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Towards the Development of Intelligent Insulin Injection Controller For Diabetic Patients

Adeyinka P. ADEDIGBA*, Abdul Razak ZUBAIR†, Abiodun M. AIBINU*, Steve A. ADESHINA ‡
Olumide Okubadejo §, and Taliha A. FOLORUNSO *
*Department of Mechatronics Engineering, Federal University of Technology, Minna, Nigeria
Email: adeyinka.adedigba@futminna.edu.ng
†University of Ibadan, Ibadan, Nigeria
‡ Nile University of Nigeria, Abuja
§Audionamix, Paris, France

***Abstract*—Diabetes Mellitus (DM) is a disease of the glucose-insulin regulatory system where the insulin producing beta-cells has been damaged thereby producing none to very little insulin leaving the body with no means of regulating glucose. DM has high socioeconomic costs because it needs long term monitoring and individual care to prevent or decrease complications. Uncontrolled or poorly controlled diabetes lead to evolution or development of microvascular and macrovascular complications. It has been shown that adequate or even tight glycaemic control can prevent or delay complications and finally can reduce these complications. One of this glycaemic control is insulin therapy, meanwhile, non-adherence to the therapy due to its sever pain is prevalent among patients. In this paper, a review of research efforts towards the development of automatic insulin injection from control engineering perspective is presented. The reviewed techniques are basically closed loop approach, which include PID controllers, Model Predictive Controllers and Adaptive Controller techniques using machine learning approaches.**

***Index Terms*—Adaptive Controller Technique, Artificial Intelligence, Bergman, Diabetes mellitus, Feedback control, Model Predictive Controller, Palumbo, PID controller, Reinforcement Learning.**

I. Introduction

Diabetes is a disorder where the pancreas produces insufficient insulin to match excess blood sugar in the body. Three most common diabetes include: Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM) and Hyperglycaemia in pregnancy. Diabetes mellitus is a disease of the glucose-insulin regulatory system [1] [2] where the insulin producing beta-cells has been damaged thereby producing none to very little insulin leaving the body with no means of regulating glucose in the blood stream as in the case of T1DM. T2DM is the condition when body has developed resistance to insulin.

Diabetes is a threat to health and human development especially in developing countries such as Nigeria and other African countries. Available information from International Diabetes Federation confirms that the prevalence of diabetes is increasing globally especially in African countries with about 10.4 million adults aged 20-79 years diagnosed of diabetics in 2007 contributing 3% to global diabetic prevalence [3]. This number grows to 15.5 million in 2017 representing 6% of global diabetic prevalence and approaching 40.7 million in 2045. In Nigeria, about 1.7 million adults live with diabetics while about 40.33 million diabetic related deaths were recorded in 2017 [4]. These statistics necessitate the need to explore various methods of reducing this alarming growth rate and the need for this research.

The pancreatic endocrine hormones insulin and glucagon are responsible for regulating the glucose concentration level in the blood as illustrated in Fig. 1. These hormones - glucagon and insulin , are secreted in α-cell and β-cell respectively, which are contained in the Langerhans islets in the pancreas. When the concentration level of blood glucose (BG) is high, the β-cells release insulin, which results in lowering the BG concentration level by inducing the liver and other cells (e.g. brain) to uptake the excess glucose and by inhibiting hepatic glucose production. When the BG level is low, the α-cells cells release glucagon, which results in increasing the BG level by acting on liver cells and causing them to release glucose into the blood [5] [6] [7] [8]. If a person's glucose concentration level is constantly out of the range (70–110 mg/dl), this person is considered to have BG problems known as dysglycaemia (hyperglycaemia or hypoglycaemia).

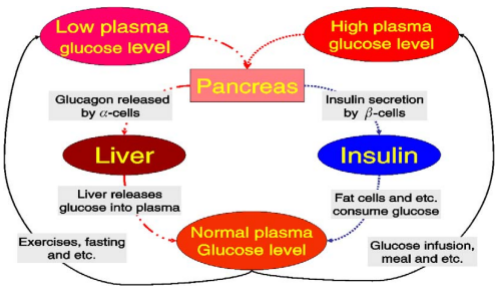

Fig. 1. Blood Glucose Level regulation [7]

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care to prevent or decrease complications [9]. Uncontrolled or poorly controlled diabetes, which cause dysglycaemia (hyperglycaemia or hypoglycaemia) lead to evolution or development of microvascular and macrovascular complications.

