Performance Comparison of Blood Glucose Controllers for Diabetic Patients

A.P. Adedigba
Department of Mechatronics Engineering
Federal University of Technology Minna, Nigeria

A.R. Zubair
Dept. of Electrical and Electronic Engineering
University of Ibadan, Ibadan, Nigeria

ABSTRACT
Diabetes remains a significant health problem that demands serious attention and costly to maintain in the western world and developing countries adopting western lifestyles and diets. Since the development of insulin in the 1920s, there have been myriad problems in developing suitable technology for optimal administration of correct dosage to maintain normoglycaemic state in both type 1 and type 2 diabetic patients. A promising direction is the development of artificial pancreas (AP), a control engineering approach that mimics the pharmacokinetic counterbalancing action of the pancreas in producing optimal insulin and glucagon for blood glucose regulation. However, the optimal controller design to properly handle postprandial disturbances has been a significant challenge in AP design. Although there is a plethora of controller design techniques in the literature, there is no generally agreed benchmark criteria for comparing these controllers. Therefore, in this paper, an experimental testbed where the popular control algorithms can be compared and their response can be studied is proposed. This was done by simulating a virtual patient using a well-designed mathematical model. Using the testbed, the performance of three controllers was studied and rich insight was gleaned from these controllers' behaviour onhow they handled the postprandial disturbances.

General Terms
Control theory, Controller design, Mathematical modelling, Diabetes, Biomedical engineering

Keywords
Insulin; Blood glucose regulation; Bergman minimal model; Dalla Mann glucose model; Model Predictive Controller; PID controller; Sliding Mode Controller

1. INTRODUCTION
Diabetes, also known as diabetes mellitus is one of the most widely spread disease. According to International Diabetes Federation, approximately 425 million people (8.8% of the world population) aged between 20 and 79 years suffered diabetes in 2017 and this number is expected to grow by 148% in the year 2045 [1]. Maintenance of diabetes is expensive, about $727 billion account for total healthcare expenditure for diabetes globally [1]. Although accurate data is unavailable for Africa, the estimated number of people suffering from diabetes in Africa is 16 million and expected to increase by 156% in 2045 [1]. In Nigeria, it is estimated that about 1.7 million adults suffered diabetes. Diabetes is a chronic disease [2].In 2019, an estimate of 1.5 million deaths were directly caused by diabetes [1].

Diabetes disease occurs when the blood glucose level increases because the body cannot produce any or enough hormone insulin or make adequate use of the insulin available in the body. In human body, the pancreas is responsible for the delicate balancing of blood glucose level by producing and releasing the counteracting hormones insulin and glucagon [3]. The glucagon hormone, produced in the alpha cells of the pancreas increases the blood glucose while insulin hormone, produced in the beta cells of the pancreas decreases the blood glucose level. In a healthy individual the counteracting work of insulin and glucagon stabilizes the blood glucose concentration within the physiological range of 65 to 110 mmol/L [3].

Insulin is a very important hormone; it transports glucose from the bloodstream into peripheral cells where glucose is converted to adenosine triphosphate (ATP) which is the cell's energy [4]. When the beta cells produce insufficient insulin or when cells' sensitivity to insulin falls, it leads to high concentration of glucose in the blood stream, a condition known as hyperglycaemia. Hyperglycaemia occurs when blood glucose exceeds 120mmol/L and if left unchecked over a long period, the excess blood glucose can cause serious damage to various body organs leading to dysfunction of such organs and fatal health complications such as cardiovascular diseases, neuropathy, nephropathy, and retinopathy [4].

On the other hand, hypoglycaemia occurs when the body lacks sufficient glucose to carry out its normal function. This results when the fasting glucose level falls below 60mmol/L. This could result from insufficient production of glucagon in the alpha cells or poor healthy lifestyle. When left unchecked for a long period, hypoglycaemia can lead to diabetes-induced coma and eventual death.

Diabetes remains a major health problem that demands serious attention and costly to maintain both in western world and developing countries which are adopting western lifestyle and diet [1]. Since the development of insulin in the 1920s, there have been myriad of problems in developing suitable technology for optimal administration of correct dosage to maintain normoglycaemic state in both type 1 diabetic mellitus(T1DM) and type 2 diabetic mellitus(T2DM) patients. Such developed techniques range from multiple daily insulin injection, nasal inhalations and enzymatic supplementation; however, each comes with its associated challenges [5]. A promising direction is the development of artificial pancreas (AP), a control engineering approach which mimic the pharmacokinetic counterbalancing action of pancreas in producing optimal insulin and glucagon for blood glucose regulation.

AP is a closed-loop control technique, a miniaturized automated insulin delivery system which consists of one or multiple continuous Blood Glucose (BG) sensor, a mechanical insulin pump (or insulin injecting device) and a controller. The sensor (or sensors) which continuously measure the value of BG is fed into the controller; the controller estimates the optimal insulin injection rate and controls the insulin pump to supply it to the blood stream of the patient [6].

Although AP technology has witnessed many advancements, it still faces challenges of sensor delays and inaccurate insulin delivery especially when the patient takes meal (due to the mathematical model employed), this causes the BG to rise quickly. A speedy response to this will cause the system to oscillate, hence, results in unstable and erratic behaviour of the system. A slow response controller design allows this disturbance to wear off before taking action; however, this cannot provide the required attenuation of postprandial glucose spikes [7]. Thus, the design of AP is to find an optimal controller in terms of speedy time response, which will guarantee stability of the system.

There is plethora of controller design techniques in the literature, however, there is no generally agreed benchmark criteria of comparing these controllers. Although, there exist control design criteria such as settling time, percentage overshoot, and rising time, the criteria for regulating a biological system are more complex than these.

Therefore, in this paper, an experimental workbench where the popular control algorithms can be compared and their response could be studied is proposed. This was done by simulating a virtual patient using a well-designed mathematical model. The proposed system can lend a rich insight into the behaviour of controllers in different situations in a real patient.

