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PAPER

A Narrative Review of Control Strategies for Blood Glucose Regulation

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ABSTRACT

Effective blood glucose regulation is critical for managing type 1 diabetes mellitus (T1DM). This narrative review explores various control strategies for blood glucose regulation, incorporating simulations of the Bergman minimal model. We provide an in-depth review of both single and dual hormone systems, evaluating their respective advantages and limitations. The review focuses on the most widely adopted controllers, including proportional-integral-derivative (PID), model predictive control (MPC), and fuzzy logic controllers, highlighting their design principles and performances. Additionally, we discuss coordinated control strategies that integrate multiple controllers to enhance overall glucose regulation. Through this comprehensive analysis, we aim to identify the most effective control strategies for artificial pancreas systems, contributing to improved diabetes management.

KEYWORDS

diabetes, fuzzy-logic, glucose, insulin, model predictive control (MPC), Meal, proportional-integral-derivative (PID)

1 INTRODUCTION

Recent technological advancements offer enhanced preventive measures and medical assistance with minimal user intervention [1]. The pancreas, an organ located near the stomach that releases fluids and insulin to aid digestion, plays a crucial role in this process [2–5]. The pancreas's exocrine system manages food breakdown, while the endocrine system regulates blood glucose levels [6]. Insulin, a hormone produced by the pancreas, maintains glucose homeostasis in the blood, which is essential for the body's proper functioning [7]. In healthy individuals, overnight fasting glucose levels should range between 3.9 and 10 mmol/l, or 70 and 180 mg/dl [8]. For diabetics, blood glucose levels rise rapidly after meals, necessitating a control mechanism. In healthy individuals, this regulation typically occurs within 2–3 hours due to the presence of beta cells [9].

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Individuals with type 1 diabetes often experience hypoglycemia, a condition where blood glucose levels fall below normal, at least once in their lives [10]. Conversely, hyperglycemia occurs when glucose levels exceed the acceptable range [11, 12]. Diabetes is characterized by impaired insulin production and utilization, leading to elevated blood glucose levels and affecting digestion [13–15]. Individuals with diabetes must either manually inject insulin several times daily or use a subcutaneous pump for automatic infusion [16]. Various factors, including diet, sleep, stress, and physical activity, can adversely affect glucose levels [17]. According to the International Diabetes Federation (IDF), an estimated 783 million people will have diabetes worldwide by 2045 [18]. In 2021, 24 million adults aged 20 to 79 had diabetes; this number is projected to rise to 33 million by 2030 and 55 million by 2045. These alarming statistics underscore the need for effective management strategies for type 1 diabetic patients and the development of artificial pancreas systems (APS).

The objective of this review is to provide an overview of the various control methods adopted by APS for diabetes therapy. The review covers both single and dual hormone systems to ensure superior glycemic control. Section 2 presents an overview of controllers in APS; Section 3 highlights equations related to blood glucose dynamics in single hormonal systems; and Section 4 reviews several control methods for APS, including proportional-integral-derivative (PID) control, model predictive control (MPC), and fuzzy logic. Section 5 discusses some of the findings; and Section 6 critical issues and the way forward are addressed, and finally, a conclusion is drawn in Section 7.

2 OVERVIEW OF THE CONTROLLER AS A COMPONENT OF AN ARTIFICIAL PANCREAS SYSTEM

An APS comprises an actuator or pump, continuous glucose monitors (CGMs), and a controller. The controller processes data from the CGM sensor to determine and deliver the appropriate insulin dose via the pump [19]. This process relies on an error signal generated by the deviation between the target and actual glucose levels, which serves as the input for all controllers, including PID, MPC, and fuzzy logic control (FLC) frameworks [20, 21].

The closed-loop system of an APS benefits from a feedback mechanism, unlike open-loop systems. PID controllers regulate the insulin injection rate based on the CGM's set point and output value, adjusting the controller's aggressiveness according to changes in glucose levels [22]. The proportional action provides an immediate response, the integral action eliminates the steady-state offset, and the derivative action offers a preemptive response based on the gradient of the latest deviation [9]. However, PID controllers do not account for other factors influencing blood glucose levels, such as stress, sleep, exercise, and meals, and do not predict insulin introduction rates.

In contrast, MPC uses mathematical models for prediction, considering various constraints that may affect blood glucose levels [23]. Additionally, "black box" approaches, such as those using artificial neural networks (ANNs), can model blood glucose levels by identifying patterns in datasets [24]. These neural systems are versatile tools for tasks such as pattern classification, time-series forecasting, and regression [25]. They operate without detailed knowledge of the underlying structure linking necessary parameters [26] or the relationships between basic parameters, relying instead on pattern recognition learned from datasets [27].