Microvascular and macrovascular disease are two forms of the long-term complications of diabetes. Microvascular disease includes neuropathy, retinopathy (which results in reduced vision and finally blindness), nephropathy (which causes renal failure and finally may require dialysis or kidney transplantation). Macrovascular disease includes heart disease. The most important concern in very young children is that hyperglycaemia or hypoglycaemia are related to neuro-cognitive impairments [10] [11]. It has been shown that adequate or even tight glycaemic control can prevent or delay complications and finally can reduce them [9]. One of this glycaemic control is insulin therapy. Insulin therapies have various routes such as subcutaneous, intramuscular, intravenous, intraperitoneal injections and inhaled insulin [12] [13]. Oral, gastrointestinal and transdermal routes are no longer recommended because the insulin could destroy the digestive tract [14]. Intravenous route has a little dead time, thus, it is not suitable for some patients [13].

Insulin therapy is a routine part of daily life for patients with T1DM and T2DM who are in constant need of insulin injection [15]. Despite advance in pharmacologic therapy of DM, drugs are mostly administered by subcutaneous injection. Historical trend shows that majority of insulin therapy patients are self-injected using vial, syringe or insulin pen; this trend continues to rise in many developed and developing countries around the world [15]. However, non-adherence to insulin therapy is prevalent among patients with DM. Researches associate this to factors such as severe pain and fear of using the injection, complications and difficulty in using injection, lifestyle burden and restrictive regiments [16].

Furthermore, complications associated with insulin subcutaneous injections include the following: bleeding, bruising, lipohypertrophy, lipoatrophy and idiosyncratic skin pigmentation [15] [17]. Lipohypertrophy is a critical complication of subcutaneous insulin administration that delays insulin absorption from the injection site and worsen BG control, necessitating increasing dose of insulin [15]. Lipohypertrophy can result in large oscillations in BG level with hypoglycaemic episodes followed by glucose spikes.

II. Introduction to Control Engineering Techniques for Blood Glucose Regulation

Generally, control techniques for Blood Glucose Regulation (BGR) systems fall into three categories namely: open and closed loop [17] [18]. In open-loop control techniques, the diabetologist injects an amount of insulin dose subcutaneously to the patient regularly, usually, three to four times a day, while monitoring the patient's conditions. This control technique has been automated and developed to what is known as insulin injection or insulin pen [17]. While this control technique is widely used due to its simplicity, it is not efficient, especially if the patient subjected to various variation in glucose concentration level [17] [18] [19] [20]. The hidden limitation placed on open-loop control technique (insulin pen or insulin injection) is that, unlike the physiological insulin release that takes place in the pancreas, the level of insulin in the blood is not dynamically matched to BG concentration in the insulin injection. Another limitation of open-loop control technique is that patients are required to live a considerable predictable lifestyle to allow efficient estimation of concentration level of insulin/glucose [21]. Thus, a glucose-responsive closed-loop insulin delivery system, which functions as continuous subcutaneous insulin infusion system, has been proposed to remove this limitation [17].

In closed-loop control techniques, the insulin is continuously delivered with online BG sensor that provides feedback loop to the controller. This closed-loop technique is called Artificial Pancreas (AP) [17]. AP is a miniaturized automated insulin delivery system which consists of one or multiple continuous BG sensor, a mechanical insulin pump (or insulin injecting device) and a controller (mathematical model of glucose-insulin regulatory system and the control algorithm based on the mathematical model) as shown in Fig. 2. 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 [22].

