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PAPER

Optimizing Blood Glucose Regulation in Type 1 Diabetes Patients via Genetic Algorithm-Based Fuzzy Logic Controller Considering Substantial Meal Protocol

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ABSTRACT

Effective management of blood glucose levels in individuals with type 1 diabetes, especially after meals, is crucial for diabetes care. Artificial pancreas systems (APS) perform automated insulin delivery in subjects with type 1 diabetes mellitus (T1DM). In this study, an optimized fuzzy logic controller was designed to achieve a euglycemic range after a substantial meal intake. All in silico simulations were performed using the MATLAB/Simulink environment, leveraging control variability grid analysis (CVGA), and the performance of the controller was evaluated. The proposed controller is based on a fuzzy-logic control law designed in three stages. First, a nonlinear framework of the glucose-insulin regulatory system was identified based on the heavy meal protocol of three patients given as follows: for subject ID 117-1, a total of 295 gCHO; for subject ID 126-1, 236 gCHO; and subject ID 128-1, 394 gCHO over a day. Then, an iterative tree structure was employed to establish a stabilizing control rule for insulin delivery, integrating inputs from two Mamdani Fuzzy Inference System (FIS) objects. Finally, a genetic algorithm refines the control system by fine-tuning the uncertainty of the fuzzy membership functions. Two scenarios were considered for three patients to assess the performance of the proposed controller. The results indicated its effectiveness under various conditions, achieving a time in the range of 61.25%, 71% and 61.10% respectively for the three subjects. The obtained results are analyzed and compared with IMC and multi-objective output feedback controllers. The findings of the study reveal that the proposed controller shows promising advancements in tailored strategies for type 1 diabetes patients, outperforming the other controllers in terms of blood glucose regulation.

KEYWORDS

artificial pancreas system, CVGA, diabetes, fuzzy logic controller, insulin, meal, optimization

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1 INTRODUCTION

Diabetes is a complex physiological condition characterized by disrupted insulin production and utilization, leading to elevated blood glucose levels [1–3]. It is categorized into two primary types: Type 1 and Type 2 [4, 5]. In Type 1 diabetes, the pancreatic β-cells responsible for insulin regulation are progressively destroyed, rendering precise blood glucose management elusive [6–9]. Even in Type 2 diabetes, in which some insulin remains in the patient's body, challenges persist because of the inadequacy of insulin for effective glucose control [10]. This study primarily focused on type 1 diabetes; a condition characterized by the inability of the pancreas to produce insulin. Effective blood glucose control in such cases necessitates continuous or infusion-based insulin administration [11]. Diabetes is a growing global health concern worldwide [12]. By 2045, an estimated 700 million people are projected to be affected, up to 463 million by 2021 [13, 14]. Diabetes does not discriminate; it can affect individuals regardless of their characteristics such as height, weight, ethnicity, blood group, age, or gender [15]. Multiple factors contribute to the development of diabetes, including dietary choices, physical activity, stress levels, and sleep patterns [16]. Current methods for managing diabetes, such as manual daily insulin injection (MDII) or continuous subcutaneous insulin injection (CSII), have limitations [17]. MDII often lacks precise data and accuracy because the insulin dose must be manually selected [18]. By contrast, CSII offers greater precision and effectiveness [19]. However, commercial CSII devices typically employ a single hormonal channel for insulin delivery [20]. Proper glucose homeostasis relies on the coordinated function of the liver and pancreas [21]. The pancreas, upon detecting fluctuations in blood glucose, instructs the islets of Langerhans to regulate insulin production, prompting the liver to either reduce or increase glucose release [22–24]. Inadequate control of blood glucose levels can lead to severe complications [25]. Hypoglycemia, in which glucose levels fall below the euglycemic range, results in symptoms such as dizziness, confusion, severe cases, coma, and death [26–28]. Conversely, hyperglycemia, with glucose levels above the euglycemic range, leads to symptoms such as increased thirst, fatigue, skin issues, frequent urination, dry mouth, and blurry vision, potentially causing long-term complications, such as cardiovascular diseases, kidney damage, and eye and ear defects [29]. Artificial pancreatic systems (APS) have been developed as a closed-loop system [30]. These closed-loop automated insulin administration systems aim to mimic the action of a healthy pancreas and to maintain physiological glucose levels [31]. An APS typically comprises a sensor, actuator, and controller responsible for modulating insulin administration based on sensor measurements [32]. Figure 1 shows a schematic of the closed-loop control system used for glucose management. In general, developing a control algorithm for insulin infusion faces challenges due to nonlinearities, time-varying parameters, and uncertainties in the glucose-insulin regulatory system. Additionally, subcutaneous sensing and insulin delivery introduce delays. Addressing these complexities is crucial for effective artificial pancreas (AP) control. Extensive efforts, including diverse mathematical models and controller design techniques, have been employed to overcome these challenges, as detailed in comprehensive reviews such as [33, 34] on existing models and the utilized controllers. MPC and PID are widely applied in APS [35, 36]. Additionally, various advanced control design methods are systematically employed for improved automatic regulation system performance. In [37], an IMC algorithm was designed for subjects with T1DM. A multi-objective output feedback controller, addressing BG regulation under regular and irregular meal scenarios over four days with a reduced carbohydrate count, was proposed and solved using the linear matrix inequality technique [38]. In [39], Mamdani-type

fuzzy structure was used to develop an insulin advisory system for TIDM patients. A machine-learning algorithm has also been used to achieve safer blood glucose regulation [36, 40]. Furthermore, fuzzy logic has found other applications as mentioned in [41–43]. Despite the promising outcomes achieved through these endeavors, striking a balance between the assertiveness of control actions and postprandial glucose excursion remains a challenging issue, particularly in cases where the controller necessitates meal announcement. Certainly, extended periods of elevated blood glucose levels may arise when the controller lacks aggressiveness in response to a meal disturbance. Conversely, if the controller is overly aggressive, there is an elevated risk of experiencing postprandial hypoglycemia. It therefore becomes imperative to have an approach that can address optimal insulin infusion and proffer better performance.

In this study, to fulfil the optimality requirement and strike a balance between control action aggressiveness and postprandial glucose excursion in individuals with T1DM, a unique approach is introduced. The method employs a fuzzy logic controller to delicately manage hyperglycemia and hypoglycemia. Using an iterative tree structure, a stabilizing control rule for insulin delivery is established by integrating controller inputs. This technique involves two Mamdani Fuzzy Inference System (FIS) objects alongside Hovorka's model, known for its capacity to address patient-specific parameters based on daily variations in meal consumption. Additionally, a genetic algorithm is applied as a meta-heuristic tool to fine-tune the uncertainty footprint in fuzzy membership functions, enhancing the control system's precision. To evaluate the effectiveness of the proposed controller, we examined two scenarios for three patients. Our approach surpassed the performance of the other two controllers in terms of blood glucose regulation, indicating significant advancements in tailored strategies for managing type 1 diabetes in patients. In summary, this paper makes the following key contributions:

- If the patient experiences an increase in blood glucose (BG) levels following a substantial meal, the suggested controller effectively mitigates the adverse impacts of the meal and minimizes the potential for induced postprandial hypoglycemia. As demonstrated through our computational simulations, the proposed model consistently maintains BG levels within the safe target range of 70–180 mg/dl for the majority of the time (as detailed in Section 4: 61.25% for subject 117-1, 71% for subject 126-1, and 61.10% for subject 128-1)
- An iterative tree structure was adopted to stabilize a control rule for insulin delivery by using two Mamdani FIS in other to achieve the optimal dose of insulin infusion for each patient
- The integration of a genetic algorithm enabled the attainment of an optimized control architecture and optimal insulin infusion, facilitating the adjustment of uncertainty in the fuzzy membership function
- The Hovorka model was employed to estimate parameters, addressing diverse profiles of diabetic patients

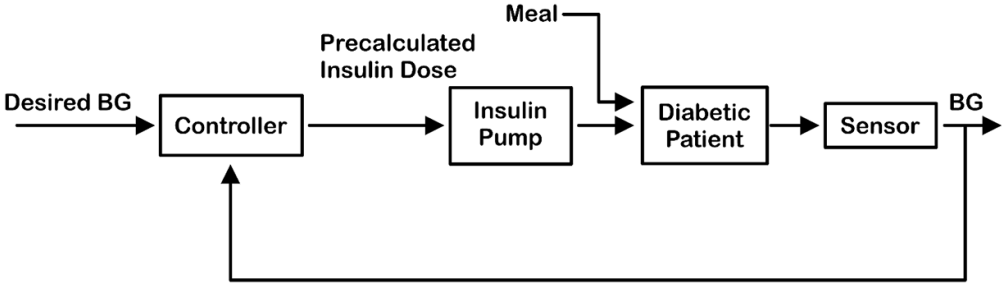

Fig. 1. Closed-loop insulin administration architecture

The paper follows the subsequent organization. Section 2 outlines the adopted methods. Results and discussions are detailed in Section 3, and Section 4 highlights the evaluation metrics. Finally, Section 5 concludes the paper alongside future perspectives.