Fuzzy logic aims to automate medical decisions by modeling human judgment [28]. However, a significant challenge in deploying APS is developing a robust process that accurately forecasts glucose levels and determines the appropriate insulin dosage [29]. Consequently, three distinct types of models have been developed for estimating glucose rates: physiological models, data-driven models, and hybrid models [30].

2.1 The coordinated control architecture

Another notable control method is the coordinated control architecture, which is commonly used in various other fields but has not been extensively applied in APS [31]. Coordinated control architecture involves the integration of multiple controllers that work together in a harmonized manner to achieve a common objective. This method is designed to mimic the cooperative functions of different components within a system, allowing for more precise and effective control.

In the context of APS, a coordinated control architecture could significantly improve the management of blood glucose levels by emulating the natural regulatory mechanisms of the pancreatic system. The pancreas regulates blood glucose through a complex interaction between insulin production and other hormonal responses. By implementing a coordinated control architecture, APS could achieve more dynamic and responsive control of insulin delivery, closely replicating the body's physiological processes.

This approach could potentially lead to better glycemic control, reducing the risk of both hyperglycemia and hypoglycemia. Moreover, it could enhance the robustness and adaptability of the APS, making it more effective in handling the varying and unpredictable factors that affect blood glucose levels, such as diet, physical activity, stress, and illness.

Figure 1 illustrates how the coordinated control architecture could function within an APS, showing the interactions between the different controllers and their combined effect on regulating blood glucose levels. By harnessing the principles of coordinated control, APS could offer a more sophisticated and reliable solution for diabetes management, improving the quality of life for individuals with diabetes.

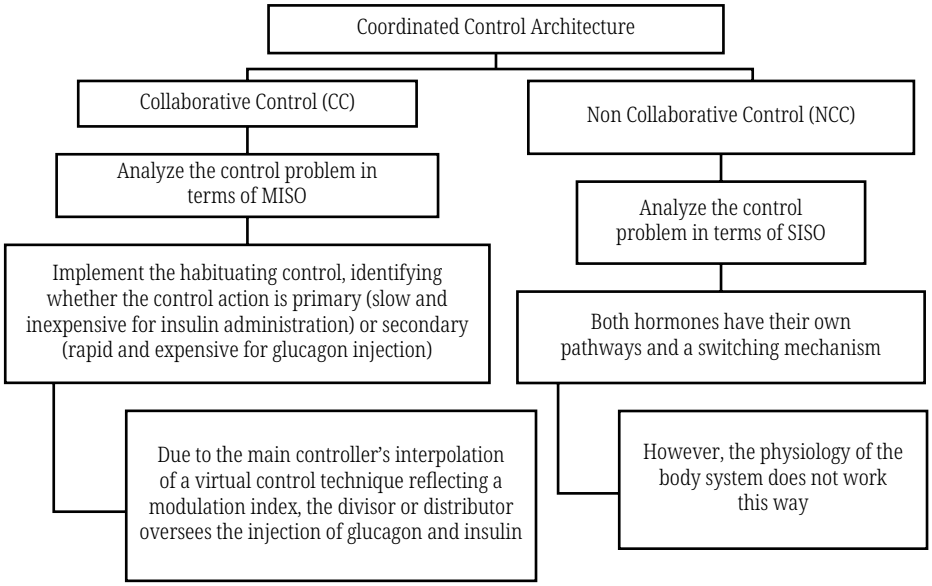

Fig. 1. Block diagram of the coordinated control architecture

3 EQUATIONS RELATING THE DYNAMICS OF BLOOD GLUCOSE

This section discusses the Bergman model, widely recognized as the most commonly adopted model among researchers. It covers aspects such as the software implementation of the model as well as its strengths and weaknesses.

3.1 The Bergman minimal framework

The minimal framework proposed by [32] presents a straightforward physiological paradigm consisting of three distinct steps and measurable parameters. It explores the intricate interplay between insulin delay and glucose efficacy within the human body. The Bergman model, renowned as the predominant mathematical model, offers a nonlinear representation of the dynamic relationship between glucose and insulin. Its prominence stems from its ability to articulate various physiological factors using a concise set of parameters, earning widespread acceptance.

The Bergman minimal model adopts a compartmental approach to simulate the glucose regulation system, ensuring simplicity for comprehension, dissection, and modification for further investigation. However, its limitation lies in modeling only glucose delivery into the bloodstream and employing lumped compartments, overlooking physiological nuances between distinct organs or tissues.