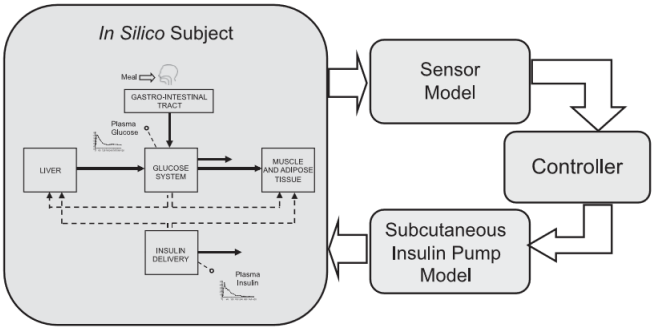

Fig. 2. Closed-loop Insulin Control Technique [23]

The success of AP depends largely on the accuracy of the mathematical model used to express BG dynamics in order to determine the best insulin injection rate to deliver at a time. Thus, it can be argued that model-based insulin injection has inherent limitation placed on them by the mathematical model used. Despite various researches conducted in the field of control engineering, we still lack efficient AP that can control the glycaemic levels [18] [22]. Although AP technology has witness many advancements, nevertheless, due to the mathematical model employed, it may be plagued with challenges of sensor delays and inaccurate insulin delivery especially when the patient takes meal which results in erratic BG spikes. A speedy response to this will cause the system to oscillate, hence, results in unstable and erratic behaviour of the system [23]. 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. Thus,

the design of AP is to find an optimal controller in terms of speedy time response, which will guarantee stability of the system against postprandial spikes.

III. Review of Recent Literature

The problem of closed-loop BG level regulation has been a subject of investigation for decades. Different controllers have been proposed by various researcher. In this section a review is presented under controller families such as Proportional Integral Derivative (PID) and Model Predictive Controllers (MPC). Following the success of machine learning techniques in solving engineering problems, a family of controller called adaptive controllers found in literature is also reviewed.

A. Proportional Integral Derivative (PID) controller

The simplest family of controllers designed for BGR is PID controllers [24] [25] [26]. The P-controller estimates the rate of insulin as a difference between measured BG level and a reference value; the I-controller acts to reduce the patient's insulin resistance by enhancing the P-controller insulin injection rate due to observed errors over a short time-window; and the D-controller introduces a correction factor to the P-controller by multiplying the derivative of the actual BG level with respect to the BG reference value and the derivative gain factor of the controller [18].

The general form of representing continuous-time PID algorithm uses insulin delivery rate (1) as a function of deviation of BG level from the desired set-point (2), as follows:

$$u(t) = u(t_0) + K_c e(t) + \tau_i \int e(t)dt + \tau_d \frac{de(t)}{dt} \quad (1)$$

$$e(t) = r(t) - y(t) \quad (2)$$

For the patient under Intensive Care Unit (ICU), $u(t)$ is the manipulated input (i.e. insulin delivery rate), $u(t_0)$ is the basal insulin infusion rate. $e(t)$ is the error, which measures the deviation of the measured BG level ($y(t)$) from the set-point ($r(t)$, the desired BG level). K_c, τ_i andτ_d is the proportional gain, integral gain and derivative gain respectively: these three parameters are tuned in a typical PID application.

On the other hand, the discretized PID controller algorithm is represented as:

$$u[n] = u[0] + k_c e[n] + \frac{\delta t}{\tau_i} \sum_{i=0}^{n} e[n] + \frac{\tau_d}{\delta t} \left(e[n] - e[n-1]\right) \quad (3)$$

Often time, PID controller algorithm for BGR is desired to be implemented in what is known as velocity form. This is obtained by subtracting (3) evaluated at time-step $n-1$ from (3) evaluated at time-step n to yield:

$$u[n] = u[n-1] + k_c[\zeta e[n] + \xi e[n-1] + \psi e[n-2]] \quad (4)$$

Where: $\zeta = (1 + \frac{\delta t}{\tau_i} + \frac{\tau_d}{\delta t}), \xi = (-1 - \frac{2\tau_d}{\delta t})$ and $\psi = \frac{\tau_d}{\delta t}$

In both (3) and (4), $u(n)$ is the current control action, $u[0]$ is the basal insulin infusion rate, $u[n-1]$ is the control action taken in the previous time-step. $e[n], e[n-1]$ and $e[n-2]$ is the error in current time-step, error in previous time-step and error the previous two time-steps respectively.