The rest of this paper is organized as follows.The review of literature is presented in section 2 followed by the design of mathematical model for the simulation of virtual patient in section 3.In section 4, the simulation of virtual patient is presented. The design of three controllers whose performance are to be compared is presented in section 5followed by the simulation results in section 6.

2. REVIEW OF LITERATURE

In this section, a concise review of literature is presented. The review is focused on the Proportional Integral Derivative(PID) controller and the Model Predictive Control (MPC) controllers. For MPC controllers, the mathematical model as well as optimization technique are reviewed. Again, it is difficult to compare the performance of these controllers since there is no general benchmark.However, the review presents a theoretical background for readers.

A fuzzy logic based PID control system for regulation of BG in diabetic patients was proposed in [8]. The model consists of single-glucose compartment in which patient insulin is assumed to act through a remote compartment to influence net glucose uptake. The inflow of glucose and the infused exogenous insulin are modelled using nonlinear differential equations. Plasma glucose concentration and its rate of change serve as inputs to the Fuzzy Logic Controller (FLC) while insulin infusion rate is the output [8].

Similarly, a fuzzy logic based active insulin infusion closed-loop controller was developed in [9] based on Bergman mathematical model. A Mamdani Fuzzy logic expert system was used to tune the mathematical model by designing linguistic rules to set the output of the model. The controller's ability to handle multiple meal disturbances was accessed and was found to perform satisfactorily.

Motivated by Bergman model, Parker*et. al.*developed a blood glucose regulation controller where all the body compartments capable of being affected by diabetes was modelled using Linear Predictive Model which used internal parameters based on past inputs to predict future output values [10]. The numerical estimate of the model was carried out using Kalman Filtering algorithm. The simulation results were compared with internal model controller and non-linear model estimated using first-order differential equation plus time-delay [10].

A mathematical model for accurate capturing of the complex dynamics of BG time series observed in real world measurement using fractional calculus concepts was presented in [11]. A time dependent fractional model of BG dynamics was employed to capture the BG characteristics using a real-world measurement from a public database. The control algorithm was obtained by formulating an average glycaemic risk index as cost function. Thus, the controller was tasked with the goal of finding the best amount of insulin that minimize average glycaemic risk. To measure the performance of the model, the distribution of difference of risk index between the predicted and actual measured data was observed [11].

A hybrid BGLevel controller based on Palumbo model was proposed in [12]. The Palumbo delayed model was hybridized with Fuzzy logic rules for setting the output of the controller. Genetic algorithm was used to select parameters for the model. The result shows superiority of the hybridized model over using pure Palumbo delayed model and Palumbo delayed model with fuzzy logic [12]. Palumbo nonlinear delay model serves as the mathematical model employed. The inputs to the model are the rate of change of BG and the impaired BG with reference glucose. A Mamdani Fuzzy logic controller was used to speed up the setting time of the model. Genetic Algorithm was used for optimal model parameter selection.

The control of blood glucose level in diabetic patient using predictive controller and delay differential equation was presented in [13]. The model takes the quantity of glucose intake (from food) as input to model the glucose-dependent insulin secretion; insulin-independent glucose consumption by the brain and nerve cells; glucose-dependent insulin consumption by muscle cells and fat; and glucose production controlled by insulin concentration. To ensure the stability of the controller, the model was subjected to constraints to form an objective function which was optimized using Genetic Algorithm [13].

3. MATHEMATICAL MODEL FOR BLOOD GLUCOSE REGULATION

The blood glucose regulation process starts from food intake. During food ingestion, the mass of glucose in the food increases the blood glucose concentration such that it tends to result in hyperglycaemia. The hormone called insulin is released from the beta-cell of the pancreas which instructed the remote compartments to take up excess glucose from the blood and store it up for later use as illustrated in Figure 1. The continual removal of glucose will eventually result in hypoglycaemia, which is prevented by the release of hormone called glucagon from the alpha-cell of the pancreas. The glucagon's effect is to inhibit the production of insulin or causes glucose to be released from storage when the plasma glucose concentration is critically low.

In type 1 diabetic mellitus(T1DM) patients, the beta-cell has been damaged and could not produce adequate insulin to regulate the excess plasma glucose.In type 2 diabetic mellitus(T2DM) patients, the remote compartment cells have developed a form of resistance to insulin such that the excess plasma glucose is not absorbed.

Hence, to augment the performance of insulin in glucose regulation, it is necessary to model the complete interaction of glucose and insulin in the body. The glucose dynamics was modelled to provide information on how glucose is released from the meal, how it increases the plasma glucose

concentration, how glucose is absorbed and utilized in the remote compartment, and how glucose is released from storage via the action of glucagon. Furthermore, for diabetic patients, insulin infusion was modelled to reflect the behaviour of long-acting and short-acting insulin, as well as other effects arising from insulin injection.

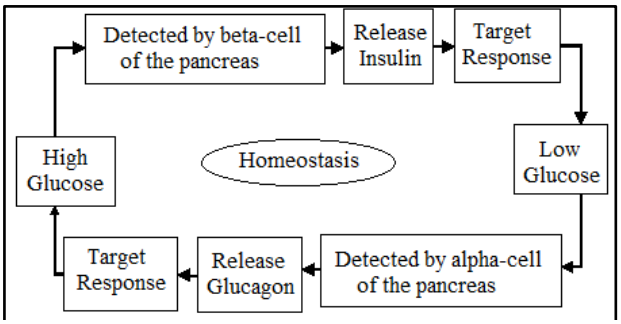

Figure 1: Glucose Homeostasis as a Closed-loop control system

In this work, the Bergman Minimal Model [14] was used to simulate the dynamics of the glucose regulatory system.The plasma insulin levels arising from subcutaneous insulin infusion was simulated using Berger and Rodbard method[15]as modified by Østerberg *et al.* in [16]. Finally, the effect of meals on plasma glucose concentration was simulated using an aspect of Dalla Man model [18].