Primarily designed to fit frequently sampled intravenous glucose tolerance data in humans and dogs, the model's visualization, depicted in Figure 2, elucidates the intricate interaction among plasma insulin, plasma glucose, and insulin action states. This graphical representation enhances understanding, revealing how reaction kinetics and mass balance contribute to the ordinary differential equations (ODEs) encapsulated in equations (1), (2), and (3). Insights derived from Figure 2 underscore the critical dynamics captured by the Bergman minimal model.

Key observations from the model include the influence of administering external insulin injections on blood insulin levels, subsequently affecting insulin concentrations in the interstitial region. The term "interstitial insulin" was coined to describe the insulin required to lower blood glucose levels effectively. Regulating the pace of glucose transport into and out of the blood can effectively minimize the duration of glucose insufficiency.

Additionally, extracellular initiation of glucose leads to an increase in glucose levels. The interplay between the interstitial tissue compartment and blood insulin levels involves insulin exiting the compartment when blood insulin levels drop below the basal level and entering when they rise above the basal level. The values of g_b (basal blood glucose concentration) and I_b (basal blood insulin concentration) are determined by measuring concentrations either before or 180 minutes after glucose intake.

Using the minimal model, a regulation problem can be defined to asymptotically stabilize the desired equilibrium point $X^*[g_b\ 0\ I_b]^T$. Two metabolic indices can be computed by fitting the glucose minimal model to the results of the Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT) and obtaining parameter estimates for $P1$, $P2$, and $P3$.

$$\frac{dg_t}{d_t} = -P1[g_t - g_b] - x_t g_t + p_t \quad (1)$$

$$\frac{dx_t}{d_t} = -P2x_t + P3[I_t - I_b] \quad (2)$$

$$\frac{dI_t}{d_t} = -n[I_t - I_b] + \gamma(G-h)t + u_t \quad (3)$$

Given:

g_t = blood glucose magnitude (mg/dl)
I_t = blood insulin intensity (mU/l)
x_t = interstitial insulin (min^{-1})
g_b = basal glucose in units of (mg/dl)
I_b = basal insulin (mU/l)
g_0 = initial value of infused glucose
I_0 = initial value of infused insulin
η = apportioned insulin dissipation in the blood compartment (min^{-1})
u_t = extracellularly infusion of insulin (mU/min)
p_t = extracellularly infusion of glucose (mg/dl/min)
$P1$ = percentage of glucose conveyed from and to the blood segment (min^{-1})
$P2$ = percentage of insulin conveyed in the interstitial section (min^{-1})
$P3$ = percentage of insulin convoyed between the blood and the interstitial section ($ml/\mu Umin^2$)
h = pancreatic glycemic index
γ = ratio at which insulin is produced as the level of glucose exceeds a desired glycemic index.

Furthermore, the extracellular infusion of glucose can be expressed in equation (4).

$$P_t = \frac{P_G A_G t e^{-t/T_{maxI}}}{V_G T_{maxG}^{\ 2}} \quad (4)$$

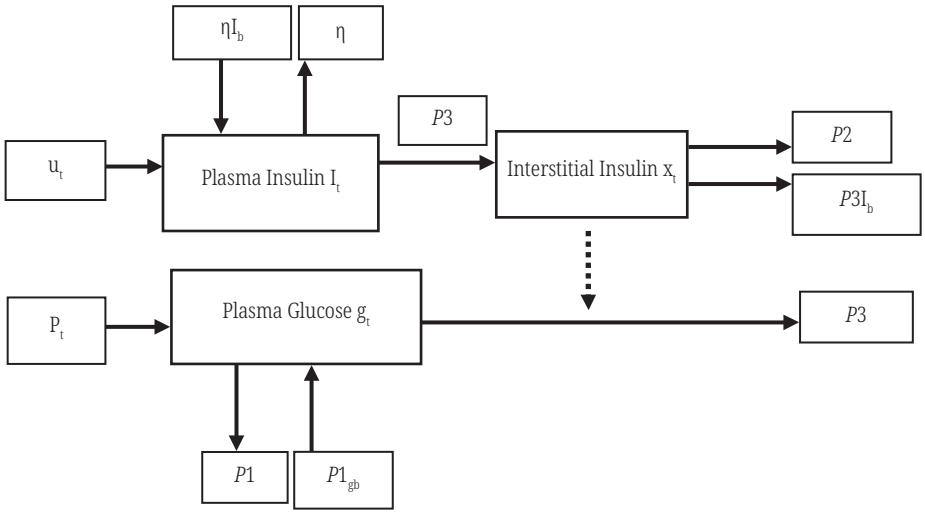

Fig. 2. Compartmental analysis

The execution of the Bergman minimal model within the software. The ordinary differential equations (ODEs) provided in equations (1), (2), and (3) were simulated within the MATLAB SIMULINK environment to study the behavioral patterns

of individuals, as outlined in Table 1. The parameters utilized were derived from the data presented in reference [33]. Following the simulation, Figures 3–5 illustrate the graphical representations of individuals without diabetes as well as individuals with diabetes.