2 METHODS

2.1 The nonlinear framework of type 1 diabetes mellitus (T1DM)

A precise mathematical representation of the glucose-insulin regulatory system is crucial for the development of effective control strategies. Several mathematical models related to the glucose-insulin system have been previously introduced. These models encompass varying numbers of parameters within the glucose-insulin regulatory system, ranging from a few to several, depending on the application of mass balance equations and the consideration of flow rates. The ability to accurately solve and estimate parameters in mathematical models for patients with diabetes has the potential to revolutionize diabetes care and ultimately achieve optimal control. Hovorka's model stands out because of its ability to effectively elucidate the dynamics of the glucose-insulin regulation system using a modest number of easily identifiable parameters considering its nonlinear framework.

Hovorka model. Hovorka's model is divided into three sections [44]: a glucose subsystem for glucose absorption, distribution, and disposal; an insulin subsystem for insulin absorption, distribution, and disposal; and an insulin action subsystem for insulin action on glucose transport, disposal, and endogenous production. The ordinary differential equations (ODEs) defined by the model were implemented and analyzed in the MATLAB SIMULINK environment to gain insights into the behavioral patterns exhibited by typical patients. This framework serves as a fundamental tool for understanding glucose-insulin regulation systems.

- In the context of the research paper, the glucose subsystem is a critical component, and it encompasses several key elements. Specifically, it comprises a representation of the heart's behavior, which is articulated through a pair of compartmental equations that describe the glucose dynamics. These equations are denoted by (1) and (2), respectively. Additionally, the glucose subsystem incorporates a model that characterizes the rate at which the gut takes up glucose, as shown in equation (3). This section of the research paper delineates the essential components of the glucose subsystem and the mathematical expressions used to capture their behavior

$$\frac{DQ_1(t)}{D_{(t)}} = -\left[\frac{F_{01}c}{V_G G(t)} + x_1(t)\right]Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP_0[1 - x_3(t)] \tag{1}$$

$$\frac{DQ_2(t)}{D_{(t)}} = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t)\, y(t)\, G(t) = Q_1(t)/V_G \tag{2}$$

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{maxG}}}{t^2_{maxG}} \tag{3}$$

Where Q_1 and Q_2 are the quantities of glucose in the reachable and non-reachable chambers, respectively; k_{12} is the transfer rate constant from the non-reachable to

the reachable portion; V_G is the reachable chamber dispersion volume; y and G are the glucose concentrations; and EGP_0 is endogenous glucose production hypothesized to be zero. Furthermore, $F_{01}c$ depicts total non-insulin-dependent glucose flow slated for the outer glucose rates, F_R stands for renal glucose elimination above its threshold, the gut intake rate is symbolized by U_G, t_{maxG} represents the duration of maximal appearance of glucose in the reachable glucose chamber, D_G corresponds to the number of carbohydrates broken down, and A_G represents carbohydrate bioavailability. It should be noted that;

$F_{01}c$ = Total non-insulin-dependent glucose flux corrected for the ambient glucose concentration and is expressed as = $F_{01}c = \begin{cases} F_{01}, \text{ if } G \geq 4.5 mmol/L \\ F_{01}, \ G/4.5 \text{ Otherwise} \end{cases}$

F_R = Renal glucose clearance above the glucose threshold of 9 *mmol/L*, expressed as:

$$F_R = \begin{cases} 0.003(G-9)V_G, & \text{if } G \geq 9 mmol/L \\ 0, & \text{Otherwise} \end{cases}$$

- Within the context of the insulin segment, the process of insulin uptake is specifically described through equations (4) and (5), whereas equation (6) represents the concentration of insulin within the plasma. This section provides a comprehensive overview of the handling and quantification of insulin in the system

$$\frac{DS_1(t)}{D_{(t)}} = u(t) - \frac{S_1(t)}{t_{maxI}} \tag{4}$$

$$\frac{DS_2(t)}{D_{(t)}} = \frac{S_1(t)}{t_{maxI}} - \frac{S_2(t)}{t_{maxI}} \tag{5}$$

$$\frac{DI(t)}{D_{(t)}} = \frac{U_I(t)}{V_1} - k_e I(t) \tag{6}$$

S_1 and S_2 reflect the uptake of subcutaneously injected short-acting insulin; $u(t)$ represents insulin delivery; and t_{maxI} is the time to maximum insulin uptake. The insulin uptake rate was calculated as $U_I = S_2(t)/t_{maxI}$. Furthermore, k_e is the fractional clearance ratio and V_1 is the dispersion volume.

- In the segment regarding the influence of insulin, it is notable that the subsystem incorporates three distinct effects of insulin on glucose dynamics, which are encapsulated by equations (7), (8), and (9). Furthermore, within this subsystem, the modelling extends to encompass the intricacies of insulin uptake rates in both the slow and fast channels within the subcutaneous layer, a representation achieved through equations (10), (11), (12), and (13). Additionally, these equations are employed to capture the localized breakdown of insulin at the point of administration, thus providing a comprehensive portrayal of the impact of insulin on the overall system dynamics

$$\frac{Dx_1}{D_{(t)}} = -k_{a1}x_1(t) + k_{b1}I(t) \tag{7}$$

$$\frac{Dx_2}{D_{(t)}} = -k_{a2}x_2(t) + k_{b2}I(t) \tag{8}$$

$$\frac{Dx_3}{D_{(t)}} = -k_{a3}x_3(t) + k_{b3}I(t) \tag{9}$$

$$\frac{DQ_{1a}}{D_{(t)}} = ku - k_{a1}Q_{1a} - LD_a \tag{10}$$

$$\frac{DQ_{1b}}{D_{(t)}} = (1-k)u - k_{a2}Q_{1b} - LD_b \tag{11}$$

$$\frac{DQ_2}{D_{(t)}} = k_{a1}Q_{1a} - k_{a1}Q_2 \tag{12}$$

$$\frac{DQ_3}{D_{(t)}} = k_{a1}Q_2 + k_{a2}Q_{1b} - k_eQ_3 \tag{13}$$

where x_1, x_2, and x_3 represent the impact of insulin on glucose transport, glucose elimination, and endogenous glucose production; k_{a1}, k_{a2}, and k_{a3} depict deactivation rates; and k_{b1}, k_{b2}, and k_{b3} symbolize activation rates, respectively. Furthermore, u is the insulin input, Q_{1a}, and Q_{1b} state the quantity of insulin in the slow uptake channel composed of two chambers, Q_2 is the amount of insulin in the fast uptake region, V denotes the insulin dispersion volume, k reflects the fraction of the sum of input flux distributed via the slow uptake region, k_{a1}, k_{a2}, and k_e are the transfer rates, and LD_a and LD_b indicate the local insulin degradation rate at the infusion location. The Michaelis-Menten dynamics depicted by (14) and (15) are assumed for LD_a and LD_b;

$$LD_a = V_{max,LD}\, Q_{1a} /(\mathrm{K}_{\mathrm{M,LD}} + Q_{1a}) \tag{14}$$

$$LD_b = V_{max,LD}\, Q_{1b} /(\mathrm{K}_{\mathrm{M,LD}} + Q_{1b}) \tag{15}$$

where $V_{max,LD}$ is the saturation rate and $\mathrm{K}_{\mathrm{M,LD}}$ denotes the amount of insulin at which insulin breakdown is equivalent to half of its zenith point.

Hovorka's model nominal parameters, constants and it's definitions. To reduce complexity while still effectively representing the diverse glucose fluctuations observed in patients with type 1 diabetes under physiological conditions, model quantities were categorized into parameters and constants. The parameters and constant values for the diabetic patient model were adopted from [44], as shown in Tables 1 and 2.

Table 1. The model constants

Symbol	Definition	Value	Unit
k_{12}	Transfer rate	0.006	min^{-1}
k_{a1}	Deactivation rate	6×10^{-3}	min^{-1}
k_{a2}	Deactivation rate	6×10^{-2}	min^{-1}
k_{a3}	Deactivation rate	3×10^{-2}	min^{-1}
k_e	Fractional clearance ratio of insulin	0.138	min^{-1}
V_I	Insulin distribution volume	0.12	Lkg^{-1}
V_G	Glucose dispersion volume	0.16	Lkg^{-1}
A_G	CHO bioavailability	0.8	unitless
t_{maxG}	Time-to-maximum CHO uptake	40	min

Table 2. The model parameters

Symbol	Definition	Value	Unit
$S_{IT}f = \frac{k_{b1}}{k_{a1}}$	Insulin sensitivity of distribution	0.0512	min^{-1} per mU L^{-1}
$S_{ID}f = \frac{k_{b2}}{k_{a2}}$	Insulin sensitivity of disposal	0.0082	min^{-1} per mU L^{-1}
$S_{IE}f = \frac{k_{b3}}{k_{a3}}$	Insulin sensitivity of EGP	520×10^{-4}	min^{-1} per mU L^{-1}
EGP_0	EGP hypothesized to zero amount of insulin	0.0161	mmol kg^{-1} min^{-1}
$F_{01}c$	Non-insulin-dependent glucose flux	0.0097	mmol kg^{-1} min^{-1}
Q_{1a} and Q_{1b}	Slow chamber transfer rate	0.0112	sec^{-1}
Q_2	Rapid chamber transfer rate	0.0210	sec^{-1}
$V_{max,LD}$	Saturation level	1.93	mU/sec
k	Proportion in slow channel	0.67	unitless
$t_{max,I}$	Time-to-maximum subcutaneous infusion of short-acting insulin	55	min

Note: a = The parameter's mean value for Bayesian parameter estimation; b = The utilization of an alternative parameterization.