3.1 Modelling of Glucose Dynamics

Bergman Minimal model took a compartmental approach in modelling the glucose regulatory system which makes it easy to understand, decoupled and reassembled for modifications and other research purposes. This dynamic is exploited in this work. The glucose compartment and the effect of glucose on remote compartment is given by Bergman as:

$$\dot{G} = -p_1(G - G_b) - S_i X G + \frac{f k_{abs}}{V_G} G_{gut} \quad (1)$$

$$\dot{X} = -p_2(X - I) \quad (2)$$

$$\dot{I} = -\eta[I - I_b] + \frac{1}{V} u(t) \quad (3)$$

Where $\dot{G}$ is the rate of change of plasma glucose concentration; p_1 is a patient-specific parameter that specify glucose effectiveness ($\frac{1}{p_1}$,reciprocal of p_1, is the time constant for the speed at which plasma glucose returns to equilibrium position in the absence of insulin); p_2 is called fractional rate of remote insulin clearance which measures the effectiveness of insulin in the remote compartment; G is the plasma glucose concentration; G_b is the basal or steady-state plasma glucose concentration (the basal value is different for both TIDM and T2DM, its value indicates the patient's tendency to hyperglycaemia);S_i is the measure of insulin effectiveness; X is the effect of insulin action on remote compartments; f is the fraction of carbohydrates in meal available for absorption from the gut; k_{abs} is a parameter specifying the rate of absorption of carbohydrates from the gut into the bloodstream; V_G is the volume of plasma glucose distribution; G_{gut} is the mass of carbohydrates in the gut; and I is the plasma insulin concentration.

In summary, equations (1) and (2) modelled the glucose absorption from the food into the bloodstream and the effect of insulin released in the beta-cells on the remote compartment which leads to the rate of disappearance of glucose. Next, the modelling of insulin infusion and how it affects glucose utilization and plasma glucose regulation is presented.

3.2 Modelling of Insulin infusion

Diabetic patients depend on insulin, hence, designing a controller for regulation of glucose concentration for them requires modelling of insulin infusion. Insulin administration to human patients has been extensively studied with intent of modelling the pharmacokinetics of insulin drug so as to administer the drug within its pharmacodynamics. In the development of blood glucose controller, modelling of insulin is very important.

Berger and Rodbard [15] insulin model serves as the base insulin model in this work. The model assumes that the absorption profile of insulin by the body is dose-dependent and its elimination from a central compartment follows a first-order kinetics. The Berger and Rodbardinsulin model modified by Østerberg is illustrated in Figure 2 and is given as:

$$\dot{I} = \frac{s t^{s-1} T_{50}^s}{(T_{50}^s + t^s)^2} I_d - k_e I \quad (4)$$

Where$I$ is the concentration of exogenous insulin available inthe plasma; $\dot{I}$ is the rate of change of the concentration of exogenous insulin available inthe plasma; s is the unit-less constant that describes the sigmoidicity (nonlinearity) observed in the time course of the insulin absorption, I_d is the subcutaneous injected insulin dose; k_e is the first-order elimination constant; and$T_{50}$is the absorption time.

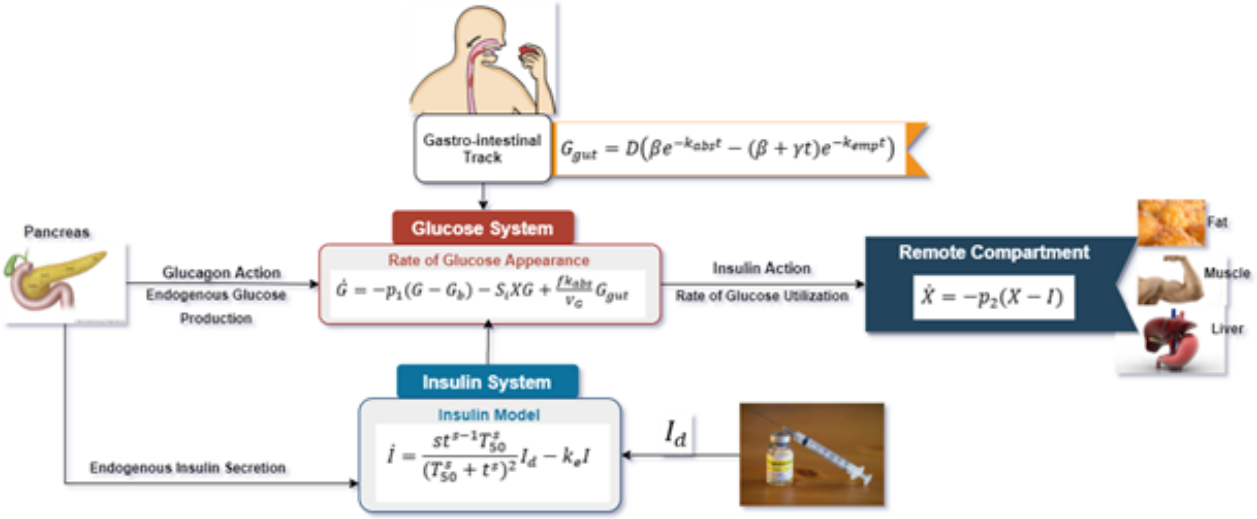

Figure 2: Summary of the mathematical model for glucose homeostasis

The model includes two parameters which describes the time constant specifying the time required for 50% of the insulin dose to be absorbed (T_{50}):I_d, the subcutaneous injected insulin doseand a, the dose dependency of the absorption time. Equation (5) describes the absorption time in term of these two parameters. However, according to Østerberg *et al.* [16], the second parameter was found to be uncorrelated with the practical insulin dose.

$$T_{50} = a \cdot I_d \tag{5}$$

It can be easily verified that this model, equation (4), is much better than Bergman's approach of modelling the insulin infusion rate in equation (3). Bergman modelled insulin infusion rate simply as a fractional difference between the basal level of plasma insulin and its distribution, without accounting for the pharmacokinetics of the insulin dose itself. Hence, equation (4) is preferred over equation (3).