Table 1. The model constants

S/N	Parameters	Values for Individuals without Diabetes	Values for Individuals (1) with Diabetes	Values for Individual (2) with Diabetes
1	$P1$	0.0317	0	0
2	$P2$	0.0123	0.072	0.0072
3	$P3$	4.92×10^{-6}	0.00000216	0.0000994
4	η	0.2659	0.2465	0.2814
5	g_b	70.0	70.0	70.0
6	I_b	7.0	7.0	7.0
7	g_0	291.20	200	180
8	I_0	364.80	55	60
9	γ	0.0039	0.0038	0.0046
10	h	79.0353	77.5783	82.937

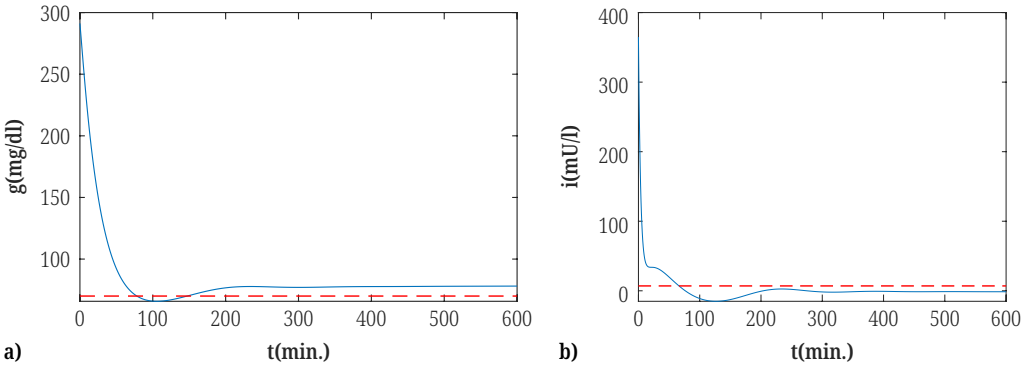

Fig. 3. Graphical representation of the plasma glucose concentration (g) and plasma insulin concentration (i) against the time (t) of the individuals without diabetes

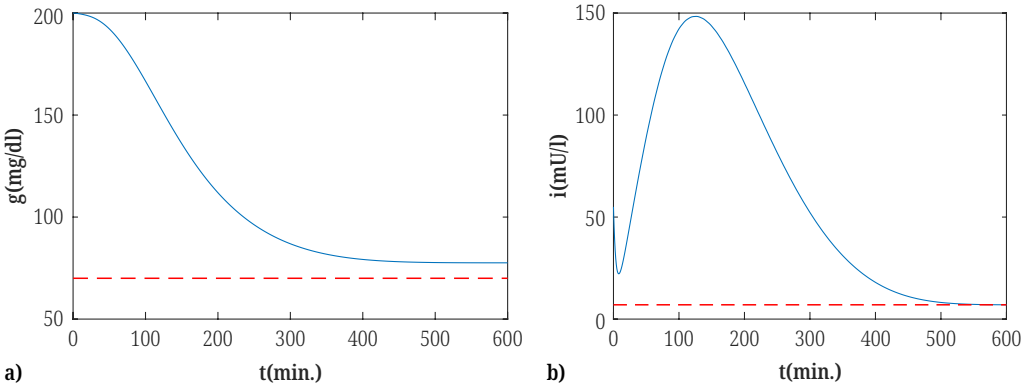

Fig. 4. Graphical representation of the plasma glucose concentration (g) and plasma insulin concentration (i) against the time (t) of the individuals (1) with diabetes