Estimating Hovorka's model parameters using the Bayesian technique. The nonlinearity in Hovorka's model arises from the influence of insulin on various parameters related to glucose synthesis, distribution, and disposal. Bayesian parameter estimation, a method applied to ascertain time-varying model parameters, was used to mitigate the issues related to posterior identifiability. This technique involves the derivation of a multivariate log-normal distribution for specific parameters $S_{IT}f$, $S_{ID}f$, $S_{IE}f$, F_{01} and EGP_0, as established by [44]. To facilitate ease of implementation and enhance numerical stability during optimization, this multivariate normal distribution was represented as a linear combination of five individual univariate normal distributions, each characterized by a mean of zero and standard deviation of one ($pi \sim N(0, 1)$, i = 1,2,3,4, and 5) as shown in (16)–(20). The random variable transformation technique was used to determine coefficients a_{ij} and b_i. In addition, the log-normal prior distribution for the remaining parameter $t_{max,I}$, was obtained from the existing literature [44], standardized to ensure numerical stability, and streamlined the implementation.

$$\ln S_{IT}f = a11p1 + b1 \quad (16)$$

$$\ln S_{ID}f = a12p1 + a22p2 + b2 \quad (17)$$

$$\ln S_{IE}f = a13p1 + a23p2 + a33p3 + b3 \quad (18)$$

$$\ln F_{01} = a14p1 + a24p2 + a34p3 + a44p4 + b4 \quad (19)$$

$$\ln EGP_0 = a15p1 + a25p2 + a35p3 + a45p4 + a55p5 + b5 \quad (20)$$

Stability analysis of the Hovorka's model. The model's distinct equilibrium point is defined as (Q^*, I^*), and is determined by solving the equations dG/dt = 0 and dI/dt = 0. However, finding a clear solution for Q and I in the Hovorka model

is rather challenging [44]. To assess the stability of the nonlinear model at equilibrium points (Q, I), we employed the linearized approach method described by the Jacobian matrix.

Considering the model parameters by Hovorka's model as follows [44]:

K_{12} = 0.006 per min (transfer rate); K_{a1} = 0.006 per min (deactivation rate)

K_{a2} = 0.006 per minute (deactivation rate), K_{a3} = 0.003 per minute (deactivation rate)

K_e = 0.138 per minute (fractional clearance), $S_{IT}f = \frac{k_{b1}}{k_{a1}} = 0.0512\ \text{min}^{-1}\text{per mUL}^{-1}$ $S_{ID}f = \frac{k_{b2}}{k_{a2}} = 0.0082\ \text{min}^{-1}\text{per mUL}^{-1}$ (insulin sensitivity of disposal).

The system was linearized around an equilibrium point representing the desired glucose and insulin levels. We set the equilibrium points to Q* and I*.

So; linearizing glucose dynamics considering the first compartment gives equation (21);

$$\frac{\delta Q_1(t)}{\delta_{(t)}} = -\left[\frac{F_{01}c}{V_G G(t)} + x_1(t)\right]\delta Q_1(t) + k_{12}\delta Q_2(t) - \delta F_R + \delta U_G(t) + \delta EGP_0[1 - x_3(t)] \quad (21)$$

Furthermore, linearizing glucose dynamics in the second compartment results in (22);

$$\frac{\delta Q_2(t)}{\delta_{(t)}} = \delta x_1(t)Q_1(t) - [k_{12} + x_2(t)]\delta Q_2(t)\, y(t)G(t) = Q_1(t)/V_G \quad (22)$$

where $\delta Q_1(t) = Q_1(t) - Q^*$ represents the deviation of glucose from its equilibrium point. In essence, the dynamic parameters of glucose become $[K_{12}\, Q_2]$.

Also; linearizing insulin dynamics results in (23);

$$\frac{\delta I(t)}{\delta_{(t)}} = \frac{\delta U_I(t)}{\delta V_1} - \delta k_e I(t) \quad (23)$$

where $\delta I(t) = I(t) - I^*$ represents the deviation of insulin from its equilibrium points, $\delta U_I(t)$ represents the deviation of external control, and δV_1 represents the deviation of the insulin distribution volume.

The eigenvalues of the Jacobian matrix of the linearized system were calculated. The Jacobian matrix A is given by;

$$A = \begin{bmatrix} -K_{12} & Q_2 \\ V_I & -K_e \end{bmatrix} = \begin{bmatrix} -0.006 & 0.021 \\ 0.12 & -0.138 \end{bmatrix} \quad (24)$$

Applying the concept of characteristic equations results in;

det (A–λI) = 0 where A is the Jacobian matrix, λ = eigenvalues, and I = Identity matrix.

So;

$$\begin{bmatrix} -0.006 - \lambda & 0.021 \\ 0.12 & -0.138 - \lambda \end{bmatrix} \quad (25)$$

$$\lambda^2 + 0.144\lambda + 0.003348 = 0 \quad (26)$$

Therefore, the solution to the quadratic equation is given as;

$$\lambda = -0.072 \text{ and } \lambda = -0.216 \quad (27)$$

As all eigenvalues have negative real parts, the system is asymptotically stable (i.e., returns to equilibrium). Therefore, based on the stability analysis result, there was no need to increase the insulin therapy regimen, because a stable and effective glucose control was attained.

2.2 Controller's design architecture

The proposed fuzzy logic controller based on the Mamdani fuzzy system consists of a comprehensive architecture. It comprises two input linguistic variables and one output linguistic variable, making use of dynamic parameters for effective control of blood glucose levels in individuals with Type 1 Diabetes Mellitus (T1DM). The two input linguistic variables employed in the system were the current glucose level (g(t)) and rate of change (dg/dt). These variables are essential for quantifying the glucose dynamics and enabling real-time glucose control. The output linguistic variable in the controller corresponds to the calculated insulin volume, which is crucial for maintaining glucose homeostasis. Fuzzy logic principles have been extensively employed in the development of this controller. Fuzzy sets were defined, and membership functions for these sets were determined through a detailed process of fuzzy classification of both input and output variables. In this context, the FLC utilizes a triangular membership function, which is a representative choice for fuzzy systems owing to its simplicity and efficiency. Figure 2 shows the membership functions of the input variables. A vital component of the FLC is the set of 75 IF-THEN rules that govern its operation. These rules were meticulously crafted to establish a connection between desired and actual glucose concentrations. These rules were designed as minimum-type antecedents to optimize the capacity of the controller and minimize discrepancies. Moreover, the rule base is associated with the input and output membership functions (MFs), further fine-tuning its control capabilities. To obtain precise values for the control actions, the CENTROID defuzzification method was employed to ensure that the output decisions were aligned with the desired control objectives. To enhance the effectiveness of FLC, a novel Fuzzy Inference System (FIS) tree controller structure is introduced. Although expert knowledge was initially used to build a single FIS with 75 rules, the complexity of manually constructing fuzzy rules for various combinations of input MFs prompted the exploration of alternative approaches. This new methodology resulted in the creation of two Mamdani FISs by using an incremental design strategy. The first-tier FIS aimed to pre-calculate the insulin injection rate by combining the effects of the blood glucose level (BGL) and blood glucose rate (BGR). Because blood glucose acceleration is typically less significant and can introduce noise into the output, it is handled in the second tier of the FIS. Within this framework, the blood glucose level was characterized by three membership functions (low, medium, and high) and the blood glucose rate was categorized using three membership functions (negative, zero, and positive). The FIS generated five distinct membership functions for the output representing various insulin dosage levels (low, medium, high, very low, and very high). The fuzzy rules of the FLC, displayed in Tables 3 and 4, along with a surface view of the control operation in Figure 3, illustrate the decision-making process. To further enhance the controller's performance, the rule and MF parameters of the FIS object underwent optimization using the "tunefis" function. Genetic algorithms were employed for this optimization process, with the parameters set to a maximum of 3 generations and a population size of 100. These adjustments were facilitated by a cost function evaluation that ultimately selected the rule base with the lowest cost function to be integrated into the fuzzy system within the FIS tree.