3.3 Modelling of Meal effect on Glucose Concentration

The rate of appearance of glucose is modelled to describe the transition of glucose from meal through the stomach and intestine. By assuming that the stomach consists of two compartments (one for solid food and one for triturated phase)and thatthe gut has a single compartment, Dalla Man [18] presented a model of glucose rate of appearance which is employed in this work.The two compartments of the stomach which consists of the solid and liquid (triturated phase) is modelled as:

$$q_{sto} = q_{sto\,1} + q_{sto\,2} \tag{6}$$

where $q_{sto\,1}$ represents the glucose in the solid compartment and $q_{sto\,2}$represents the glucose appearance in the liquid compartment. These are given as:

$$\dot{q}_{sto\,1} = u - k_{emp}\, q_{sto\,1} \tag{7}$$

$$\dot{q}_{sto\,2} = k_{emp}\,(q_{sto\,1} - q_{sto\,2}) \tag{8}$$

Similarly, the rate of appearance of glucose in the intestine is given as

$$\dot{G}_{gut} = k_{emp}\, q_{sto\,2} - k_{abs}\, G_{gut} \tag{9}$$

$$G_{gut} = D\left(\beta e^{-k_{abs}\,t} - (\beta + \gamma t) e^{-k_{emp}\,t}\right) \tag{10}$$

where

$$\beta = \frac{k_{emp}^2}{(k_{emp} - k_{abs})^2} \tag{11}$$

and

$$\gamma = \frac{k_{emp}^2}{(k_{emp} - k_{abs})} \tag{12}$$

The parameters are defined as follows. u is the meal input, usually modelled as time-impulse function; D is the mass of carbohydrate in the meal; k_{emp} is a constant specifying the rate of gastric emptying; similarly, k_{abs} is the rate of absorption of carbohydrate from the gut.

Most research works based on Bergman Minimal model and its variants modelled food intake as a disturbance to the system. However, in this work, meal serves as input to the system.This is close to real-life situation where meal and insulin are inputs to the gluco-regulation system for diabetic patients. Hence, in this work, u, the meal input, is modelled as food and snacks, given as:

$$u = \begin{cases} De^{Dt}\sin(\omega t + \phi), food \\ \frac{D}{5}\sin\left(\frac{1}{2}\omega t\right), snacks \end{cases} \tag{13}$$

where D is the mass of carbohydrate in the meal, ω is the frequency and ϕ is the phase angle. In summary, the developed mathematical model is presented using state space approach as given by equations (14) and (15).

4. DEVELOPMENT OF VIRTUAL PATIENT AND SIMULATION

The development of virtual diabetic patients and the simulation of his day-to-day activities are presented in this section. The aim is to see how the controllers are able to regulate the glucose spikes caused by food ingestion.

The equations (14) and (15) represent the patient in the state-space domain. All states were initialized according to values reported in the literature [19]. The initialization is given in Table 1.

Table 1. Initial values of the model variables

Model state	Symbol	Initial value
Blood glucose (mg/dl)	G	76.2159
Insulin in the remote compartment	X	33.3333
Plasma Insulin	I	33.3333
Rate of glucose appearance in solid phase	$q_{sto\,1}$	16.6667
Rate of glucose appearance in liquid phase	$q_{sto\,2}$	16.6667
Glucose concentration in the gut	G_{gut}	250.0000

The simulation runs on a twenty-four-hour basis starting from 12:00 midnight. The virtual patient is assumed to fast overnight, since the human patient will be sleeping by then, no glucose is ingested into the body. Next, the virtual patient is assumed to wake up by 7:00am, took breakfast by 8:00am and snacks by 12:00 noon. The lunch is served by 2:00pm, by 3:00pm the virtual patient went for sporting activities which depletes the blood glucose level. Finally, the dinner is served by 7:00pm, and some snacks by 10pm before going to bed.

The scenario simulated here is common to average human being. Basically, on average, people take breakfast, snacks, lunch, dinner and dessert; all these activities increase glucose level. Conversely, people engage in activities that result in the depletion of glucose concentration.Such activities have been simulated as exercise.

5. DESIGN OF CONTROLLERS

In this section, the methods of regulating or stabilizing the plant using different controllers are discussed. The design of these controllers is presented.

$$\begin{bmatrix} \dot{G} \\ \dot{X} \\ \dot{I} \\ \dot{q}_{sto\,1} \\ \dot{q}_{sto\,2} \\ \dot{G}_{gut} \end{bmatrix} = \begin{bmatrix} -p_1(1-G_b) & -S_i G & 0 & 0 & 0 & \frac{f k_{abs}}{V_g} \\ 0 & -p_2 & -p_2 & 0 & 0 & 0 \\ 0 & 0 & -k_e & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{emp} & 0 & 0 \\ 0 & 0 & 0 & k_{emp} & -k_{emp} & 0 \\ 0 & 0 & 0 & 0 & k_{emp} & -k_{abs} \end{bmatrix} \begin{bmatrix} G \\ X \\ I \\ q_{sto\,1} \\ q_{sto\,2} \\ G_{gut} \end{bmatrix} + \begin{bmatrix} 0 & \frac{f}{V_g} \\ 0 & 0 \\ 1 & 0 \\ 1 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} [I \quad u] \tag{14}$$

$$y = [1 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0] \begin{bmatrix} G \\ X \\ I \\ q_{sto1} \\ q_{sto2} \\ G_{gut} \end{bmatrix} + [0 \quad 0] \begin{bmatrix} I \\ u \end{bmatrix} \tag{15}$$

5.1 PID Controller

The PID controllers contains three parameters: the proportional, the integral, and the derivative parameters. These parameters manipulate the system error in typical manners. These parameters can be used individually or collectively and in different combination. PID can be connected in series or parallel, this forms the structure of the PID controller [20] and is described as:

$$u(t) = K_c \left(e(t) + \frac{1}{T_i} \int_0^t e(t)dt + T_d \frac{de(t)}{dt} \right) \tag{16}$$

WhereK_c is the controller gain, T_i is the integral time and T_d is the derivative time. These parameters can be related to the PID parameters as

$$K_p = K_c \tag{17}$$

$$K_i = \frac{K_c}{T_i} \tag{18}$$

$$K_d = K_c T_d \tag{19}$$

Hence, each parameter can be tuned independently of the other and their combined effect can be summed up to produce the total controller action on the plant.