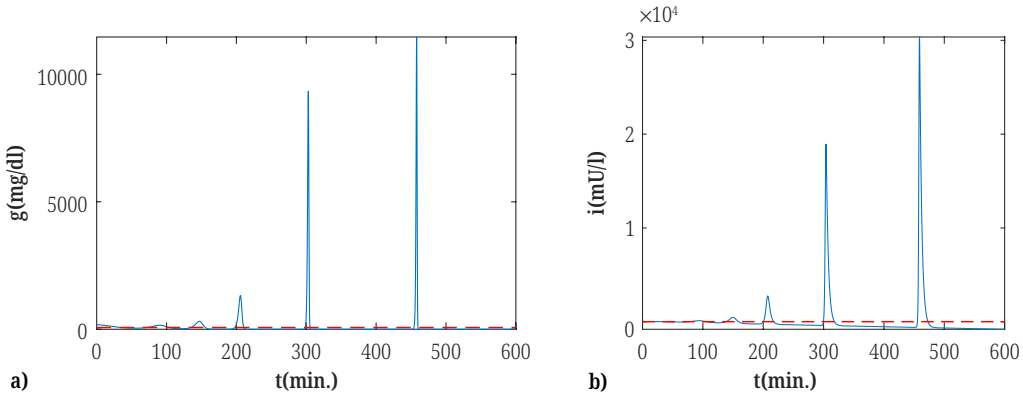

Fig. 5. Graphical representation of the plasma glucose concentration (g) and plasma insulin concentration (i) against the time (t) of the individuals (2) with diabetes

The glycemic condition of the individual without diabetes stabilized quickly due to the presence of functioning beta cells responsible for insulin regulation. In contrast, the glycemic condition of individuals (1) with diabetes required more computational resources, although the condition itself was not as pronounced. Conversely, individuals (2) with diabetes experienced a significant spike in hyperglycemia. Therefore, the development of a control algorithm or function U(t) capable of addressing these fluctuations is crucial for managing both hyperglycemic and hypoglycemic conditions effectively.

4 CONTROLLERS IN BLOOD GLUCOSE REGULATION

This section delves into diverse control strategies utilized in blood glucose regulation for diabetes therapy. Certain studies explored herein determined the most effective insulin infusion using a PID control mechanism, while others leaned towards model predictive control (MPC) or fuzzy logic control architecture. The following sections of the review will elaborate on these three methodologies for administering insulin.

4.1 Proportional-integral-derivative controller

Reference [34] proposed an advanced artificial pancreas system employing an enhanced PID controller, aiming to ensure safe and effective glucose regulation across diverse meal scenarios. Their innovative PID-based framework addresses challenges arising from prolonged lag times between glucose detection and the onset of interstitial insulin action. They employed statistical model checking to assess benchmarks and safety attributes, comparing the results with established closed-loop techniques. Their research demonstrated that one of the proposed methods significantly improved glucose control, particularly in the presence of sensor noise. The study revealed that 90% of participants met hypoglycemia safety criteria, with food portions ranging from 75 to 125 grams per 100 kilograms. However, it's essential to acknowledge the significant limitations of the PID controller. Challenges include suboptimal performance in handling various constraints, managing multiple variables with intricate interdependencies, and processing substantial dead time and nonlinearities. Potential enhancements may involve incorporating a deadtime compensator, reset feedback, a feedforward system with additive and

multiplicative components, and implementing a cascaded loop. Furthermore, a study by [35] examined the closed-loop regulation of glucose and insulin in dogs. The experiment involved fasting the dogs overnight, followed by a sequence of steps: a 30-minute somatostatin equilibration period, a 30-minute glucose loading period, an intraperitoneal insulin bolus, and a 150-minute glucose and insulin sampling period. To implement a PID controller in incremental form, a digital control version of the Internal Model Control (IMC) tuning rules was applied. However, the small sample size in this study may affect the reliability of the modeling scheme due to variability in parameter estimation. Additionally, obtaining population-level parameters with confidence intervals can be challenging.

Additionally, in [36], a combination of Ziegler-Nichols and Chien, Hrones, and Reswick (CHR) tuning methods was used to optimize the PID controller for blood glucose regulation, using the Bergman minimal model as the physiological framework. Despite its utility, the Ziegler-Nichols method does not account for the system's stability margin requirements.

Reference [37] introduced a novel complex-order PID (CO-PID) control algorithm to stabilize blood glucose levels, also based on the Bergman minimal model for glucose-insulin dynamics. The controller parameters were numerically optimized offline. Compared to the FO-PID controller, the CO-PID controller demonstrated improvements in reference tracking error, transient recovery time, and control expenditure by 13.1%, 33.4%, and 28.1%, respectively. However, the CO-PID controller lacks enhancements such as intelligent systems, online supervised learning algorithms, or model-free expert adaptive systems, which could dynamically self-tune the controller parameters to enhance robustness against hyperglycemia and external disturbances.

