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RESEARCH ARTICLE

Optimizing Inotropic Infusion With Cluster Specific AI Decision Models and Digital Twins

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ABSTRACT Inotropes are critical care medications essential for maintaining normal blood pressure (BP) in hospitalized patients. Titrating infusion rates of inotropes such as noradrenaline, vasopressin, and adrenaline based on fluctuating BP presents significant challenges in critical care settings. Typically, clinicians set a constant infusion rate for one hour, which may not accommodate the dynamic variability of BP inherent in critically ill patients, potentially leading to inadvertent hypotension or hypertension. Conventional feedback controllers, including fuzzy logic controllers (FLC), struggle to adapt to complex BP variations due to fixed algorithms and intracohort variability in drug responses. We propose an AI-enhanced closed-loop noradrenaline infusion control mechanism utilizing long short-term memory (LSTM) networks. This approach captures variability in drug responses through clustering of patients using LSTM autoencoders and K-means algorithms, subsequently developing LSTM-based decision models for infusion rates tailored to clusters. Additionally, a digital twin cardiac model serves as a simulation tool for validating the impact of inotropic infusion as indicated by the decision model. Comparative performance analyses demonstrate that our AI-enhanced closed-loop feedback method outperforms conventional systems like FLC regulators and pharmacokinetic-pharmacodynamic (PK-PD) models while ensuring patient safety as well as reducing the workload of clinicians.

INDEX TERMS AI infusion pump, cardiac digital twin, infusion control, LSTM, noradrenaline, precision medicine.

I. INTRODUCTION

Syringe pumps are medical devices used to transfer drugs intravenously to patients. Inotropes such as noradrenaline, vasopressin, and adrenaline are delivered to the patient with the help of a syringe attached to the device. These inotropes are used to maintain the BP of patients at a target range [1], [2]. Each patient's target BP requirement varies according to their demographics and current clinical conditions. Vital parameters such as systolic BP, diastolic BP, mean arterial pressure (MAP), and heart rate (HR) are complex and vary unpredictably [3], [4], [5]. Therefore, the currently employed clinical practice of the infusion process may cause dosage errors [6], [7].

In a real-world clinical setting, a preprogrammed amount of inotrope is delivered to the patient. The infusion rate is usually preset for one hour, and a constant amount of drug is delivered during that period. This preset infusion for a particular duration further causes hypotension or hypertension. During abnormal patient conditions, doctors

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manually change the infusion rate, which may lead to delays in infusion changes. Critical care clinicians and nurses have to spend considerable time and attention on frequent adjustments in infusion rates [8], [9]. During clinical emergencies, sudden infusion adjustments may even lead to human errors [10], [11]. There are reported instances of dosage errors due to manual infusion adjustment and the stressful workload of the clinicians [8].

Conventional control algorithms such as proportional integral derivative (PID) and FLC have been used to automate infusion rates in syringe pumps [12], [13], [14], [15], [16]. Due to the complex BP variations as well as unknown drug response behaviors, these controllers are unable to adapt amply [14], [15], [17], [18]. PID and FLC, along with PK-PD patient models, are conventionally used to validate closed-loop automation of various drugs [15], [19]. These controllers are used in medical applications to maintain BP, glucose levels, anesthesia, and cancer treatment [20], [21], [22], [23]. The main limitation of the PK-PD patient model is that it assumes the human body as various compartments, and the drug distribution algorithms are designed by the assumption of uniform distribution of drugs across the compartments. Therefore, a PK-PD patient profile does not fully capture the hemodynamic behavior of the whole human population. Hence, we designed and developed a prototype AI-driven digital twin cardiac model and decision support system for inotropic drug control. Our main contributions include the following:

- Data-driven assessment and reporting of potential drug dosage errors and evidence of intracohort variability, as well as the complexity of BP variations among intensive care unit (ICU) patients.
- Hierarchical and personalized infusion rate decision models by employing time series clustering for patient subgrouping.
- Advanced digital twin cardiac patient models that capture complex hemodynamics are utilized to test and validate the performance of the infusion rate decision models.
- Validation of the infusion rate decision model by closed-loop virtual demonstration of digital twin and infusion rate models.

Our paper is organized as follows: Section II explains the related works. Section III describes methodology, which consists of data-driven analysis and the design of both AI-enhanced infusion control and conventional FLC control. Section IV details the experiments, performance analysis, and validation of both AI models and the FLC method. Section V explains our key research findings, limitations, and future directions of our research. We conclude our study in Section VI.

II. RELATED WORKS

Real-world clinical challenges associated with controlling the infusion rate of inotropes are majorly due to the preprogrammed infusion rates, delay in manual infusion change, limitations of existing control algorithms, and complexity of the human cardiac system. There are studies related to the use of conventional controllers and patient models to optimize the infusion rate of drugs such as inotropes, insulin, anesthetics, etc.