5.2 Sliding Mode Control

One of the major problems every control engineer face is the inability to accurately model the plant – there is always a discrepancy between the actual plant and the way it is modelled for controller design. The factors that contribute to these discrepancies include inaccurate plant parameter estimation, unmodelled plant dynamics and unknown external disturbances. Typically, all these factors can be accounted for by employing robust control methods. One of such robust control methodin the literature is the Sliding Mode Control (SMC) technique.

SMC is a nonlinear robust control technique which shows remarkable properties of accuracy, robustness to disturbances, easy of tuning, and ease of implementation. It is designed to drive a plant's state onto a particular surface in the state space called sliding surface where the error basically slides on the $e = 0$ surface. Once the states are driven to this surface, then the control action is such as to keep the states on the close neighbourhood of the sliding surface.

Recall that the plant here is a biological system representing the glucose regulation. This system is subjected to significant parameter uncertainties which varies from individual to individual. Furthermore, modelling of this system is still an active research area which means, the plant is subjected to substantial unmodelled plant dynamics. Lastly, the insulin action, the gastrointestinal action and the effects of insulin on the remote compartments are not linear. These show that the plant under consideration is similar to the ones SMC is particularly designed for.

SMC controller design involves the design of a sliding surface that satisfies control objective and the selection of a control law that ensures the switching surface is attractive to the system states, hence keeping the states close to the sliding surface.The sliding surface is the surface where perfect tracking is achieved;where $e = 0$. However, this is a function of the error and a number of its derivatives. That is:

$$\sigma = \sigma(e, \dot{e}, \ddot{e}, \dots, e^k) \tag{20}$$

Where σ is called the sliding surface.

Equation (20) means that σ must be vanishing to give rise to a stable differential equation which forces error, e to zero. Typically, according to Shtessel *et al.*[21], σ can be the sum of the error and its derivatives. σ is given by either equation (21) or equation (22) or generally as in equation (23).

$$\sigma = \dot{e} + c_0 e \tag{21}$$

$$\sigma = \ddot{e} + c_1 \dot{e} + c_0 e \tag{22}$$

$$\sigma = e^k + \sum_{i=0}^{k-1} c_i e^i \tag{23}$$

Where k is the number of derivatives and c_i is the coefficient of the derivatives.

Geometrically, $\sigma = 0$ corresponds to the surface of minimum error space. Hence, the state space, system specifications and the control law are forced onto this sliding surface. In this work, the sliding surface is selected to satisfy

$$\sigma = \left(\frac{d}{dt} + p \right)^k e \tag{24}$$

Where p is a positive parameter selected to reduce the system dynamic when in the sliding mode; its effect is not as significant compared to k which specifies the relative degree of flexibility of the surface. $k = 2$which defines a quadratic surface is selected.Hence, equation (21) becomes

$$\sigma = \ddot{e} + 2p\dot{e} + p^2 e \tag{25}$$

This surface presents a convex surface, with a unique minimum point. The next phase is to design a control law that drives and keep the system states on this sliding surface.

The control law is designed such that σ is driven to zero in finite time by the control input. The control law is based on state feedback given as:

$$u = -K\chi \tag{26}$$

where χ is the state vector on the sliding surface. Hence, the control law can be re-written as:

$$u = -Usign(\sigma) \tag{27}$$

However, since the control signal is discontinuous along the sliding surface at $\sigma = 0$, σ is replaced with a sign function and the control equation is derived as shown in equation (27).

Where

$$u = \begin{cases} -U & \sigma > 0 \\ U & \sigma < 0 \end{cases} \tag{28}$$

U is the control gain which is large enough to drive the error to zero.The chattering effect associated with SMC can be reduced by replacing the sign function in equation (27) with a sigmoid function as shown in equation (29) or by using the super twisting SMC algorithm presented as shown in equation (30).

$$u = -Usat(\sigma) = \frac{\sigma}{|\sigma| + \varepsilon} \tag{29}$$

$$u = -\lambda \sqrt{|\sigma|} sign(\sigma) + v \tag{30}$$

Where

$$\dot{v} = -Wsign(\sigma) \tag{31}$$

$$\lambda = \sqrt{U} \tag{32}$$

$$W = 1.1U \tag{33}$$

5.3 Model Predictive Control

The design objective of MPC presented here is similar to all other controllers considered in this project work which is to perform an accurate reference tracking. To do this, MPC is used to compute the trajectory of the future manipulated variable (or control action), u is to optimize the future behaviour of the plant y within a limited time window.

The optimization objective is to find the best control parameter vector δU that brings the predicted output as close to the desired set-point as possible within a prediction horizon. Given the set-point signal $r(k_i)$ at sample time k_i within a prediction horizon, the vector of set-point is defined as

$$R_s = \begin{bmatrix} r(k_i+1\,|k_i)^T \\ r(k_i+2\,|k_i)^T \\ \vdots \\ r\big(k_i+N_p\big|k_i\big)^T \end{bmatrix}. \quad (34)$$

Then the optimization cost function can be defined to reflect the control objective as

$$J = (R_S - Y)^T(R_S - Y) + \delta U^T \bar{R}\delta U \quad (35)$$

The first term is the quadratic error function linked to the objective of minimizing the error between the predicted output and the desired set-point while the second term is a penalty function that reflects the constrains placed on the size of δU where $\bar{R}$ is a diagonal matrix used to tune the penalty function. Y is given as:

$$Y = \Psi x(k_i) + \Phi\delta U \quad (36)$$

Where

$$\Psi = \begin{bmatrix} CA \\ CA^2 \\ CA^3 \\ \vdots \\ CA^{N_p} \end{bmatrix} \quad (37)$$

and

$$\Phi = \begin{bmatrix} CB & 0 & 0 & \dots & 0 \\ CAB & CB & 0 & \dots & 0 \\ CA^2B & CAB & CB & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ CA^{N_p-1}B & CA^{N_p-2}B & CA^{N_p-3}B & \dots & CA^{N_p-N_c-1}B \end{bmatrix} \quad (38)$$