To evaluate the effectiveness of the controller, the average results, considering the meal protocols of the three subjects, were compared when utilizing the FLC with and without optimization. The results of these evaluations are listed in Table 6. This comprehensive controller framework plays a pivotal role in maintaining glycemic control in individuals with T1DM, offering enhanced accuracy and adaptability in managing blood glucose levels. Furthermore, an optimization problem is formulated based on the disparity between the outcomes of Hovorka's model and the glucose-insulin regulatory system. The variables K_{12}, K_e, Q_2, and V_i are to be determined to minimize the cost function represented by equation 28. This cost function (Y_0), seeking minimization, is defined with respect to the measured blood glucose level $G_m(T)$, the predicted glucose level $G_p(T)$ from Hovorka's model, and Z_f, which represents the total number of blood glucose samples. The optimization problem described in equation 28 is addressed using the widely recognized genetic algorithm (GA). The genetic algorithm is configured with a population size and generation set at 100 and 3, respectively.

$$Y_0(K_{12}, K_e, Q_2 \text{ and } V_i) = \frac{1}{Z_f}\sum_{Z=1}^{Z_f}(G_m(T) - G_p(T))^2 \tag{28}$$

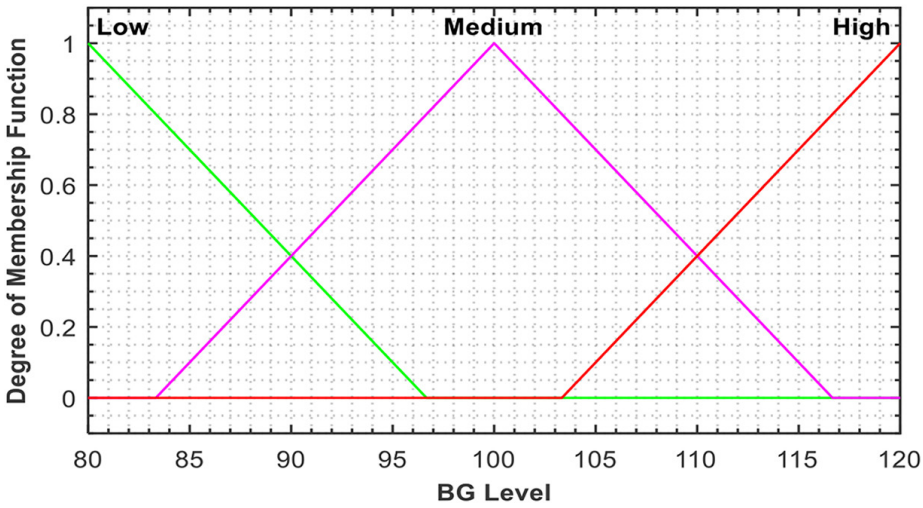

Fig. 2. Membership function of input variables

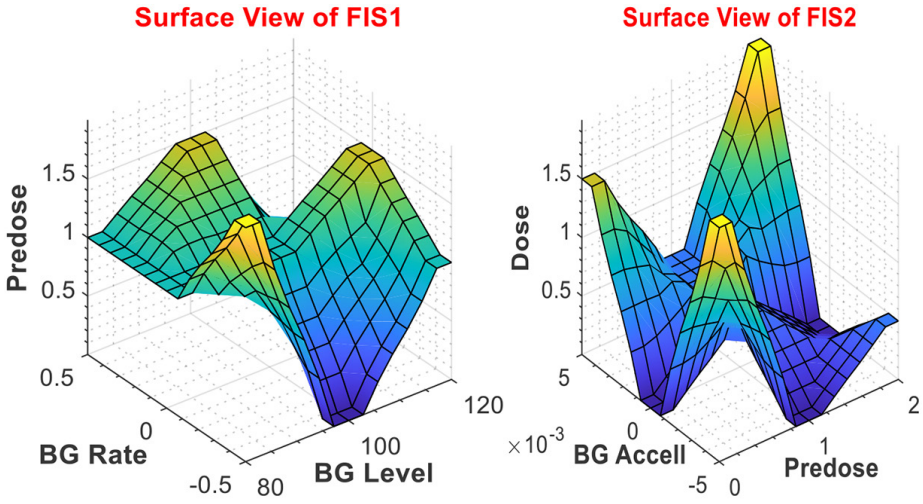

Fig. 3. Surface view of the control operation

Table 3. Rule base of FIS1

	BG Rate: N	BG Rate: Z	BG Rate: P
BG Level: L	Predose: VH	Predose: M	Predose: M
BG Level: M	Predose: VL	Predose: M	Predose: H
BG Level: H	Predose: M	Predose: H	Predose: VL

Table 4. Rule base of FIS2

	BG Accell: N	BG Accell: Z	BG Accell: P
Predose: L	Dose: VH	Dose: VL	Dose: H
Predose: M	Dose: VL	Dose: L	Dose: L
Predose: H	Dose: L	Dose: VL	Dose: VL

Proposed system for the regulation of blood glucose level (BGL). An optimized fuzzy logic controller (FLC) is proposed to regulate blood glucose levels (BGL) in individuals with type 1 diabetes mellitus (T1DP). The Hovorka's model was employed to assess the performance of the controller, thereby providing an accurate representation of the patient's physiological dynamics. Acknowledging the parameter variations in Hovorka's model across different patients, the FLC controller was designed to be adaptive rather than fixed and its parameters were fine-tuned using a metaheuristic technique. In this case, a Genetic Algorithm (GA) was utilized to modify the membership function uncertainties, allowing the FLC controller to effectively handle changing uncertainties and perturbations. Figure 4 illustrates a schematic representation of the proposed BGL regulation, with the controller taking the inputs of the error signal (e) and its rate of change (Δe).

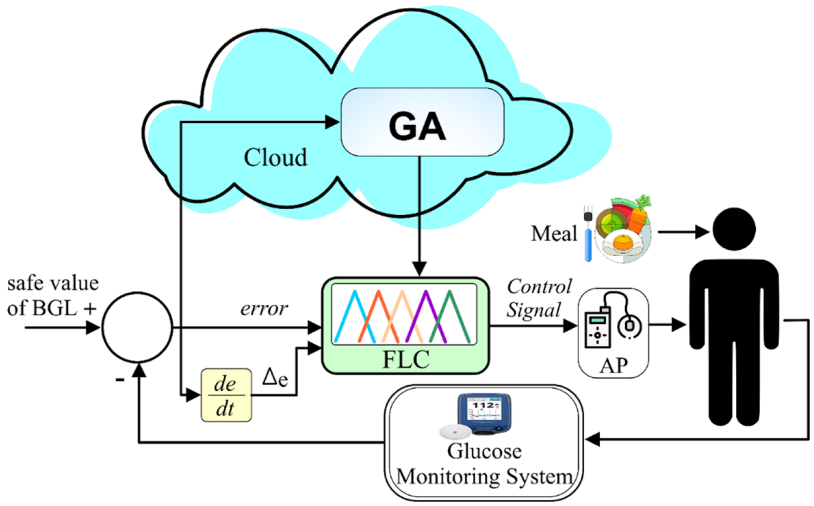

Fig. 4. Block diagram for the proposed fuzzy logic-based controller for type 1 diabetes patients

2.3 Numerical simulation

The numerical simulation phase involved the development and testing of the proposed Fuzzy Logic controller system, integrated with the Hovorka model, to assess its performance and effectiveness in regulating blood glucose levels for individuals with Type 1 Diabetes Mellitus (T1DM). The simulation framework was implemented

using the MATLAB-Simulink software. The primary objective of this simulation was to enable the fuzzy-logic controller to effectively manage the input insulin rate, ensuring that the blood glucose concentration remained within a normal and desirable range. The simulation spanned 24 hours, commencing at 0s and ending at 84600s. The Fuzzy Logic controller received essential inputs related to blood glucose levels, rate of blood glucose change, and rate of acceleration. These inputs are crucial for guiding the controller's decision-making process, which aims to maintain optimal blood glucose levels. To achieve this objective, a Fuzzy Logic controller was designed with a hierarchical structure consisting of two Mamdani Fuzzy Inference System (FIS) objects. This hierarchical architecture facilitates the integration of the input data and streamlines the decision-making process. It is important to note that control responses were primarily influenced by the quantity and rate of change in blood glucose levels rather than by acceleration, which typically has a negligible impact and the potential to introduce output distortion. This hierarchy featured two levels, with the first tier focusing on pre-calculating the insulin dosage by considering the effects of blood glucose levels and their rate of change. However, the second tier incorporated the rate of acceleration to further refine insulin dosage calculation. Performance tests were carried out on the controller, considering two challenging scenarios: performance analysis of a challenging scenario considering the meal protocol, and performance analysis of insulin clearance rate variability.