Sasmal et al. [8] conducted a six-month retrospective observational study on the impact of medication errors in a tertiary care hospital in Kolkata, India. They reported 50% medication errors during drug administration; out of 136 drug administration errors, 33 cases (24.26%) were classified as overdoses, and 20 cases were classified (14.70%) as underdoses.

To optimize the infusion rate of drugs, Parihar et al. [24] introduced the potential of model predictive control (MPC) in therapeutic automation. They proposed the use of the MPC algorithm for cancer, HIV, anesthesia, fibromyalgia, and diabetes management. The MPC method involves solving an optimization problem at each time step, which is computationally complex. To complete the optimization process as quickly as possible, the MPC may be forced to produce erroneous results [25], [26].

Sharma et al. [12] developed an interval type 2 fuzzy logic control (IT2FLC) method to regulate BP. Their architecture shows that the IT2FLC tries to reduce the uncertainties and variations of the MAP, with a considerable improvement over traditional PID controllers. However, after a certain duration of infusion, the patient's drug response may vary, and the fixed rule-based algorithms would require alterations in the dosage rules for each patient.

A fractional order proportional integral derivative (FOPID) control for modeling the infusion pump framework was proposed by Tharimela et al. [13]. They used Matlab software to program and mechanically simulate the infusion pump. The optimal drug quantity is decided by changing the tuning parameters of the FOPID controller. However, the FOPID parameters of patients may need to change at any time due to differences in demographics and physiological factors such as drug metabolism, distribution, and response time during infusion [27], [28].

Sasaki et al. [21] introduced a closed-loop norepinephrine infusion system to control MAP. The system utilizes a fixed PID control algorithm to adjust the infusion rate of noradrenaline based on real-time BP readings. A small sample of six dogs was used to test the performance of the controller that lacked generalizability, and they used isoflurane medicine to induce hypotension.

A closed-loop system for norepinephrine infusion was proposed by Joosten et al. [20] to reduce the occurrence of hypotension by maintaining MAP within the therapeutic range of the patient. They compared the performance of manual noradrenaline titration with a closed-loop PID system. The use of a PID controller automates the infusion process and performs better than manual control. However, their proposed system lacks an advanced patient model that resembles hemodynamics to validate the performance of the PID controller.

The conventional approach for building personalized patient models is employing PK-PD models [29], [30], [31], [32]. Baum et al. [19] proposed a closed-loop drug delivery system to maintain the BP of the patients. They designed a PK-PD mathematical model that outputs the BP values for the given infusion rate. This patient model was designed by assuming the human body as different compartments and a uniform distribution of inotropes throughout the compartments. Based on these assumptions, they calculated dosage rates and tried to maintain BP in the target range.

Thamotharan et al. [33] proposed a digital twin model to personalize insulin infusion for elderly type 2 diabetic patients. They used the LSTM network for the time series prediction of glucose values. This digital twin model consists of a data aggregation module, a glucose prediction module, a diagnostic module to predict intracohort variations, and a management module to maintain blood glucose levels in the target range. However, the study was conducted on geriatric patients, and the sample size needs to be increased to assess the generalizability of the model.

Meijer et al. [34]. introduced the design of digital twin patient models for personalized patient care. Their case studies show the possibility of digital twin modeling for building cardiac models for electrocardiogram (ECG) prediction, artificial pancreas for glucose monitoring, single-cell models for cancer research, and predicting drug effectiveness. However, they report challenges concerning data quality, data integration, computational power, and patient safety that prevent the advancement of digital twin technology in personalized treatment.

Practical implementation of personalized inotropic infusion systems would require overcoming several challenging steps, such as research in developing advanced control algorithms with capabilities to capture intracohort variability of drug responses while adapting to physiological responses [35], [36], [37], [38].

To overcome these challenges, we report the development and in vitro pilot validation of an AI-enhanced closed-loop inotropic infusion titration methodology that aims to capture both complex physiological responses and intracohort variability among patients.

III. METHODOLOGY

A. DATA-DRIVEN ANALYSIS

Our data-driven analysis consists of the assessment of dosage errors, intracohort variability of drug response, and complexity measurement in BP variations. This analysis helps to understand the nature of BP variations and the need for personalized infusion therapy.