The optimal δU that minimizes the cost function J is estimated as follows. First, substitute for Y in equation (34) to give J as:

$$\begin{aligned} J = {} & \big(R_S - \Psi x(k_i)\big)^T\big(R_S - \Psi x(k_i)\big) \\ & -2\delta U^T\Phi^T\big(R_S - \Psi x(k_i)\big) \\ & +\delta U^T(\Phi^T\Phi + \bar{R})\delta U \end{aligned} \quad (39)$$

Taking the partial derivative of cost function J with respect to control vector δU yields

$$U\frac{\partial J}{\partial \delta U} = -2\Phi^T\big(R_S - \Psi x(k_i)\big) + 2(\Phi^T\Phi + \bar{R})\delta U \quad (40)$$

The necessary condition for minimal J is obtained at $\frac{\partial J}{\partial \delta U} = 0$ from which δU can be solvedis given as:

$$\delta U = (\Phi^T\Phi + \bar{R})^{-1}\Phi^T\big(R_S - \Psi x(k_i)\big) \quad (41)$$

$(\Phi^T\Phi + \bar{R})^{-1} = \boldsymbol{\mathcal{H}}$ is called the Hessian matrix in most optimization textbooks. Hence,

$$\delta U = \boldsymbol{\mathcal{H}}\Phi^T\big(R_S - \Psi x(k_i)\big) \quad (42)$$

This gives the optimal δU that minimizes the cost function J provided that the Hessian matrix $\boldsymbol{\mathcal{H}}$exists. MPC heavily depends on state variable $x(k_i)$ sampled at instant k_i which can be measured or estimated via a state observer. The state estimation is constructed such that the error is used to improve the estimate at every time instant as in equation (43).

$$\hat{x}(k_i+1) = A\hat{x}(k_i) + B\delta u(k_i) + \kappa\big(y(k_i) - C\hat{x}(k_i)\big) \quad (43)$$

The term $\kappa\big(y(k_i) - C\hat{x}(k_i)\big)$ is the correction term where κ is the observer gain which can be calculated recursively using Kalman filter. If the iteration index is $i, where\ i = 0, 1, 2, \dots$, the observer gain is given as

$$\kappa = AP(i)C^T(\Sigma + CP(i)C^T)^{-1} \quad (44)$$

$$P(i+1) = A[P(i) - P(i)C^T(\Sigma + CP(i)C^T)^{-1}CP(i)]A^T + \Omega \quad (45)$$

Where Σ and Ω are the covariance matrices of the noise signal $\eta(k)$ and disturbance $\bar{\xi}(k)$.

Since our plant is completely observable, detectable and stabilizable, then the designed Kalman Filter satisfies the Algebraic Riccati-Equation:

$$\begin{aligned} P(\infty) = \Omega\ + A[P(\infty) \\ - P(\infty)C^T(\Sigma + P(\infty)C^T)^{-1}CP(\infty)]A^T \end{aligned} \quad (46)$$

and

$$\kappa(\infty) = AP(\infty)C^T(\Sigma + CP(\infty)C^T)^{-1} \quad (47)$$

The eigenvalues of $A - \kappa(\infty)C$ are inside the unit circle. They are stable.

Using the receding horizon control strategy, the implementation algorithm is presented in Algorithm 1.

ALGORITHM 1: MPC IMPLEMENTATION

***Input**: control input $u(t+k)$*
***Output**: predictive output $\hat{y}(t+1)$*
Initialise the control system
$\delta u(0) \leftarrow 0$
$\hat{x}(0) \leftarrow 0$
$y(0) \leftarrow 0$
Calculate the state estimate $\hat{x}(k+1)$.
Calculate the control signal
$u_p(k+1) = \bar{u} + \delta u(k)$
Where $\bar{u}$ is the measured input and u_p is the control input
Apply the receding horizon control law by applying only the current control action $u_p(1{:}p)$ to the process.
Calculate δU
Calculate $\delta u(k+1) = \delta U(1{:}p)$ i.e.using receding control scheme
Estimate the error and update $y(k+1)$
***Goto**step 2*
end

6. RESULTS AND DISCUSSION OF RESULTS

The mathematical model and controller design presented in the previous sectionswere implemented in MATLAB and Simulink. Simulink was used for the implementation of the mathematical model and controllers while MATLAB was used for backend functions, result generation, and plotting of graphs. The simulation results for various controllers are presented and compared in this section.

The PID controller was deployed to the virtual patient and simulated in a 24-hours scenario, the result is shown in Figure 3. The PID controller successfully regulated the blood glucose within the save region despite the heavy meal intake and strenuous exercise but at the expense of high dose of insulin injection at the moment of meal intake.

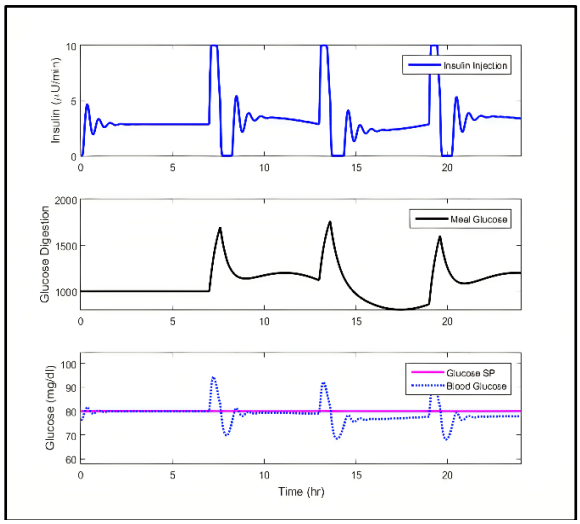

Figure 3: Simulation Result of the PID controller on the Virtual Patient

The SMC controller first identified the sliding mode of a system and then chose its control action so as to keep the system's state within the sliding region. The result of the SMC controller on the virtual patient is presented in Figure 4. While SMC does not stay on the 80g/mol set-point line like the PID, it minimised the glucose swing during the postprandial season. This was beautifully executed with minimal use of insulin injection compared to the PID.