Performance analysis of challenging scenario considering meal protocol. In this section, we present a comprehensive evaluation of the performance of our proposed controller. This analysis was conducted by simulating a challenging scenario in which we considered the meal protocol of three distinct subjects over a day, as outlined in Table 5 [45]. To add an aspect of the meal protocol to create a supper scenario, one-third of breakfast was consumed, thus emulating real-world dietary variations. Key time vectors were identified to assess meal intake at different hours, including the 1st, 5th, 11th, and 13th hours, corresponding to breakfast, lunch, dinner, and supper, respectively. Moreover, the simulation tracked parameters related to glucose utilization and carbohydrate (CHO) intake for each subject, namely ID 117-1, 126-1, and 128-1. Figures 5–10 visually represent the glucose utilization and CHO intake patterns for these subjects. To gain insight into the dynamics of blood glucose levels when the body absorbs glucose without corrective insulin infusion, a simulation with constant zero control action was executed. The results were analyzed. For the initial subject, ID 117-1, the patient's blood glucose level fluctuated between 100 mg/dl and 1250 mg/dl, ultimately settling at approximately 600 mg/dl. This stable glycemic state was not reached, as shown in Figure 11, and the corresponding insulin injection rate is shown in Figure 12. A similar pattern was observed for subject 126-1, with blood glucose levels oscillating between 100 mg/dl and 1200 mg/dl. Ultimately, the glucose concentration settled at approximately 580 mg/dl, failing to achieve a stable glycemic state, as shown in Figure 13, along with the insulin injection rate illustrated in Figure 14. Subject 128-1's blood glucose levels displayed similar fluctuations, varying between 100 mg/dl and 1500 mg/dl. Eventually, the glycemic state settled at approximately 700 mg/dl; however, like the other subjects, a stable glucose level was not achieved, as demonstrated in Figure 15, along with the corresponding insulin injection rate captured in Figure 16. In light of these findings, we reintroduced a Fuzzy Logic controller, both with and without the incorporation of a genetic algorithm, to optimize insulin infusion to achieve improved glycemic control. The details of these findings are presented more comprehensively in the results section. This performance analysis serves as a vital precursor to understanding the effectiveness and adaptability of the proposed controller under challenging real-world conditions.

Table 5. The adopted subjects' meal protocol

Subject ID	Breakfast at (7 am), g	Lunch at (noon), g	Dinner at (6 pm), g	Supper at (8 pm), g	Total gCHO
117-1	80	80	108	27	295
126-1	64	64	87	21	236
128-1	107	107	144	36	394