1) DATA SET AND PREPROCESSING

We conducted a prospective study consisting of 55 patients (adults above 30 years, 38 males, 17 females) at our university super specialty hospital, Amrita Institute of Medical Sciences and Research Centre, India. We obtained the requisite approvals from the independent institutional ethics committee at Amrita Hospital, Kochi, India. Data were collected from the ICUs of cardiac surgery, gastric surgery, neurosurgery, and infection control. Among the 55 patients, 24 patients were supported with multiple inotropes, and the remaining 31 patients were supported with noradrenaline alone. Their time series data consist of systolic BP, diastolic BP, MAP, HR, and corresponding infusion rates. Vital parameters were collected from the bedside monitor, and the corresponding infusion rate details were recorded from the patient's ICU chart. Since the time taken for drug metabolism and hemodynamic response to infusion medicines is observed to take between 5 to 10 minutes [39], we collected data at intervals of every 5 minutes. Distribution of the monitored duration of drug delivery in patients is shown in Figure 1.

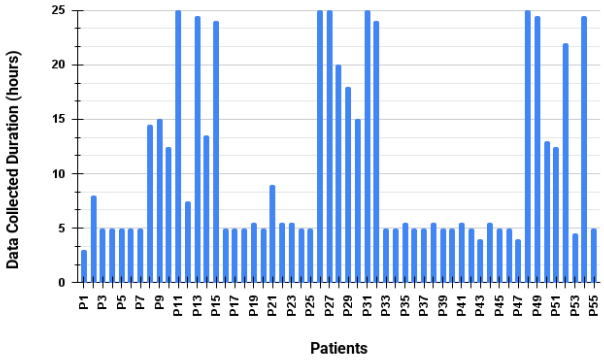

FIGURE 1. Data collected duration of 55 patients from various ICUs.

The duration of data collection for each patient was different, ranging from a minimum of 3 hours to a maximum of 25 hours, depending on their condition and duration of infusion. Among the collected data, two patients had intermittent missing values in their BP readings. The first patient had a total missing value for 30 minutes, and the second one had 45 minutes. We filled it using the average data imputation method using the previous 15-minute BP data. For our complex time series data normalization, we used the standard scalar method as it preserves the temporal patterns and periodic behavior.

2) ASSESSMENT OF DOSAGE ERRORS

Our study included a diverse set of patients admitted with renal failure, post-cardiac surgery, hypertension, and gastrointestinal diseases. The recommended target MAP in each of these clinical conditions is marginally different. It is recommended to maintain MAP at 65-70 mmHg in cirrhotic patients. On the other hand, a hypertensive patient with renal dysfunction requires a MAP of 75 to 80 mmHg. Furthermore, in cardiac surgical patients, the recommended MAP is between 60 to 80 mmHg [40]. In postoperative patients, the incidence of hypotension requiring treatment is more frequent than hypertension. The guideline recommends treating BP if it reaches a threshold of 180 mmHg

TABLE 1. Dosage error assessment criteria for overdose and underdose conditions.

Condition	Change in MAP Limit	Dosage Error Assessment Time
Overdose	MAP_δ >50	Every 15 minutes (critical condition)
Overdose	16> MAP_δ <50	Every 30 minutes
Underdose	MAP_δ >5	Every 15 minutes (critical condition)

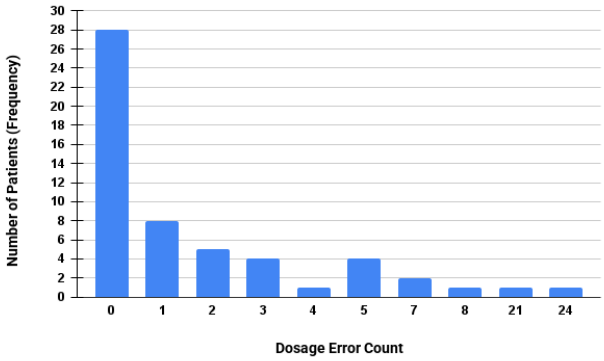

FIGURE 2. Assessment of the dosage error count and its frequency among 55 patients.

(systolic) / 110-120 mmHg (diastolic), which correlates to a MAP of 130 to 150 mmHg, as it is associated with hypertensive emergencies like acute coronary syndrome, cerebral hemorrhage, and pulmonary edema. We selected a safe upper target limit of 80 mmHg to prevent the occurrence of these emergencies [41]. More relevant than the absolute values of MAP, it is vital to maintain it within the limit of 20% of a patient's preoperative MAP. It is also established that the variation in MAP has a stronger association with 28-day mortality than the absolute MAP values [42]. To capture these complexities in hemodynamic management, we set the lower and upper MAP target values as 60 and 80 mmHg, respectively. Based on this, we also define overdose and underdose as follows:

Overdose: The patient's MAP is continuously sustained above the target of $MAP_{high} = 80$ mmHg, with a delta change MAP_δ of at least 16 mmHg (20% of 80), prolonged over a duration of 30 minutes or more. (applying much more liberal bounds based on Yao et al. [42]).