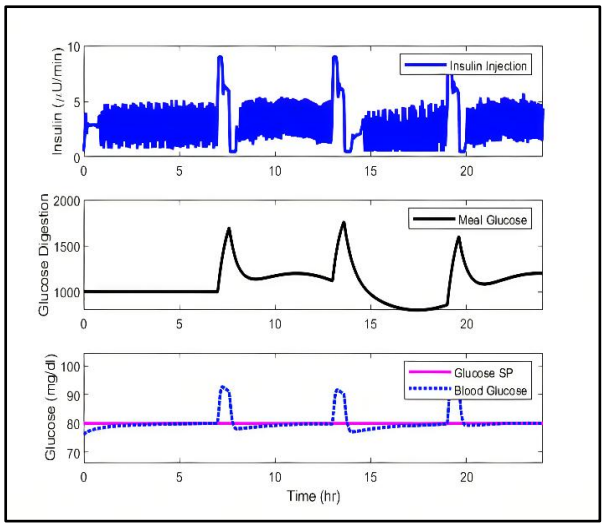

Figure 4: Simulation Result of the SMC controller on the Virtual Patient

The result of the MPC controller on the virtual patient over the 24-hours simulation is presented in Figure 5. The MPC controller was able to manage the postprandial disturbances with very little glucose swing. The MPC successfully achieved normoglycaemia, although with a higher amount of insulin injection compared to the SMC.

The three controllers are comparable in the way they handled the amount of insulin needed to achieve normoglycaemia and the glucose swing during the postprandial seasons.

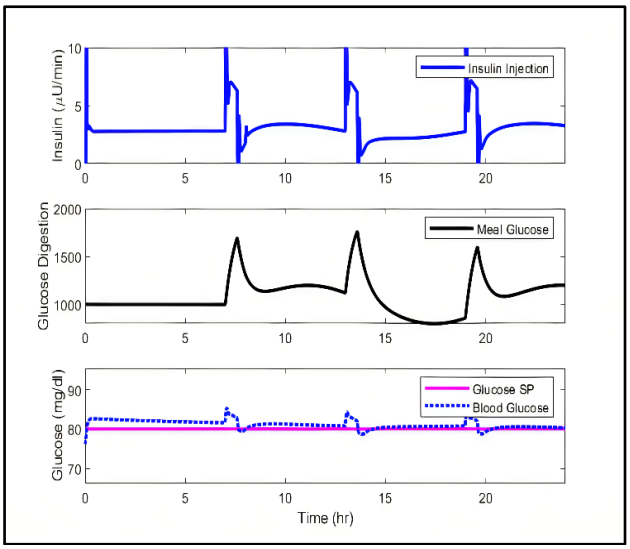

Figure 5: Simulation Result of MPC controller on the Virtual Patient

Figure 6 shows the comparison of glucose swing during the postprandial seasons of 8 am, 2pm, and 8pm when meals were served and when heavy work is done. As shown in Figure 6, the MPC achieved the minimal swing followed by the SMC with the PID controller starving the patient of glucose before asymptoticallysettling around the set-point. The MPC is quite stable to postprandial disturbances, due to the way it handles insulin injection as shown in Figure 7.

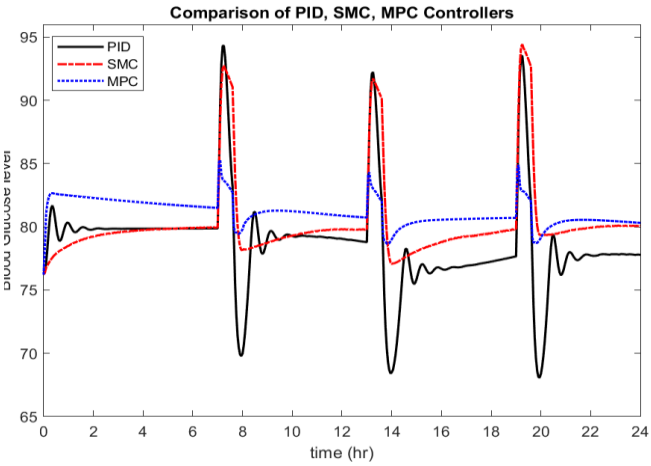

Figure 6: Comparison of Glucose swing during the postprandial seasons

Figure 7 shows the comparison of how each controller managed the amount of insulin injected into the virtual patients. This carries the cost implication of achieving the normoglycaemic glucose level. From Figure 5,the SMC injected 5-6U/min every 15min, this resulted in a reduced amount of injection needed to cancel out the postprandial effect.Both PID and MPC, on the other hand, injected the 3 U/min basal insulin and a large amount of insulin to cancel out the postprandial effect.At some point in the simulation, both the PID and the MPC could inject more than 10U/min insulin.However, this effect was reduced by enforcing a hard constrain on the controllers. Lastly, while the MPC gave a high insulin injection once, the PID persisted on this high dose for a considerable time (typically 30min). This resulted in the glucose level shooting below the desired set-point.

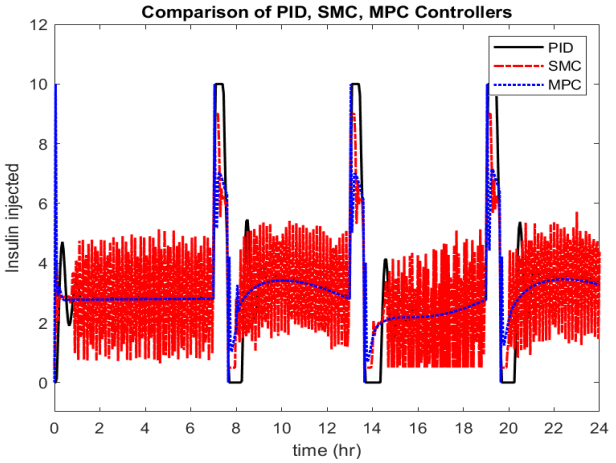

Figure 7: Comparison of the amount of insulin injected to the virtual patient to achieve normal glucose range

The results of the three popular controller designs have been presented. Intuitive results can be gleaned from the graphical illustration of the simulation which can be beneficial to Control Engineers, Biomedical Engineers, Medical practitioners, and the patients' caregivers.