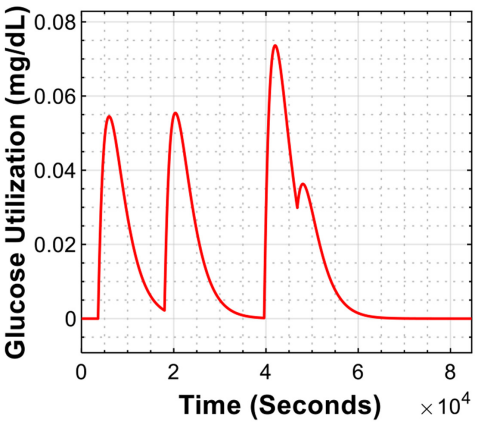

Fig. 5. Glucose utilization against time

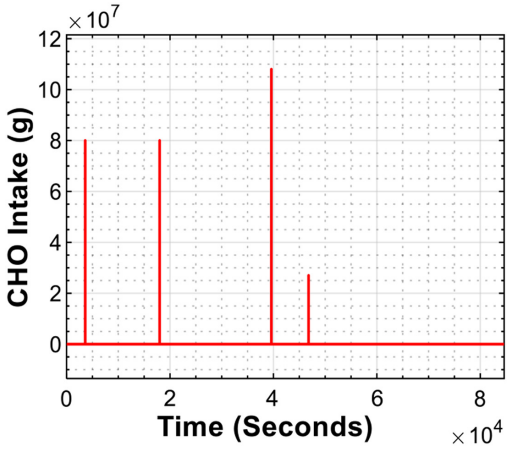

Fig. 6. CHO intake against time

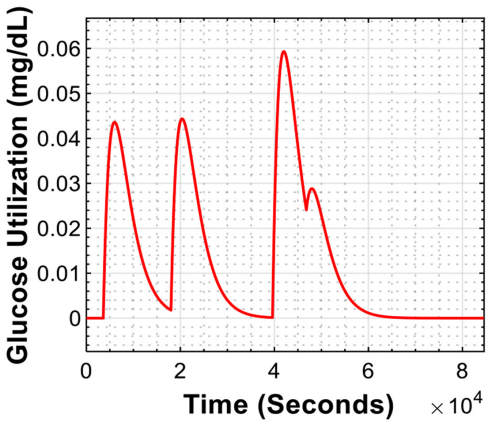

Fig. 7. Glucose utilization against time

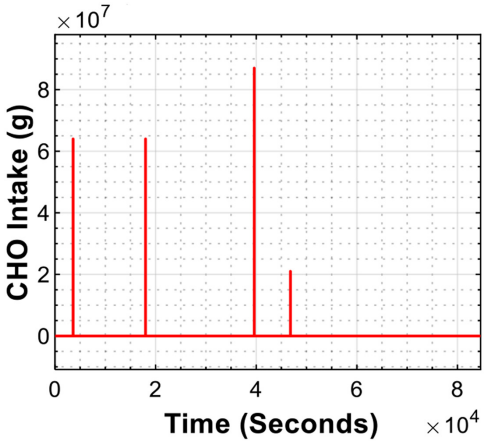

Fig. 8. CHO intake against time

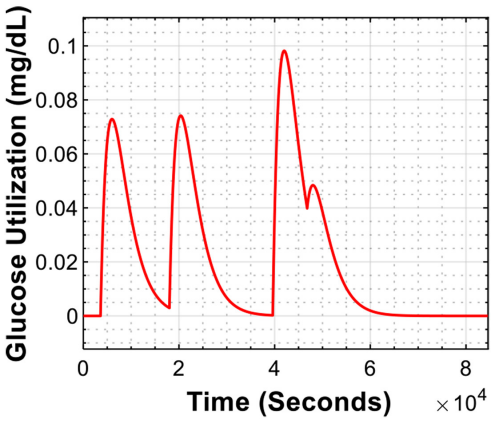

Fig. 9. Glucose utilization against time

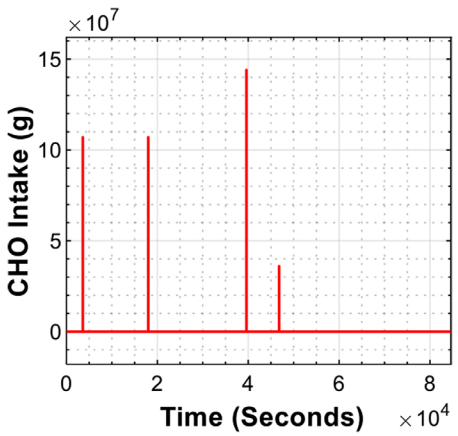

Fig. 10. CHO intake against time

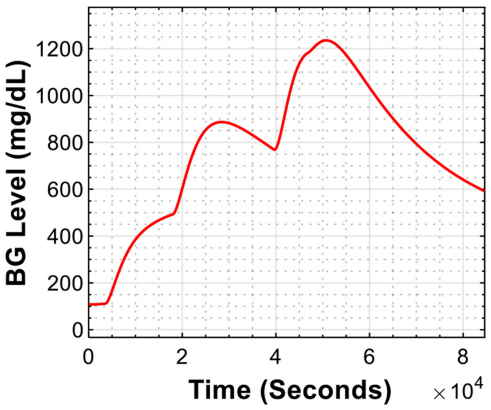

Fig. 11. BG level against time

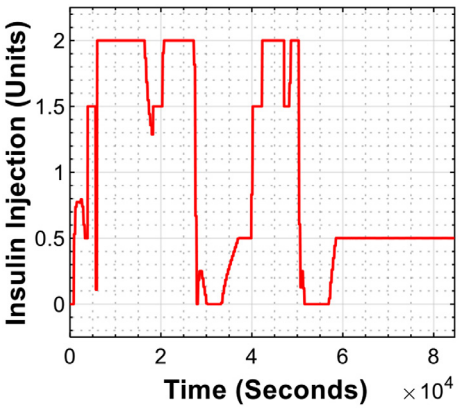

Fig. 12. Insulin injection against time

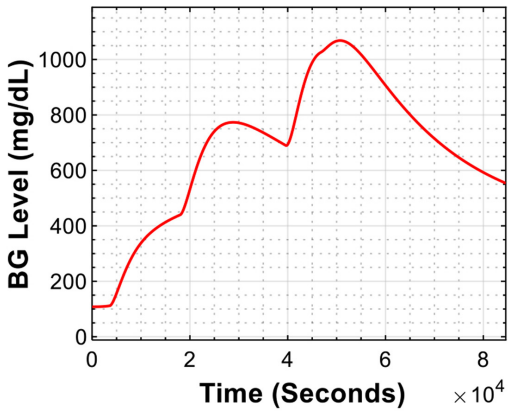

Fig. 13. BG level against time

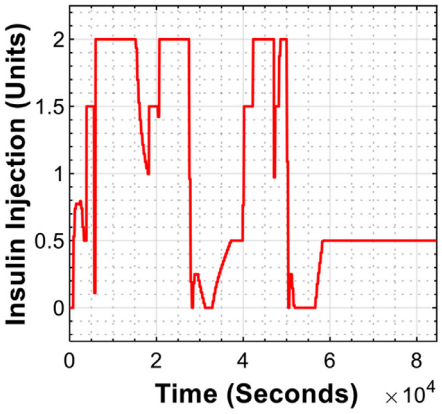

Fig. 14. Insulin injection against time

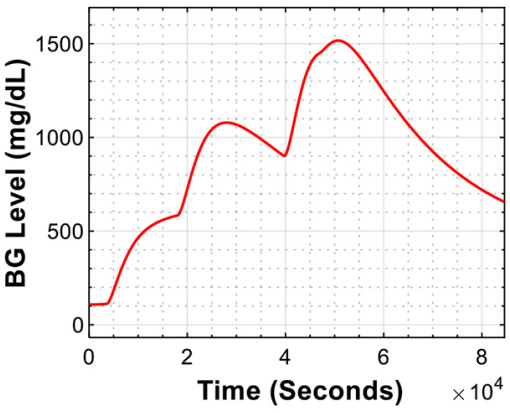

Fig. 15. BG level against time

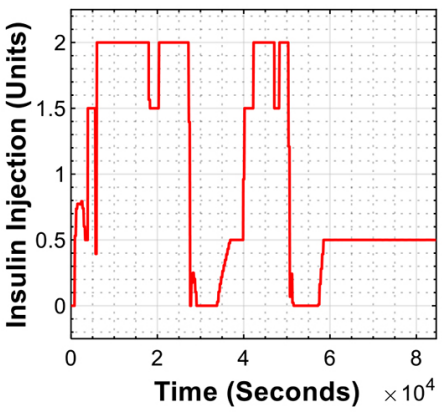

Fig. 16. Insulin injection against time

Performance analysis of insulin clearance rate variability. In this performance assessment, we examined the influence of variable insulin clearance rates among the individuals. The underlying assumption was that this parameter exhibited significant variance with an acceptable margin of ±25%. This parameter, referred to as the insulin clearance rate, governs the rate at which insulin is absorbed into the body. Notably, this rate of absorption is subject to considerable divergence among patients, resulting in an array of possible scenarios. The importance of this

variability lies in its direct connection with the degradation rate of insulin. A higher insulin clearance rate signifies accelerated insulin degradation, ultimately resulting in elevated blood glucose levels in diabetic individuals. Acknowledging this inherent variability, our analysis encompassed a parameter range extending up to 25% from the nominal value originally set at 0.08 within our model. Crucially, the optimized fuzzy logic controller that we proposed and implemented emerged as a potent tool to ensure that the glucose concentration remained well within acceptable bounds. The effectiveness of the controller in adapting to varying insulin clearance rates served as a cornerstone for the robust performance of our system in maintaining glycemic control even in the face of uncertain insulin dynamics. This performance analysis provides valuable insights into the adaptability and resilience of our proposed controller in the presence of real-world variability and challenges encountered by individuals with diabetes.

3 RESULTS AND DISCUSSIONS

This section presents the comprehensive findings of the observed performance of the fuzzy logic controller (FLC) with and without genetic optimization across three individual subjects. This study aimed to evaluate the impact of the optimization scheme on glycemic control and assess the efficacy of the controller in maintaining blood glucose levels within the desired range while optimizing the insulin dosage for each patient.

3.1 Performance of fuzzy logic controller with and without optimization for subject ID 117-1

In Figure 17, the graph illustrates the blood glucose levels, whereas Figure 18 depicts the corresponding insulin injection patterns of Subject ID 117-1 under the influence of FLC with optimization. Conversely, Figure 19a and b show a comparison between the systems with and without the optimizer. The findings revealed that when the FLC was optimized, the plasma glucose concentration fluctuated between 110 and 258 mg/dl upon glucose intake, eventually stabilizing at 80 mg/dl. This more favorable glycemic state was achieved, as opposed to the system without optimization, where the blood glucose level remained constant at 100 mg/dl.

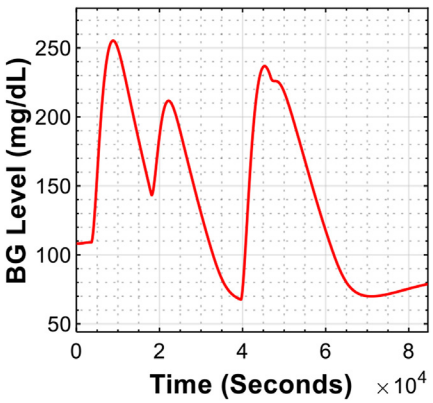

Fig. 17. BG level against time

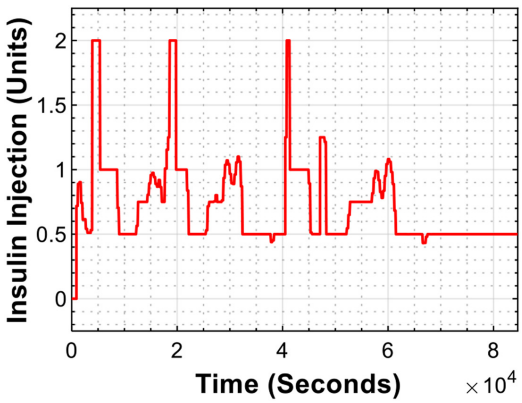

Fig. 18. Insulin injection against time

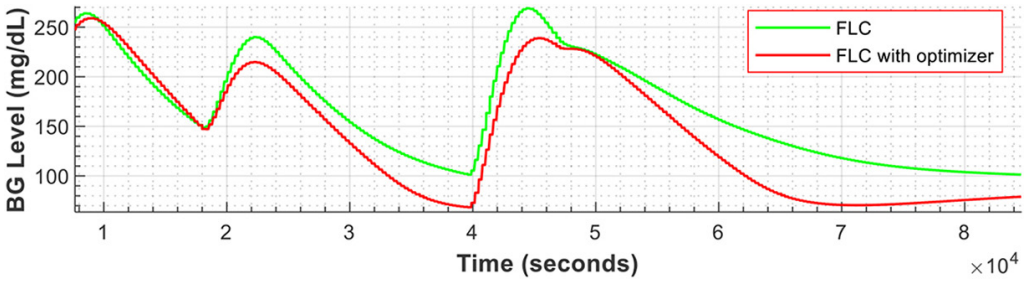

Fig. 19a. BG level against time

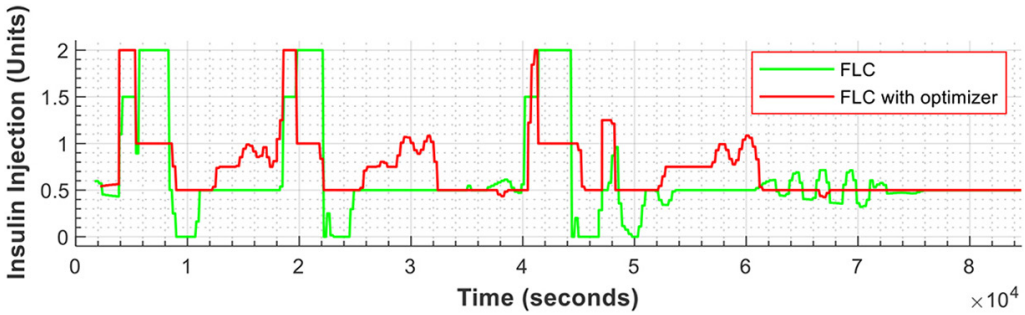

Fig. 19b. Insulin injection against time

3.2 Performance of fuzzy logic controller with and without optimization for subject ID 126-1

For Subject ID 126-1, the performance of the FLC with optimization is shown in Figures 20 (blood glucose levels) and 21 (insulin injections). Figure 22a and b compares the behavior of the system with and without the optimizer. Similar to the previous case, it was observed that FLC with optimization led to plasma glucose concentration fluctuations between 110 mg/dl and 220 mg/dl, ultimately settling at 80 mg/dl, reflecting a notably improved euglycemic state. Conversely, the system without optimization maintained a steady blood glucose level of 100 mg/dl.