Underdose: The patient's MAP is continuously sustained below the target of MAP_{low} = 60 mmHg, with MAP_δ of at least 5 mmHg, prolonged over a minimum duration of 15 minutes. (applying much tighter bounds because hypotension management is much more critical for reducing mortality [40], [41]).

Figure 2 shows the plot showing the dosage error count (overdose and underdose) and number of patients (frequency) calculated based on the criteria shown in Table 1. Among the 55 patients, 28 had no dosage errors, and the remaining 27 showed at least one. Hence, the overall reported dosage error of 55 patients is 49%.

The 49% medication error can be attributed to all the minor variations in MAP that were tracked in the study. This is because the patient's responses to vasopressor medications are varied, and this titration is performed at the nurse level after consultation with the physicians, which invariably comes with a delay. However, changes that are less than 20% from baseline may not be clinically significant unless they cross the target limit. In our study, we intend to fine-tune this titration at the machine level as long as it lies within the target so that variations in MAP can be avoided even without a human interface.

3) INTRACOHORT VARIABILITY

Intra-cohort variability in inotropic drug responses was analyzed in some of the recent studies [28], [43], [44]. These studies show the importance of personalized treatment plans by incorporating patient-specific features (demographics) and time-varying physiological features (vital variations) to enhance controlled drug delivery and patient safety. To measure intracohort variability, we clustered the 55 patients using an LSTM autoencoder and K-means algorithms. Conventional methods, such as PCA and a simple autoencoder, do not capture the temporal dependency between BP variations and infusion rates. Hence, we used the LSTM autoencoder to simplify input features into latent representations, and k-means algorithms were used to cluster patients. This method preserves the long-term and short-term dependency of the features during data simplification, noise removal, and clustering time.

Mathematically, we can represent the data simplification from the measurement space to the latent subspace. The encoder processes the input sequences represented as time series of systolic BP, diastolic BP, MAP, HR, and infusion rates (noradrenaline, adrenaline, and vasopressin) as represented by a multi-dimensional matrix $X_1 = \{X_1, X_2, \ldots\ldots X_{37}\}$, where $X_1 = \{BP_{sys}^{T1}, BP_{dia}^{T1}, MAP^{T1}, HR^{T1}, Norad^{T1}, Adren^{T1}, Vaso^{T1}\}$ represents the first time step and X_{37} represents the last time step of the patient data. It consists of 37 rows (time steps) and 7 columns (vital and infusion parameters) and returns the final multi-dimensional latent space representation given by hidden states (h_T) and cell states (c_T).

$$(\mathbf{h}_T, \mathbf{c}_T) \in \mathbb{R}_{(32,7)} = \text{LSTM}_{\text{encoder}}(\mathbf{X}) \tag{1}$$

where, T denotes the time steps in the latent space representation. $(\mathbf{h}_T, \mathbf{c}_T) \in \mathbb{R}_{(32,7)}$ are the compressed representations of input features.

In clinical ICU settings, the patient will be under continuous observation for at least 3 hours to understand the BP pattern and suitable infusion rate. In our method, the first 3 hours of vital (systolic BP, diastolic BP, MAP, HR) and infusion data were converted to latent vector form, and these simplified data were given as input to K-means algorithms. Figure 3 shows the 3 groups of patients that were separated according to their drug response. Cluster 1 consists of 17 patients who were supported with inotropes, having

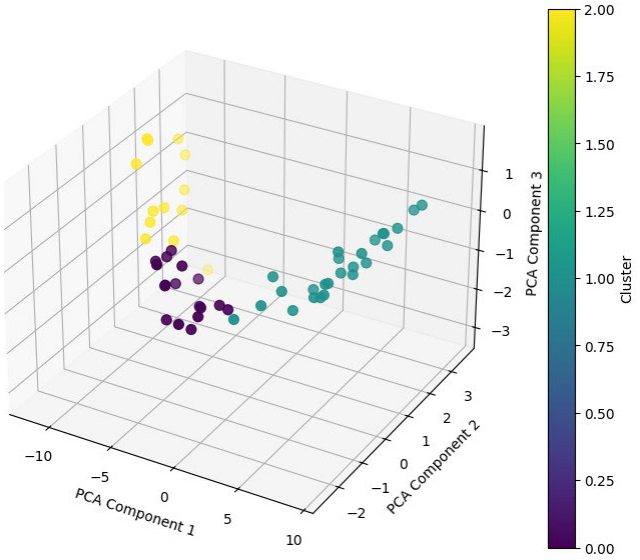

FIGURE 3. Clustered 55 patients based on intracohort variability in drug response.

higher infusion rates. Cluster 2 consists of 25 patients with low infusion rates. Cluster 3 consists of 13 patients who have higher and lower infusion rates. As we have seven input features for clustering, we performed a principal component analysis (PCA) to get a clear cluster visualization in 3D. This analysis shows that empirically there exists intracohort variability in drug responses, and we have to personalize the infusion rate based on the BP pattern of each patient. These findings are also corroborated by results from other similar studies as well [45], [46], [47], [48].