Thus, the PID estimates the control of required insulin delivery based on weighted sum of the PID terms in order to minimize the error and bring the system to desired BG level. However, despite the simplicity of design, PID is inherently a reactive controller which causes the system to oscillate especially during postprandial period [18] [27] [28]. More so, [29] observed that trying to control postprandial glucose level with PID results in life-threatening hyperglycaemia and hypoglycaemia.

The postprandial glucose spikes was associated with the use of integral action of the PID controller [30]. Thus [31] presents a modification to PID controller by considering the action of Proportional controller only. The resulting algorithm called Columnar Insulin Dosing (CID) is presented in (5) as follows:

$$u[n] = 0.8 - 0.02(100 - y[n]) \quad (5)$$

The glucose value used is an average over the past two samples, also known as two-point moving average filter.

Likewise, [32] presents a computerized control system for a surgical intensive care unit called Glucose Regulation for Intensive Care Patient (GRIP). GRIP is a gain-scheduled PID controller where the proportional gain is a function of average insulin infusion over the previous 4 hours. A four-point moving average filter was used to evaluate the glucose value. However, GRIP associated high derivative gain which makes the system to be highly unstable. A relatively stable version is presented in [30] which places a constrain on the derivative gain.

B. Model Predictive Controller

Another family of controller is called Model Predictive Controller (MPC), which attempts to model the patient's BG regulatory system with mathematical equations based on assumption of detailed knowledge of the physiology of the system under consideration. By treating BG regulatory system as model, the control problem can now be treated mathematically and optimal control strategy can be easily determined [29]. The basic approach to MPC is shown in Fig. 3 where the model is used to predict how the future Blood Glucose Concentration (BGC) level (the output) varies with perturbations in the current and future insulin infusion rates (current and future control moves). The objective of optimizer algorithm is then to find the best set of current and future insulin infusion rates that maintains the output (BGC level) within the set-point over the future prediction horizon [33].

Given the patient's glucose level, insulin delivery rate and food intake, MPC uses dynamic system model to predict glucose levels of the patient. It then estimates the appropriate insulin infusion rate by minimizing the difference between

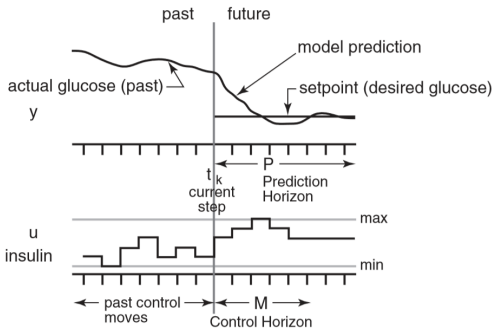

Fig. 3. Control Approach of Model Predictive Controller (MPC) [33]

model-predicted BGC level and target BGC level over the prediction horizon. This prediction horizon is usually chosen as the time in which the bulk of the effect is seen from the insulin dose used. By the mathematical model employed in the design of the MPC, it can incorporates a prediction of glucose level at different patient's metabolic conditions such as postprandial, quasi-steady state (overnight) and exercise; it can also introduce constraints to insulin delivery rate at the said conditions to prevent system oscillations as previously discussed [18] [23] [34]. Thus, the success of MPC depends on how accurate the physiological system under consideration is modeled mathematically. The more accurate the model, the more effective the control law [29].