4.2 Fuzzy logic controller

Reference [38] introduced a method aimed at managing the conditions of diabetic patients. Their approach involves applying immersion and invariance principle to address uncertainties in the system. They propose utilizing a modified type II fuzzy mechanism, enhanced by the singular value decomposition technique, to achieve error compensation and system stability. Considering the influence of both food intake and patient behaviors, reflecting the social aspects of diabetes, their research evaluated performance using a modified Bergman framework. The study involved diverse diabetic populations, demonstrating the effectiveness of the proposed method, with glucose levels of patients reaching the recommended range in nearly 99% of cases. However, the limited parameters of the Bergman minimal model could affect the system's performance. Also, [39] introduced a fuzzy-based adaptive multi-input-multi-output (MIMO) scheme for diabetes management, using the Bergman minimal model as the physiological basis. This supervisory coupling controller aims to keep blood glucose levels within the range of 60 to 300 mg/dL, with membership functions designated as "low normal" and "medium" for breakfast, lunch, and dinner. However, controlling MIMO systems is challenging due to the complexity of managing multiple inputs and outputs simultaneously while achieving optimal regulation. A study by [4] developed an optimized fuzzy logic controller for APS to maintain euglycemia in T1DM patients post-meal, effectively managing the nonlinearities and uncertainties of glucose-insulin dynamics. The controller was designed in three stages: nonlinear framework identification, stabilizing control rule establishment, and genetic algorithm optimization. Evaluated using MATLAB/Simulink simulations, it significantly improved glucose regulation, with subjects spending 61.25%, 71%, and 61.10% of the time in the target range. The fuzzy logic

controller outperformed internal model control (IMC) and multi-objective output feedback controllers. However, the study did not account for other factors affecting blood glucose levels, such as stress and exercise.

4.3 Model predictive control controller

Model predictive control, a promising technology utilized in the APS, plays a crucial role in achieving euglycemia by regulating glucose levels [40]. It stands out as one of the most effective control architectures, providing accurate control design by considering both past and projected system states. Its notable features that enhance blood glucose control include:

1. **Predictive capability:** MPC's forecasting ability enables preemptive and precise insulin administration.
2. **Compensation of dead time:** Unlike PID controllers, MPC effectively manages dead time, commonly present in glucose concentration issues.
3. **Effective feedforward technique:** MPC's feedforward technique adeptly regulates disturbances such as meals or metabolic changes.
4. **Handling of constraints:** MPC efficiently handles constraints at both input and output levels.
5. **Mitigation of metabolic disruption:** MPC surpasses metabolic disruptions caused by transdermal circulation.

Additionally, MPC facilitates easy adjustment of system settings to accommodate individual patient needs [41]. By utilizing past and forecasted inputs and outputs, the control model predicts outcomes for specific moments. Subsequent network error estimation and error elimination are achieved by feeding back predicted outputs into the optimizer, which applies existing constraints to minimize operational costs [42].

Moreover, MPC can be employed for dual insulin management. Reference [43] demonstrated the effectiveness of adding MPC and PID management methods to the APS for maintaining stable glucose levels. They utilized the Bergman Minimal Model due to its ability to handle interruptions such as eating and physical activities. Testing for meal disruptions involved a modified version of Palma's minimal model. Throughout the day, exogenous insulin was administered at a constant rate of 3μ units per minute to prevent hyperglycemia, assuming each meal included 50 grams of carbohydrates. Additionally, one hour of exercise was simulated. According to their findings, the MPC method increased time in the range by 90% of the day, with only three hypoglycemic episodes experienced. However, the PID approach maintained a glucose rate above the target of 61.74% and below the reference of 38.64%. In a study by [44], a personalized model predictive control (MPC) strategy with adaptive control rules was proposed to achieve effective and safe blood glucose concentration (BGC) regulation for individuals with type 1 diabetes (T1D). This strategy included a glucose concentration prediction model that incorporated prior knowledge by encoding exponential stability information with a kernel matrix, thereby enhancing its predictive accuracy for future BGC values. The results demonstrated that the proposed controller provided tight BGC control without requiring manual meal and exercise announcements, although it occasionally induced slight hypoglycemic states.

Reference [40] proposed a dual-model infusion of insulin and glucagon using an MPC controller to regulate blood glucose levels in patients, accounting for unmeasured disturbances occurring at random times. The Sorenson model was used as the physiological system. Performance was assessed using average tracking error (ATE)

with a setpoint of 90 mg/dl and a standard deviation limit of 14.4 mg/dl for optimal performance. However, the model exhibited minor oscillations in glucose concentration when endogenous glucose production was zero, and there were delays in adjusting glucagon and insulin flow rates due to subcutaneous infusion delays.