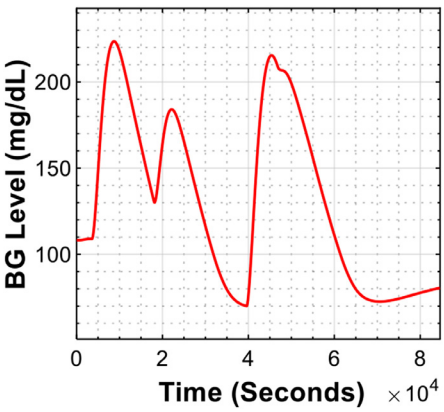

Fig. 20. BG level against time

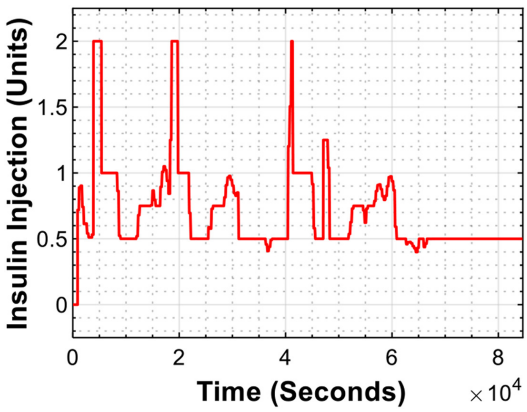

Fig. 21. Insulin injection against time

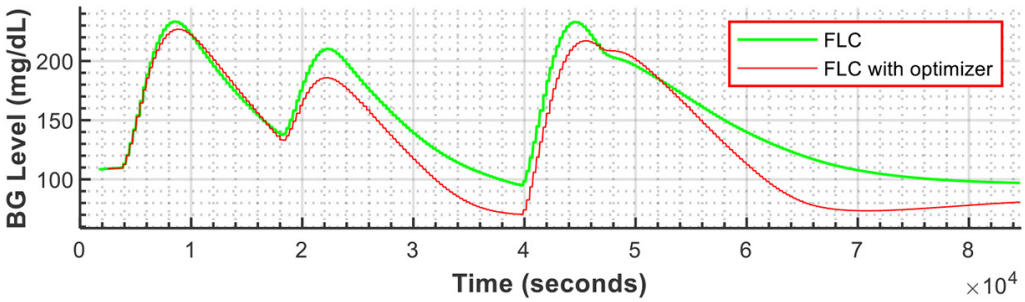

Fig. 22a. BG level against time

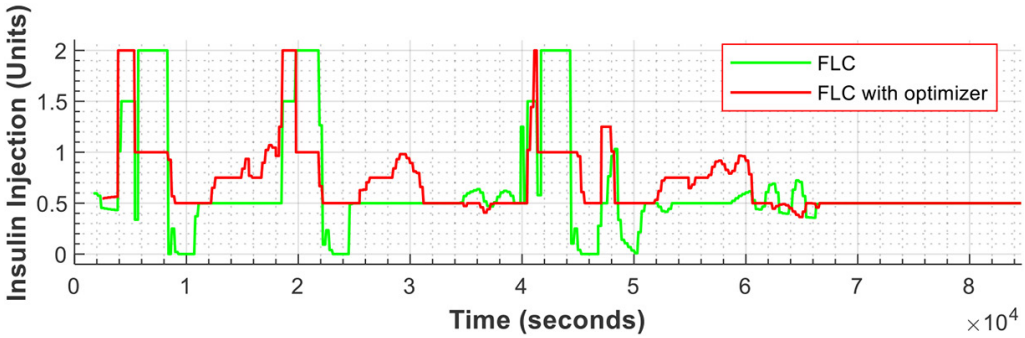

Fig. 22b. Insulin injection against time

3.3 Performance of fuzzy logic controller with and without optimization for subject ID 128-1

Subject ID 128-1's response to the FLC with optimization is presented in Figures 23 (blood glucose levels) and 24 (insulin injections), while Figure 25a and b contrast the system's performance with and without the optimization. Upon analyzing the optimized system, it was evident that the patient's plasma glucose concentration fluctuated from 110 mg/dl to 310 mg/dl and eventually settled at 80 mg/dl, thus manifesting an improved euglycemic state. In contrast, the system without optimization maintained a blood glucose level of 115 mg/dl.

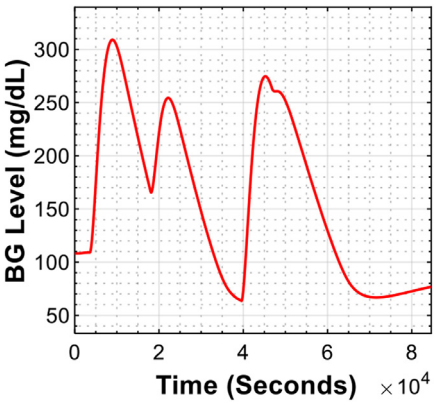

Fig. 23. BG level against time

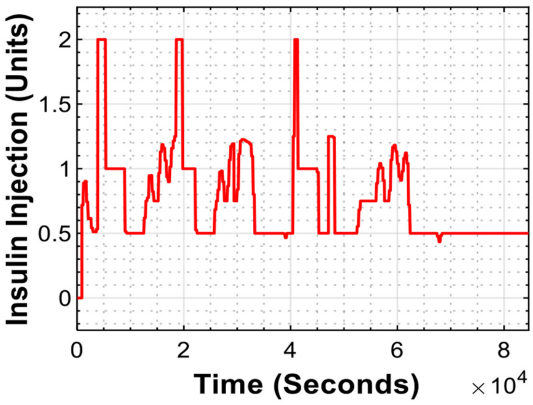

Fig. 24. Insulin injection against time

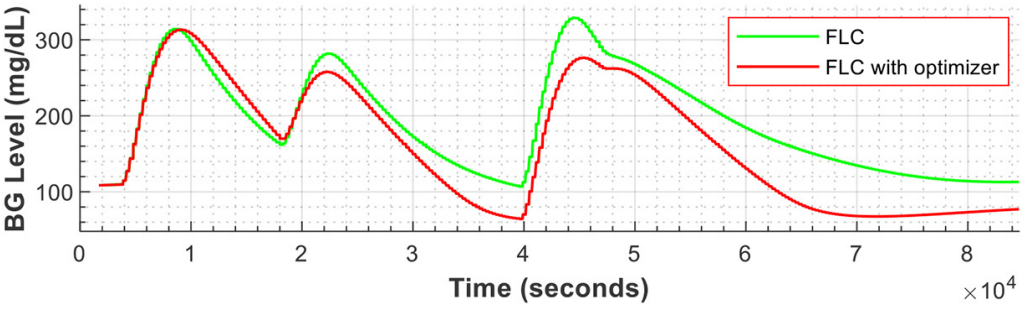

Fig. 25a. BG level against time

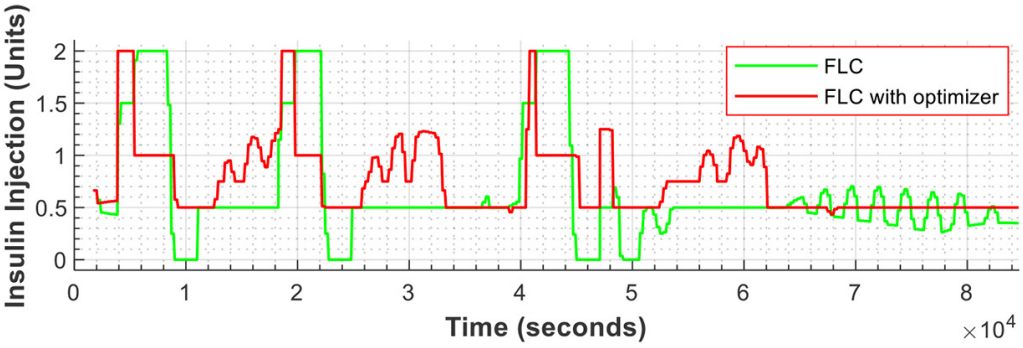

Fig. 25b. Insulin injection against time

In essence, the results obtained from the three subjects distinctly illustrate the positive influence of genetic optimization on glycemic control. The optimized FLC demonstrated the ability to respond to glucose intake more effectively, leading to improved blood glucose regulation. These findings highlight the significance of employing advanced control mechanisms, such as fuzzy logic controllers with genetic optimization, to enhance diabetes management and achieve superior glycemic outcomes.

4 EVALUATION METRICS

To assess the performance of the control systems in regulating blood glucose levels, internationally recognized glycemic control parameters [46] were employed for comprehensive comparisons. The following metrics were used.

Average Glucose Level (MG): This metric represents the mean blood glucose concentration and provides an overview of glycemic control. Time in Range (TIR): TIR indicates the proportion of time spent within the desired blood glucose range, which is a key indicator of effective glycemic management. Time Below Range (TBR) Ratio: The TBR ratio reflects the time spent with blood glucose levels below the desired range, signifying the extent of hypoglycemia risk. Time Above Range (TAR) Ratio: Conversely, the TAR ratio illustrates the time spent with elevated blood glucose levels above the desired range, indicating hyperglycemia episodes. Time below 54 mg/dL: This parameter specifies the proportion of time spent with blood glucose levels below the critical threshold of 54 mg/dL, emphasizing the risk of hypoglycemia. Standard Deviation (STD): The STD measures the dispersion of blood glucose values, offering insight into glycemic variability. Average Insulin Administration per day (INS): INS quantifies the daily insulin dosage, a vital factor in glycemic control. The evaluation was conducted in both open-loop and closed-loop scenarios (i.e., with and without the fuzzy logic optimizer) for

each subject, and the results are presented in Table 6. In addition, the Coefficient of Variation of Glucose Area (CVGA) for the optimized control architecture was computed for all three subjects, as shown in Figures 26, 27, and 28. CVGA serves as a comprehensive indicator of glycemic stability and reflects the overall performance of the control system in maintaining blood glucose levels within the desired range. Furthermore, to evaluate the efficacy of the proposed controller, a comparative analysis was conducted against the outcomes of two existing strategies: compound internal model control (IMC) [37] and a multi-objective output feedback controller [38]. Notably, our study incorporated a more extensive meal protocol (Subject ID 126-1) than those considered in the referenced papers, highlighting the robustness of our controller. The results, as presented in Table 7, underscore the superior time in the range achieved by our proposed system compared to the outcomes reported in the two aforementioned studies.