1) Bergman Model: The most popular mathematical model is the Bergman's model proposed in [35] which describes the dynamic nonlinear interaction of glucose and insulin in an individual, it gains wide acceptability due to its minimum number of relevant parameters and capability to represent different physiological parameters. Equations (6), (7) and (8) represents the rate of disappearance of BG, the effect of insulin on remote compartment and the insulin concentration in the plasma respectively.

$$\frac{dg(t)}{dt} = p_1 g(t) - [g(t) - G_b]\, x(t) + p(t) \tag{6}$$

$$\frac{dx(t)}{dt} = -p_2 x(t) + p_3 i(t) \tag{7}$$

$$\frac{di(t)}{dt} = -\eta\,[i(t) - I_b] + \vartheta u(t) \tag{8}$$

Where $g(t)$ represents the deviation of BG from its basal value G_b, similarly, $i(t)$ is the deviation of plasma insulin concentration from its basal value I_b. $X(t)$ is the proportional concentration of insulin in a remote compartment. $p(t)$ and $u(t)$ represent the rate of exogenous glucose and insulin injection respectively, p_1, p_2, p_3 are model parameters describing the physiological dynamics of glucose and insulin interaction in an individual. Meanwhile, Bergman model is a nonlinear model, it can be linearized when operated in its equilibrium position by by setting the equations to zero. The linearized model is represented in a state space model as follows:

$$\begin{bmatrix} \dot{g(t)} \\ \dot{x(t)} \\ \dot{i(t)} \end{bmatrix} = \begin{bmatrix} -p_1 - x_e & -g_e - G_b & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -\eta \end{bmatrix} \begin{bmatrix} g(t) \\ x(t) \\ i(t) \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ \vartheta \end{bmatrix}$$

Using Bergman mathematical model, a fuzzy logic based closed-loop control system for regulation of BG in diabetic patients was proposed in [6]. The model consists of single-glucose compartment in which patient's insulin is assumed to act through a remote compartment to influence net glucose uptake. The inflow of glucose and the infused exogenous insulin are modeled using nonlinear Differential Equations (DE). Plasma glucose concentration and its rate of change serve as input to the Fuzzy Logic Controller (FLC) while insulin infusion rate is the output [6].

Similarly, a fuzzy logic based active insulin infusion closed-loop controller was developed in [7] 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.

Similar to Bergman model, the model presented in [9] was motivated by compartmental design diagram where all the body compartments capable of being affected by diabetes were modeled using Linear Predictive Model which used internal parameters based on past inputs to predict future output values. The numerical estimate of the model was carried out using Kalman Filtering algorithm. The simulation results was compared with internal model controller and non-linear model estimated using first-order DE plus time-delay.

A mathematical model for accurate capturing of the complex dynamics of BG timeseries observed in real world measurement using fractional calculus concepts was presented in [18]. 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 is 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 [18].

Although simple to implement, Bergman's model (and its variants) failed to account for the rate of insulin delivery to the blood, it only model glucose delivery. To accurately model BG regulatory system, both glucose and insulin production has to be accounted for. A nonlinear mathematical model of diabetes physiological system based on Delayed Differential Equation (DDE) was proposed by Palumbo [28]. Unlike Bergman, this model takes pancreatic insulin delivery rate into consideration, which makes it suitable for both T1DM and T2DM.

2) Palumbo Model: Palumbo model is a differential equation representing BG regulation. This model is favorable in the way it accounts for the interval between the time of BG spike

and when insulin injection is applied as time-delay function. The model is given as follows:

$$\frac{dG(t)}{dt} = -\kappa_{xgi} I(t) G(t) + \frac{T_{gh}}{\nu_g} \tag{9}$$

$$\frac{dI(t)}{dt} = -\kappa_{xi} I(t) + \frac{T_{iGmax}}{\nu_i} f\left(G(t-\tau_g)\right) + u(t) \tag{10}$$

$$f(G) = \frac{\left(\frac{G}{G^*}\right)^{\gamma}}{1 + \left(\frac{G}{G^*}\right)^{\gamma}} \tag{11}$$

Where $G(t)$ and $I(t)$ denotes the plasma glucose and insulin respectively. κ_{xgi} is the insulin-dependent rate of glucose uptake by the tissue, κ_{xi} is the insulin degradation constant. T_{gh} is the net balance between hepatic glucose output and the insulin independent zero-order glucose tissue uptake, T_{iGmax} is the maximum insulin secretion in the second phase, $\frac{T_{gh}}{\nu_g}$ is the net glucose production (usually a constant). ν_g and ν_i is the glucose and insulin distribution rate. Like Bergman model, this is also a nonlinear model, given as (11).