4) COMPLEXITY OF BP VARIATIONS

A major challenge of conventional control methods is the control of complex BP changes. To measure the complexity of BP, we calculated the Shannon entropy of MAP. It quantified the level of randomness and uncertainty of BP among 55 patients. Equation 2 shows the mathematical expression to calculate the Shannon entropy of MAP. In this equation, X is the random variable, which is MAP, and $p(x_i)$ is the probability of each value of MAP in the dataset. For each patient, we separately calculated the entropy value, and we observed that among 55 patients, 42 had entropy values above 3, which shows very high fluctuations in MAP variations. This observation gives strong evidence regarding the complex behavior of MAP values.

$$H(X) = -\sum_{i=1}^{n} p(x_i) \log_2 p(x_i) \tag{2}$$

B. HIERARCHICAL CARDIAC DIGITAL TWIN AND INFUSION RATE DECISION MODELS

Figure 4 shows the architecture of our proposed system. The two major parts of our architecture are (a) infusion rate decision models and (b) cardiac digital twin patient models. Initially, we cluster the patients based on their intracohort variability by the combined use of the LSTM autoencoder and K-means clustering method. For each cluster, we separately build an infusion rate decision model and a cardiac digital twin model. To decide the suitable infusion rate for the given patient data, we built an AI decision model. The digital twin model is designed to resemble the BP pattern of that specific patient group, and it outputs the drug response in the form of systolic BP, diastolic BP, MAP, and HR. The output of the digital twin cardiac model is given as input to the infusion rate model, which together work in a closed-loop manner.

1) CLUSTERING PATIENTS

In this initial study, we narrowed down to 31 patients who were supported with only one inotrope (noradrenaline). We cluster these patients based on their drug response. The LSTM autoencoder clustering method reduces the complexity of the time series data. We used the first 3-hour infusion rate, and vital parameters (systolic BP, diastolic BP, MAP, and HR) as inputs for clustering. The encoder module converts the input data into simplified latent representations, and the decoder converts back to the original sequence by removing noise without losing information. Mean square error was used as a loss function during the training process to measure the difference between the original input and the latent representation. The LSTM module helps to reduce the reconstruction loss during training. We tuned hyperparameters such as the epochs, batch size, optimizer, and activation function, along with the early stop regularization method. After the training process, the simplified latent representation of vital and infusion data was given as input for K-means clustering. The optimal number of clusters was calculated using the elbow method, and we used the principal components of input features to get a clear cluster view in 3D.

2) NORADRENALINE DECISION MODELS

Decision models for noradrenaline control are built separately for each cluster. After understanding the pattern of BP variations and infusion rates, the model predicts a suitable infusion rate for the next instant.

The conventional artificial neural networks (ANN) lack advanced gate (input, output, and forget) mechanisms and do not capture both the long-term and short-term patterns of BP changes. Hence, we used the LSTM model as a decision model to forecast the infusion rate. The output from the model is dependent on the current and previous patient data. To forecast the infusion rate, we use current and previous time series inputs: systolic BP, diastolic BP, MAP, HR, and infusion rates. During the training process, we used hyperparameters such as input window size, batch size, epochs, optimizer, and activation function, along with the early stop regularization method. We analyzed the performance of each infusion rate model using statistical parameters such as the mean absolute percentage error