7. CONCLUSION

Three controllers were compared, each with different actions and desired responses. The PID is a reactive controller which takes sufficient time to reach the desired set-point but could keep the patient within the normoglycaemic range. The MPC achieved the minimal postprandial glucose swing but with high insulin action. However, the SMC took a different approach, it cleverly raised the basal insulin dose which minimized the amount of insulin needed to keep the patient within the normoglycaemic region during postprandial glucose spikes.

In recent times, artificial intelligence-based controllers are being introduced to blood glucose regulation such as reinforcement learning (RL) algorithm. In future research, the testbed can be used to compare the RL controller with the PID, the MPC and the SMC.

8. REFERENCES

[1] IDF Diabetes Atlas, 8th editio. 2017.

[2] A. R. Zubair, C. O. Adebayo, E. U. Ebere-Dinnie and A. O. Coker, "Development of Biomedical Devices in Africa for Africa: A Blood Glucose Meter,"International Journal of Electrical and Electronic Science, vol. 2. no. 4, pp. 102-108, 2015.

[3] L. D. S. Nogueira, "The influence of quality of life in treatment adherence of diabetic patients: a systematic review *," vol. 49, no. 5, pp. 832–839, 2014.

[4] F. J. Doyle, L. M. Huyett, J. B. Lee, H. C. Zisser, and E. Dassau, "Closed-loop artificial pancreas systems: Engineering the algorithms," Diabetes Care, vol. 37, no. 5, pp. 1191–1197, 2014.

[5] P. Grant, "A new approach to diabetic control: Fuzzy logic and insulin pump technology," Med. Eng. Phys., vol. 29, no. 7, pp. 824–827, 2007.

[6] A. P. Adedigba, A. R. Zubair, A. M. Aibinu, S. A. Adeshina, O. Okubadejo, and T. A. Folorunso, "Towards the Development of Intelligent Insulin Injection Controller For Diabetic Patients," in 15th International Conference on Electronics Computer and Computation (ICECCO 2019), 2020, no. Icecco, pp. 248–253.

[7] C. Cobelli, E. Renard, and B. Kovatchev, "Artificial pancreas: Past, present, future," Diabetes, vol. 60, no. 11, pp. 2672–2682, 2011.

[8] M. S. Ibbini and M. A. Masadeh, "A fuzzy logic based closed-loop control system for blood glucose level regulation in diabetics," J. Med. Eng. Technol., vol. 29, no. 2, pp. 64–69, 2005.

[9] S. Yasini, M. B. Naghibi-Sistani, and A. Karimpour, "Active insulin infusion using fuzzy-based closed-loop control," Proc. 2008 3rd Int. Conf. Intell. Syst. Knowl. Eng. ISKE 2008, pp. 429–434, 2008.

[10] R. S. Parker, F. J. Doyle, and N. A. Peppas, "A model-based algorithm for blood glucose control in type I diabetic patients," IEEE Trans. Biomed. Eng., vol. 46, no. 2, pp. 148–157, 1999.

[11] M. Ghorbani and P. Bogdan, "Reducing risk of closed loop control of blood glucose in artificial pancreas using fractional calculus," 2014 36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBC 2014, pp. 4839–4842, 2014.

[12] V. Heydari, A. Karsaz, and R. Heydari, "A New Hybrid Approach on Blood Glucose Level Control Based on Palumbo Delayed Model," Proc. - 19th IEEE Int. Conf. Comput. Sci. Eng. 14th IEEE Int. Conf. Embed. Ubiquitous Comput. 15th Int. Symp. Distrib. Comput. Appl. to Business, Engi, pp. 361–366, 2017.

[13] M. E. Ashari, M. Zekri, and M. Askari, "Control of the blood glucose level in diabetic patient using predictive controller and delay differential equation," Conf. Proc. 2015 2nd Int. Conf. Knowledge-Based Eng. Innov. KBEI 2015, vol. 2, no. 4, pp. 422–427, 2016.

[14] R. N. Bergman, "Minimal model: Perspective from 2005," Horm. Res., vol. 64, no. SUPPL. 3, pp. 8–15, 2005.

[15] M. Berger and D. Rodbard, "Computer simulation of plasma insulin and glucose dynamics after subcutaneous insulin injection," Diabetes Care, vol. 12, no. 10, pp. 725–736, 1989.

[16] O. Østerberg, L. Erichsen, S. H. Ingwersen, A. Plum, H. E. Poulsen, and P. Vicini, "Pharmacokinetic and pharmacodynamic properties of insulin aspart and human insulin," J. Pharmacokinet. Pharmacodyn., vol. 30, no. 3, pp. 221–235, 2003.

[17] M. Schiavon, C. D. Man, Y. C. Kudva, and A. Basu, "Quantitative Estimation of Insulin Sensitivity in Type 1 Diabetic Subjects Wearing a Sensor- Augmented Insulin Pump," vol. 37, no. May, pp. 1216–1223, 2014.

[18] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Mixed meal simulation model of glucose-insulin system," in Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings, 2006, vol. 54, no. 10, pp. 307–310.

[19] R. Palma and T. F. Edgar, "The Effect of Parameter Uncertainty on a Novel Insulin Bolus Calculator," no. 2, pp. 822–826, 2010.

[20] R. P. Borase, D. K. Maghade, S. Y. Sondkar, and S. N. Pawar, "A review of PID control, tuning methods and applications," International Journal of Dynamics and Control, no. June. Springer Berlin Heidelberg, 2020.

[21] Y. Shtessel, C. Edwards, L. Fridman, and A. Levant, Sliding Mode Control and Observation. New York: Springer Science Business Media, 2014.