Reference [45] compared constrained (C-MPC) and unconstrained (S-MPC) model predictive control for artificial pancreas systems. The MPC was formulated as a finite-horizon optimal control problem using the UVA/Padova simulator and tested in silico on 100 adult patients. Results indicated that C-MPC outperformed S-MPC in terms of average glucose levels, time spent in the target range, and time above 180 mg/dL. However, stability and convergence analysis could only be performed on individual patients by assuming knowledge of specific parameters of the nonlinear model, which may be impractical in real-world scenarios.

Reference [46] investigated the Controller Performance Assessment and Modification (CPAM) of the MPC controller. An adaptive MPC algorithm was developed, utilizing recursively identified state-space models with dynamic adjustments to constraints and objective function weights. A feature extraction method was designed to automatically detect meal times based on qualitative descriptions of CGM time-series data. The CPAM system increased the percentage of time in the target range (70–180 mg/dL) by 52.3% without causing hypoglycemia or hyperglycemia events. It was also suggested that providing users with the option to modify the controller set-point based on historical data could be beneficial.

In reference [47], an MPC controller was used to compare dual and single hormone systems for diabetic care. The proposed system employed the Sorenson model to represent the physiology of glucose, insulin, and glucagon, considering unmeasured disturbances at random times. However, the lack of separate optimizers for each hormone could lead to interaction issues between the control variables.

5 DISCUSSION AND FINDINGS

This review provides a concise examination of the methodologies utilized to achieve optimal outcomes in an APS. Researchers in APS therapy have explored both single and dual hormonal control architectures, with a particular focus on model-predictive control methods for insulin infusion. The maintenance of euglycemia in diabetic patients necessitates the adoption of specific control strategies. Each of the following quantitative objectives can be accomplished through the application of particular control methods:

1. Maintaining blood glucose levels between 3.9 and 10 mmol/l or 70 and 180 mg/dl.
2. Achieving a target blood glucose level.
3. Maximizing the time spent in the euglycemic range.

The selection of an optimal control framework typically involves choosing between one that does not consider constraints and prediction, such as PID, or one that incorporates constraints and prediction by utilizing a dual hormone system for delivery, such as MPC. In a coordinated control arrangement, the master controller calculates the optimal value, enabling the divisor to administer insulin or glucagon to the patient to prevent hyper- or hypoglycemic states, respectively. It's worth noting that the coordinated control strategy may also involve separate controllers for the delivery of insulin and glucagon. Factors affecting blood glucose concentration, such as sleep, stress, exercise, and meals, should be considered when implementing any optimal control framework. Controllers capable of executing optimal control

frameworks should incorporate constraint and prediction states. Table 2 outlines the advantages and disadvantages of some controllers used in the artificial pancreas system, while Tables 3 and 4 detail articles utilizing single and dual hormone systems for their control frameworks, respectively.

Furthermore, the review is limited to examining three primary controllers—PID, MPC, and fuzzy logic—while other emerging control strategies remain unexplored. Simulation efforts focused exclusively on the Bergman minimal model, potentially overlooking alternative physiological models that could offer complementary insights. The study provides insights primarily into single and dual hormone systems, with limited exploration of newer, integrated control approaches that may further enhance glucose regulation strategies.

Table 2. Overview of the advantages and disadvantages of the most adopted controllers in diabetic therapy

Refs	Controller	Approach	Advantages	Disadvantages
[48, 49]	PID	The controller takes input from an error function, which is based on the difference between the current and desired blood glucose levels.	– Straightforward to deploy – Not requiring information on carbohydrate intake.	– Typically, when left unaltered, it exhibits poorer performance compared to other methods. – Modeling the insulin onboard requires advancements beyond the capabilities of currently available commercial devices.
[50, 51]	MPC	Forecast the rate of glucose and administer insulin to bring it within the target range.	– Efficient operation observed in the hybrid closed-loop system under subcutaneous conditions – There is a potential to integrate additional metrics to enhance glucose management – Based on the principle, systems can be customized to suit individual needs	– Implementation poses greater challenges. – Often assumes a standard uptake pattern, which may not apply to a diverse range of individuals.
[52–54]	Fuzzy-Logic	Establish clear protocols for modifying insulin dosage based on current information	– Refined control can be achieved by integrating additional data sources and implementing actions on existing ones.	– Typically starts with a consensus among specialists to establish certain principles. – Difficult to master