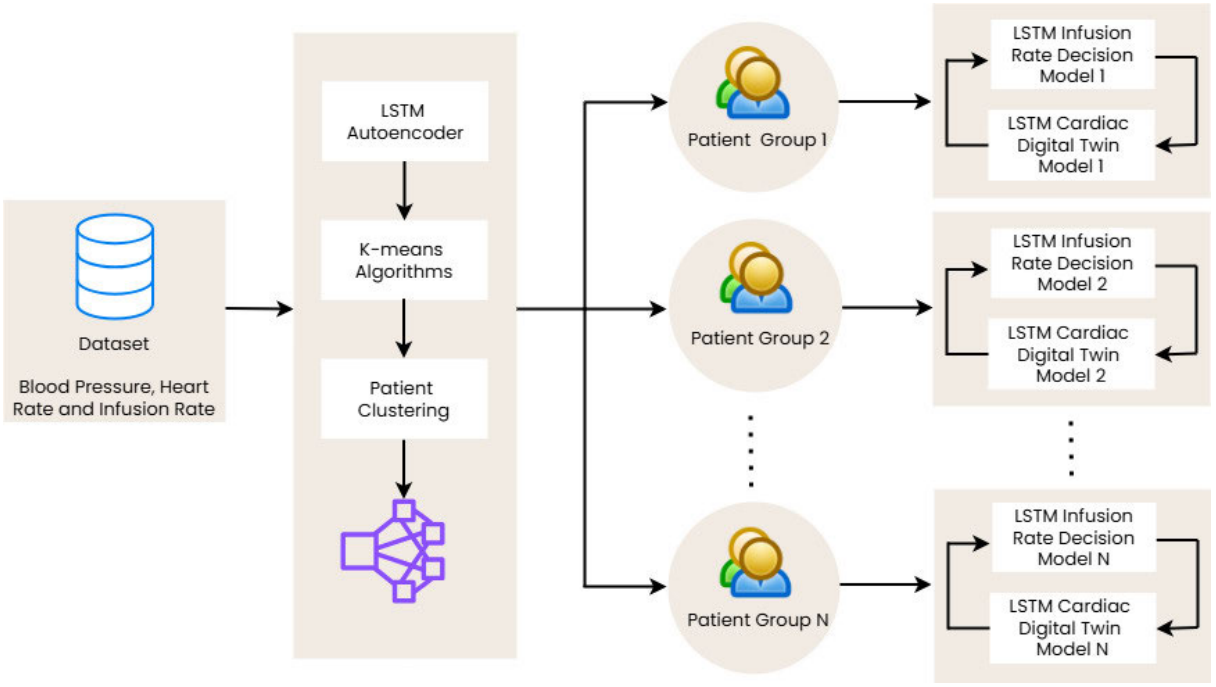

FIGURE 4. Architecture of hierarchical patient clustering and AI model building for noradrenaline infusion.

(MAPE), coefficient of determination (R^2 score), mean absolute error (MAE), and root mean square error (RMSE).

3) DIGITAL TWIN CARDIAC MODELS

Designing a personalized human cardiac system for each patient cluster is essential for validating the predicted infusion rate. The real-world fluctuations of BP should be resembled by the digital twin cardiac model. We use LSTM models as digital twins to forecast the systolic BP, diastolic BP, MAP, and HR. These vitals for the next instant are highly dependent on the current and previous patient data. Hence, the outputs from the model are forecasted by using current and previous time series input features such as infusion rates, systolic BP, diastolic BP, MAP, and HR. The models are tuned by using hyperparameters such as the input window size, batch size, epochs, optimizer, and activation function, along with the early stop regularization method. The performance of each model is evaluated using parameters such as mean absolute percentage error (MAPE), coefficient of determination (R^2 score), mean absolute error (MAE), and root mean square error (RMSE). Figure 5 shows the data flow diagram of the proposed system, starting from AI modeling to closed-loop virtual validation.

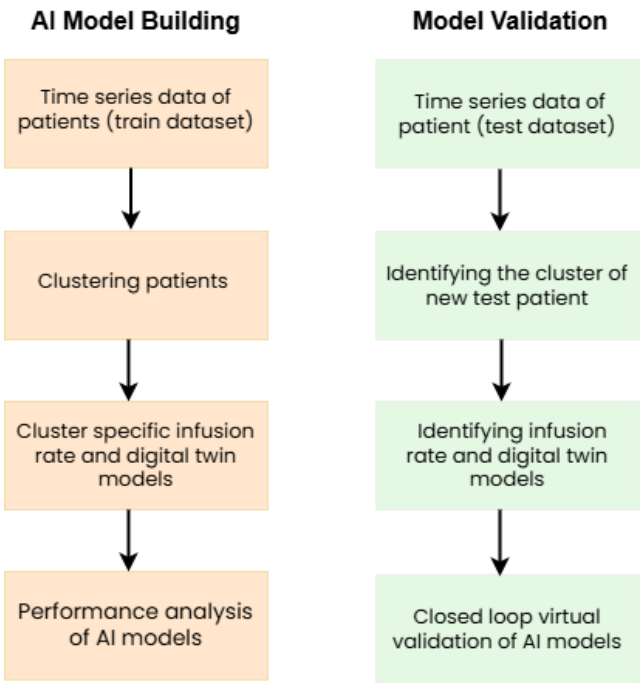

FIGURE 5. Dataflow diagram of hierarchical AI model building and validation for closed-loop noradrenaline control.