A hybrid BG controller based on Palumbo model was proposed in [10]. 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 [10]. Palumbo nonlinear delay model serves as the mathematical model employed. The input 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 [10].

Similar to Palumbo, Engelberghs predictive control model is based on DDE. 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. This model was used in [15] to control the BGL in diabetic patients. To ensure the stability of the controller, the model was subjected to constraints to form an objective function which was optimized using Genetic Algorithm (G.A) [15].

The aforementioned models and their associated controllers are limited by the accuracy of their mathematical assumptions. Furthermore, physiological makeup is different from one patient to another, thus, to achieve better performance, these differences must be put into consideration. One will have to design different MPC controller for each patient in order to minimize postprandial disturbances in minimum time.

C. Adaptive Controller Techniques

The adaptive controller techniques popularly consider the use of Artificial Neural Networks (ANN) and Reinforcement Learning (RL). These two techniques are based on pattern recognition instead of implication of a predefined hypothesis as in the case of MPC. Thus, using these techniques, physiological differences of individual patients will be automatically handled. More so, by learning directly from homeostasis information of the patients, this controller can perform regulation without impeding social activities of the patients.

The ANN considers interactions between variable, uses this interaction to find a pattern to define input-output relationship which is static in nature and ignores the glucose control as a dynamic response. Thus, it greatly over-fit without generalizing well on unforeseen scenarios.

Reinforcement Learning on the other hand, is based on the principle of interaction between a decision-making, self-learning agent (in this case, controller) and its environment (in this case, glucose homeostasis of the patient). The controller maps the state of its environment to a certain action (policy) which defines the response of the agent at each time step (e.g. increase or decrease insulin infusion rate). During training, the overall goal of this adaptive controller is to learn an optimal policy which yield maximum reward over time.

RL does not need a well-represented model (as in MPC) or labelled training data (as in ANN). After a learning procedure, the controller develops a strategy from experience to predict different unseen situations without complex mathematical specifications of the environment. Thus, RL is uniquely suited to system with delayed response such as subcutaneous glucose measurement with insulin injection where feedback can take up to hours.

For instance, RL was used in [22] to develop an adaptive BG controller. Palumbo mathematical model was used to define the controller's policy, SARSA method which is based on temporal difference technique was used to solve the model in a reinforcement learning way. In the end, the authors were able to control the insulin dosage to control BG level. Also, [1] solves BG control problems using RL. The agent's control policy was defined using H-infinity model which was minimized using dynamic programming (a RL approach). The controller has low settling time and high stability to tested postprandial disturbances.

IV. Conclusion

In this paper, a review of developed techniques towards full realization of automatic insulin injection has been presented. The review focused mainly on closed-loop techniques which are desirable due to their feedback path for quick error minimization. PID controllers due to its simplicity has been greatly desired by researchers. However, PID is inherently a reactive controller which causes the system to oscillate especially during postprandial period; furthermore, trying to control postprandial glucose level with PID results in life-threatening hyperglycaemia and hypoglycaemia. To improve PID performance, several techniques has been developed such as tuning PID with Fuzzy-Logic controllers, or minimizing error (postprandial spikes) with optimization techniques, development of Columnar Insulin Dosing (CID) and the gain-scheduled PID controller technique called GRIP. MPC

controllers are found to handle postprandial spikes better than PID controllers. By modelling patient's BG regulatory system with mathematical equations based on assumption of detailed knowledge of the physiological setup of the patients, MPC achieves superior performance. Although, the success of MPC depends largely on the mathematical model used, two most popular models are Bergman Minimal Model and Palumbo models. These models have been implemented and optimized using different methods in the literature with better and improved performances. Despite the several satisfactory results reported in literature, automatic insulin injection has not been fully accepted in clinical settings because of fundamental physiological differences in diabetic patients which cannot be fully accounted for in the mathematical models of MPC controllers. To account for these differences, researchers are now turning to Adaptive Controllers techniques based on machine learning methods such as artificial neural networks and reinforcement learning.

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