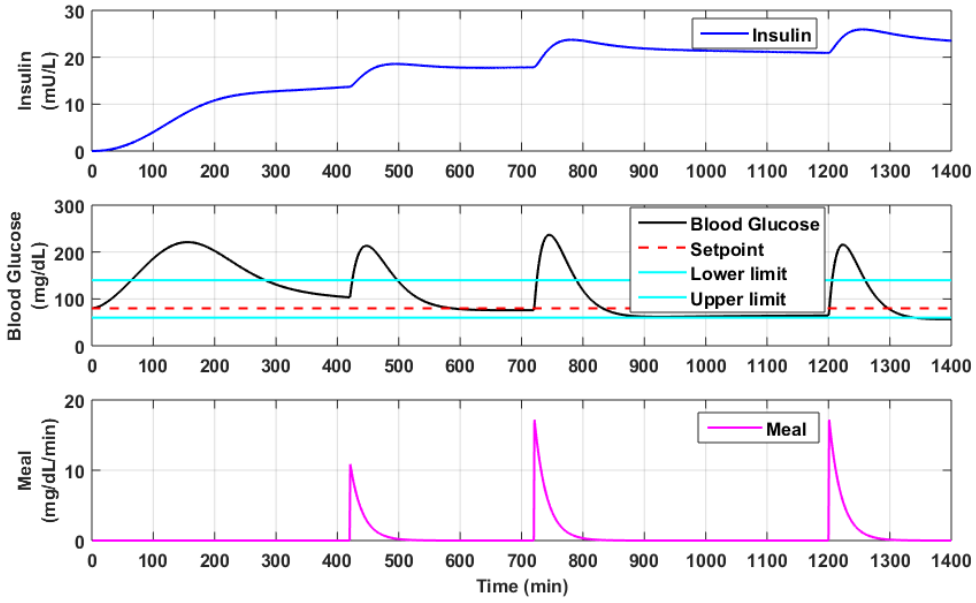

Fig 6 (g) Results for PM = 60° and ω_c = 0.05 rad/s.

5.3.3 Discussions

The simulations were done for phase margin ranging from 45 to 60 degrees in () for different values gain crossover frequency starting from 0.5 and then reducing it as in in Fig. 6(a)-(d). It was observed that when for a particular value of phase margin, gain cross over frequency was decreased from 0.5 to 0.05, there was an overall good glycaemic control. However, an increase

in insulin dose (controller output) after every each disturbance was observed, which may not be a good idea to implement owing to the fact that over delivery of drug may cause other side effects.

Chapter 6

Conclusion and Future Scope

6.1 Conclusion

In the proposed work, a new area of biomedical control systems- “Artificial pancreas system” is studied. Various mathematical models that have been developed in order to understand the physiology of the gluco-regulatory system in the body have been reviewed. On the basis of the mathematical models, existing control approaches to automate the delivery of insulin (especially for T1DM patients) are also presented. One of the major concern in the patients for using artificial pancreas is cases of hypoglycaemia where blood glucose to go below prescribed limit. With an aim to solve this problem an IMC based PI controller is designed for BMM model using identified linear model. The results obtained are further compared with existing P and PD controller and it is observed that the response of the proposed controller is able to provide desired results faster and set point tracking is better. Further as a case study, an IMC based fractional order PI controller is designed in order to check for any improvisation to integer order type. However, there was a continuous increase in insulin dosage following meal, which may be because of over-estimation of comparator output (error). Hence it is concluded that IMC based PI controller was effectively able to regulate blood glucose in due course of time, just as healthy pancreas would. Lastly, the proposed controller could be beneficial from practical implementation viewpoint as the PI controller is easy to implement on analog or digital hardware platform and it is free from derivative component which actually causes the noise amplification.

6.2 Future Scope

In actual implementation various factors like glucose sensor delay, delay in insulin absorption and constraints on various input and output variables may be required for a more realistic approach. All these factors would greatly affect the performance of the controller. A glucose sensor can be attached to the body and a mobile application can be developed so that controller may be embedded into the system to provide insulin dosage and over all glucose profile of the patient throughout the day. For this a simple IMC framework may not be at par and would needed to be coupled with more advance control schemes that can effectively achieve the desired target. Therefore possible future directions would involve incorporating sensor noise, sensor delay, delay in insulin absorption and accurate mathematical models that consider other factors such as exercise, stress, etc. to account for more realistic approach.

List of Publications

[1] S. Bhonsle and S. Saxena, “A review on control relevant glucose-insulin dynamics models and control relevant strategies,” *Journal of Systems and Control Engineering.* [Acceptance date: 23 Aug. 2019, Manuscript ID: JSCE-19-0180, DOI: 10.1177/0123456789123456]

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