4) CLOSED-LOOP VIRTUAL VALIDATION OF AI MODELS FOR NORADRENALINE INFUSION

We apply our proposed method in real-time clinical settings by using the initial few hours of patient data to identify the suitable cluster for the patient and select the corresponding infusion decision model, which can be used to automate the infusion process. Based on the current patient condition, we adjust the infusion rates more frequently and maintain the MAP in the normal range. If the patient is in a hypertension

condition, the infusion rates will decrease, and if the patient is in a hypotension condition, the infusion rates will increase.

Before implementing the infusion rate models in the real-world ICU setting, we virtually validate them using digital twin models. By using the initial few time series data of the test patient, we find out the cluster and the corresponding digital twin and infusion decision models. The initial vital and infusion data of the test patient are required to start the closed-loop automation. We started virtual automation from the digital twin cardiac model. The time series inputs, such as BP (systolic BP, diastolic BP, and MAP), HR, and infusion values, are given to the digital twin model. It forecasts the next instant BP and HR values. Then, these forecasted values, along with the previous time series patient data (BP, HR, infusion rate), are given as input to the infusion rate decision model. The model forecasts the suitable infusion rate for the next instant. Then, this output, along with the previous time series data (BP, HR, infusion), is again given as an input to the digital twin model in a closed-loop manner. The performance of the two models is validated by the analysis of infusion rate predictions and corresponding drug responses.

C. COMPARISON WITH CONVENTIONAL CONTROLLER

1) FUZZY LOGIC CONTROLLER

One of the advanced conventional control methods for controlled infusion is the FLC. There are research works based on the delivery of drugs using FLC to maintain BP [12], [14]. To test the performance of FLC, the PK-PD model is used as the patient model. For comparison with our proposed method, we design an FLC for controlling noradrenaline and also develop a PK-PD patient model to validate the performance of FLC.

2) FUZZY LOGIC CONTROL AND PK-PD

FLC is a rule-based control mechanism. It is used to calculate drug dosages. For the noradrenaline infusion, we designed seven rules to control the infusion rate for various BP conditions. Seven rules are defined based on the seven MAP and infusion conditions. The MAP and the infusion rate are the two fuzzy variables for our control system. We defined the membership function that represents the defined range of values for both MAP and infusion rate, as shown in Table 2.

The membership function range will vary from patient to patient based on the current condition of the patient. The input to the FLC is the current MAP value, and the algorithms calculate a suitable value for the infusion rate. To validate the infusion rate, we designed a single-compartment PK-PD patient model. In this model, we assume that the noradrenaline will be uniformly distributed throughout the patient's body. The PK-PD profile will vary based on the demographics and the current condition of the patient. We considered the PK-PD parameters such as the age, weight, base volume of drug distribution (V_d), drug concentration (D_c), drug elimination rate (K_e), and time of drug absorption, distribution, metabolism, and response. As it takes nearly five to 10 minutes to show a visible drug response, we calculated the next instant MAP at an interval of every 5 minutes. The simulated MAP effect of noradrenaline can be calculated using the Hill equation 3.

TABLE 2. Defined rule-based FLC membership function for MAP and infusion rate.

MAP (mmHg)	Infusion Rate (mL/hr)
Very Low	Rapid Increase
Low	Increase
Moderate	Moderate Increase
Normal	Stable
Moderate High	Moderate Decrease
High	Decrease
Very High	Rapid Decrease

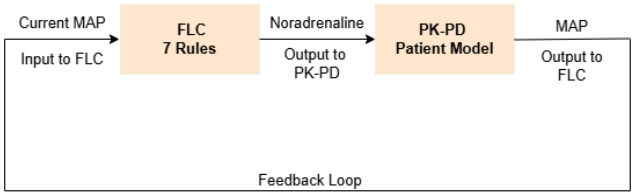

FIGURE 6. Closed-loop validation of the FLC and PK-PD model for noradrenaline infusion.

$$MAP_{\text{effect simulated}} = E_{\max} \cdot \frac{C_{\text{effect}}}{C_{\text{effect}} + EC_{50}} \tag{3}$$

$E_{\max}$ is the maximum achievable increase in MAP, EC_{50} is the concentration of the drug at which half the maximum effect is achieved, and C_{effect} models the effect of drug concentration in the central compartment. The final simulated MAP of the next instant is shown in equation 4. It is the summation of the current MAP and the effect simulated due to the noradrenaline infusion.

$$\text{MAP}_{\text{final\_simulated}} = \text{MAP}_{\text{baseline}} + \text{MAP}_{\text{effect\_simulated}} \tag{4}$$

Figure 6 shows the closed-loop validation of the FLC along with the PK-PD patient model. The current MAP of the patient is given as input to the FLC, and it outputs infusion rate, which is given as input to the PK-PD model. The PK-PD model calculates the effect of the given infusion rate on the patient and outputs the next instant MAP value. We test the performance of the two models using a test patient. The outputs of FLC and PK-PD are compared using the ground truth data of the test patient.