Table 3. Articles using a single hormone system for its control framework

Refs	Method	Remarks
[55]	For simplicity, Bergman's minimal model was converted into a state-space equation. To achieve controller flexibility, the efficacy ratio of glucose (P1) was treated as a free-floating, uncertain variable. The ODE45 solver in MATLAB was then used to analyze the system's response.	The predicted insulin dispensing rate is capped at a maximum of 180 mU/min using a saturation function at the technique's output. Starting from an initial reference condition of 80 mmol/L, a peak overshoot of 6.5 mmol/L and a settling time of 2104 seconds were observed. Additionally, at a sampling interval of 100 seconds, the deviation was measured at 0.72 mmol. In essence, the proposed controller keeps tracking four different glucose concentrations (4, 6, 8 and 10 $mMolL^{-1}$ or 70–180mg/dl respectively).
[56]	To optimize a performance index over a specified prediction window, the GT2-FLC, serving as the primary regulator, was tuned using the BBO technique. The compensatory mechanism is designed to maintain equilibrium in the feedback system. The enhanced Bergman model, which includes time-varying characteristics, unwanted noise, and meal disruptions, is used to assess the effectiveness of the proposed control method.	Using the Bergman model, it was observed that the fourth individual's kinetics were unbalanced. Considering a constant parameter model, the root means square error (RMSE) for the three patients over ten days (240 hours) was as follows: 0.1489, 0.1545, and 0.1508 at 50 mg/dl; 0.3476, 0.3542, and 0.3541 at 120 mg/dl; and 0.5788, 0.5718, and 0.5792 at 200 mg/dl. When considering a model with time-varying parameters and disturbances, the results were: 3.5843, 3.7363, and 3.7250 at 50 mg/dl; 3.7978, 3.7379, and 3.7264 at 120 mg/dl; and 3.8010, 3.7411, and 3.7298 at 200 mg/dl.

Table 4. Articles using dual hormone system for its control framework

Refs	Method	Remarks
[31]	– The primary framework was designed using a PD controller. – Scenarios A, B, and C were observed, corresponding to Meal, Meal + Snack, and Meal + Exercise.	In scenario C, which involves exercise, hypoglycemia was still observed. However, the implementation of this system, whether in hardware-in-the-loop or prototype form, was not demonstrated.
[57]	– The primary mechanism was designed using a sliding mode controller. – Scenarios A, B, and C were observed, corresponding to Meal, Meal + Snack, and Meal + Exercise, respectively.	It was noted that the daily glucagon delivery was recorded at 1.03 mg, exceeding the normal daily delivery of 1 mg/day.
[58]	Two IMC-PID controllers were utilized.	The developed model does not accurately represent the physiological processes of insulin and glucagon infusion by the pancreas.

6 CRITICAL ISSUES AND WAY FORWARD

The development of an optimal control architecture to effectively prevent hyperglycemic conditions remains a significant challenge within the realm of APS for diabetes therapy. Many patients utilizing APS still struggle with hyperglycemia, particularly during overnight periods. To address potential hypoglycemia, current devices are equipped with an "insulin on-board" mechanism, which temporarily halts insulin delivery or triggers a low glucose warning to prompt the patient to consume carbohydrates. However, there's a risk of insulin wearing off during sleep, potentially leading to severe consequences if left unmanaged.

These vulnerabilities highlight the need for further study and innovation in this area. To fully leverage the capabilities of APS and achieve the overarching goal of maintaining stable blood glucose levels, there is a critical need for the development of an integrated strategy for insulin and glucagon infusion. Such a strategy should incorporate coordinated control algorithms that consider various constraints and individual patient characteristics.

Additionally, personalized design approaches for insulin and glucagon onboard mechanisms could significantly enhance APS functionality. By tailoring these mechanisms to individual patient needs, valuable insights into insulin and glucagon dynamics could be gained. Furthermore, the inclusion of sensors providing data on parameters such as blood pressure, heart rate, and body temperature could further augment the effectiveness of APS systems.

7 CONCLUSION

In this comprehensive review, we have explored the historical deployment of artificial pancreas systems, examining both single and dual hormonal architectures. Various strategies tailored to address the unique characteristics of each model have been discussed in detail. Achieving euglycemia, or normal blood glucose levels, in diabetic patients necessitates diligent self-management. By adopting specific control strategies, such as regulating blood glucose levels, increasing time spent within the euglycemic range, and maintaining glucose within specified parameters, these control objectives can be effectively met.

Our analysis underscores the limited study focus on coordinated control methods for dual hormonal artificial pancreas systems. While much attention has been directed towards single hormone systems, particularly for insulin administration, there remains a notable gap in the exploration of coordinated dual hormonal systems. As such, we propose the development of a comprehensive system capable of simulating pancreatic function by coordinating the infusion of hormones, thus offering a promising avenue for future study and innovation in diabetes therapy.

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