Table 6. The open and closed-loop scenarios (i.e., with and without fuzzy logic optimizer) of each patient

Subject	Metrics	Open Loop System	FLC	FLC with Optimization
117-1	MG (mg/dl)	675	153	145
	TIR (%)	0	60.10	61.25
	> 180 (%)	100	39.9	38.75
	< 70 (%)	0	0	0
	< 54 (%)	0	0	0
	STD	341.3	82.5	79.53
	INS (U/day)	16.3	20.1	23.8
126-1	MG (mg/dl)	617	187	180
	TIR (%)	0	69.8	71
	> 180 (%)	100	30.2	29
	< 70 (%)	0	0	0
	< 54 (%)	0	0	0
	STD	315	100.2	99.33
	INS (U/day)	14.5	17.9	20.7
128-1	MG (mg/dl)	808.33	184	175
	TIR (%)	0	60.50	61.10
	> 180 (%)	100	39.50	38.9
	< 70 (%)	0	0	0
	< 54 (%)	0	0	0
	STD	436.29	105.66	101.45
	INS (U/day)	16.6	23.2	25.3

Table 7. Assessment of controller's performance in comparison with IMC algorithm and a multi objective output feedback controller

References	Controller	MG (mg/dl)	TIR (%)	> 180 (%)	< 70 (%)	LBGI	HBGI
[37]	Compound IMC	165.8	62.95	37.04	0	0.032	7.4
[38]	A multi-objective output feedback controller	165.51	63.89	36.11	0	0	7.43
Current study	Proposed controller	180	71	29	0	0	7.47

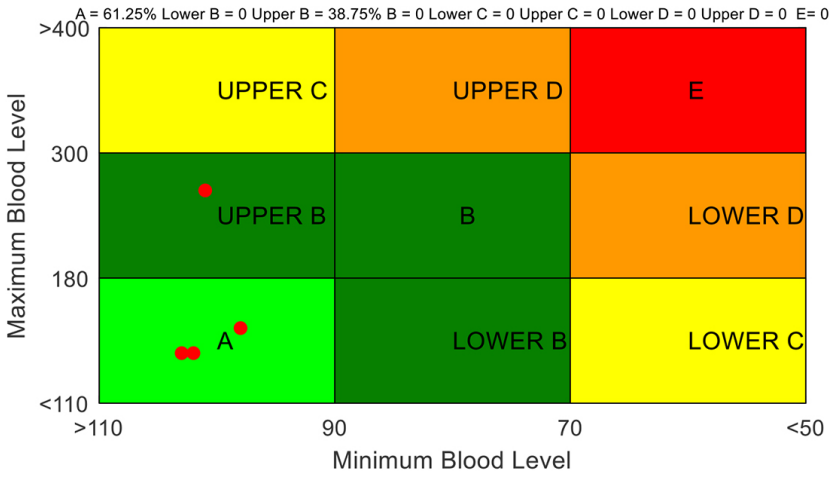

Fig. 26. CVGA plot for subject ID 117-1

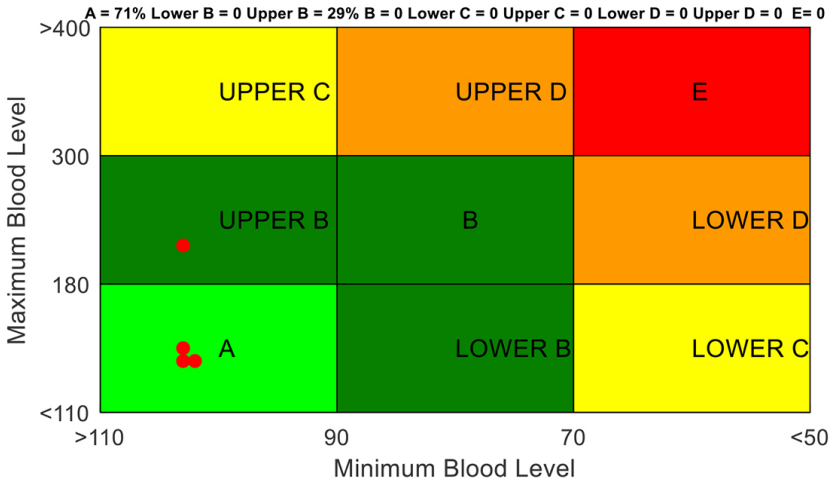

Fig. 27. CVGA plot for subject ID 126-1

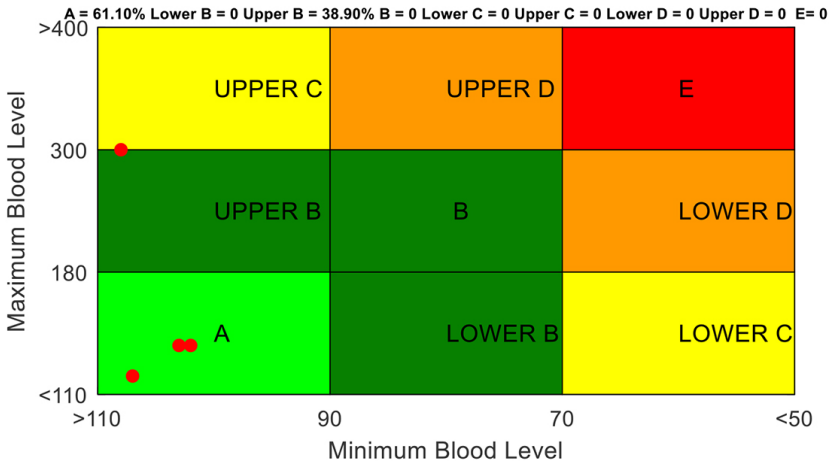

Fig. 28. CVGA plot for subject ID 128-1

Notes: The following abbreviations in the CVGA plot depict: A: Accurate control; Lower B: Benign deviations in hypoglycemia; Upper B: Benign deviations in hyperglycemia; B: Benign control deviations; Lower C: Overcorrection in hypoglycemia; Upper C: Overcorrection in hyperglycemia; Lower D: Failure to deal with hypoglycemia; Upper D: Failure to deal with hyperglycemia; E: Erroneous control.

5 CONCLUSION AND FUTURE PERSPECTIVES

In this study, an optimized fuzzy control scheme tailored for three distinct subjects with unique physiological characteristics was developed and assessed. The study yielded significant insights into the complex dynamics of blood glucose regulation. Subject 117-1 exhibited a noticeable reduction in blood glucose variability, specifically a decrease in standard deviation, upon transitioning from an open-loop to a closed-loop control system. This decline in variability indicates a smoother and more stable blood glucose profile, suggesting improved health under the closed-loop scenario. Additionally, subjects 126-1 and 128-1 showcased remarkable glycemic control when subjected to the optimized fuzzy control system, highlighting the potential efficacy of such control mechanisms in managing blood glucose levels effectively. While the primary focus of this study centered on the physiological aspects of glucose dynamics, it is imperative to acknowledge the multifaceted nature of glycemic management. To achieve a more comprehensive understanding of the glycemic significance for subjects, future research avenues should explore alternative strategies, including data-driven approaches, the design of new fuzzy artificial pancreas models considering time delays, adoption of fuzzy type 2 control designs, and the incorporation of hybrid models. Furthermore, broadening the scope of the investigation to encompass external factors such as stress, sleep patterns, and physical activity (exercise), known to influence blood glucose concentrations, will contribute to a more adaptive and encompassing model. The contributions of this study include the design of a controller aimed at maintaining blood glucose levels within the target range of 70–180 mg/dl. It introduced an iterative tree structure to stabilize insulin delivery and incorporated a genetic algorithm to achieve an optimized control architecture and insulin infusion, accommodating uncertainty in the fuzzy membership function. In summary, this study marks a significant step towards advancing our understanding of blood glucose regulation and control mechanisms. The optimization of fuzzy control schemes holds promise for enhancing the quality of life for individuals with diabetes. As we continue to explore innovative solutions, we progress towards achieving optimal glycemic control and ultimately improving the well-being of those living with this condition.

6 ACKNOWLEDGEMENTS

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