IV. RESULTS

A. AI-ENHANCED CLOSED-LOOP INFUSION

Performance analysis of AI-enhanced automation consists of visualization of patient clusters, analysis of infusion rate decision models and cardiac digital twin models, and closed-loop virtual demonstration of AI models.

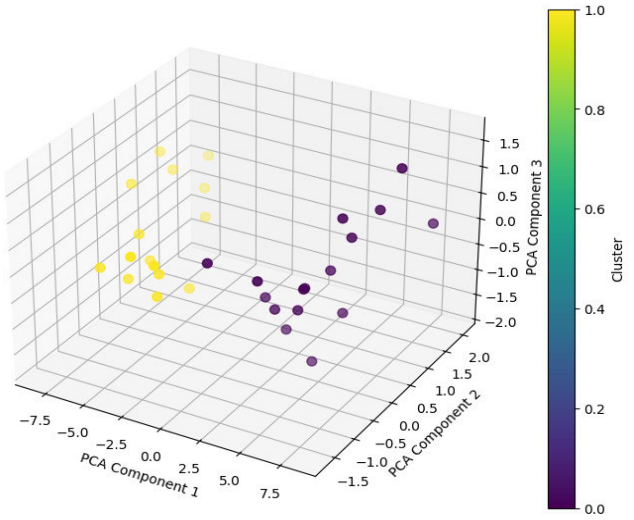

FIGURE 7. LSTM autoencoder and K-means-based clustering of 31 patients supported with noradrenaline.

1) TIME SERIES CLUSTERING OF PATIENTS

The LSTM autoencoder, along with the K-means algorithm, was used for handling the time series data to cluster the 31 patients. The encoder consists of an input layer, one hidden layer, and an output latent space layer. Similarly, the decoder module consists of three layers, and the output from the decoder is the simplified, noise-removed original data. During the LSTM training process, we used the Adam optimizer, mean square error loss function, 100 epochs, and softplus activation function. The optimum number of clusters obtained using the K-means elbow method was two.

Figure 7 shows the clusters of 31 data points. Cluster 1 consists of 16 moderately critical patients having an infusion rate below 5 mL/hr, and cluster 2 consists of 15 highly critical patients having an infusion rate above 5 mL/hr. A clear visualization of clusters is made possible using the three principal components of features. The total variance captured by each principal component is 1.

2) PERFORMANCE ANALYSIS OF INFUSION RATE MODELS

To design infusion rate decision models for each cluster, we used LSTM neural networks. The time series infusion rates and the BP values were given as input to the neural network. During the training process, we tuned the models using various window sizes (15 min, 30 min, 1 hour, 2 hours) of the input features. For both clusters, the previous 15-minute input data showed improved performance for predicting the infusion rates. We used the Adam optimizer, 200 epochs, a batch size of 16, and the softplus activation function for modeling. The model predicts the next instant infusion rate with a sliding window size of one (representing 5 minutes). To assess the generalizability, we performed a K-fold cross-validation method with a K value of 5.

Table 3 shows the performance analysis of infusion rate decision models for the two different patient clusters. It shows

TABLE 3. Performance analysis of infusion rate decision models of cluster 1 and cluster 2.

Performance Metrices	Cluster 1	Cluster 2
Mean MAPE (%)	5.2	5.3
Mean MAE (mL/hr)	0.11	0.12
Mean R^2 score	0.96	0.97
Mean SD of Error	0.23	0.28
Mean RMSE	0.23	0.28

mean values of performance matrices across all 5 folds. The mean MAPE values of the infusion rate in both clusters are less than 10, and the R^2 score is 0.9, which shows the high performance of the models. The obtained MAPE value of infusion rate using the ANN algorithm is 19.8% (cluster 1) and 25.7% (cluster 2), which shows a comparatively low performance.

3) PERFORMANCE ANALYSIS OF DIGITAL TWIN CARDIAC MODELS

The cardiac digital twin models for the two clusters were developed using the LSTM network. Input to the digital twin model is the time series infusion rate and BP values. During the training process, we evaluated the model performance by using various window sizes (15 min, 30 min, 1 hour, and 2 hours) of the input features. For both clusters, the previous 15-minute features showed improved performance for forecasting the drug response in the form of BP and HR values. The models were tuned using the Adam optimizer, softplus activation function, a batch size of 16, and 200 epochs. To assess the generalizability, we used the K-fold cross-validation method with a K value of 5.

Table 4 shows the performance analysis of the two models for forecasting the drug response. The values of the statistical parameters show that the two models have high performance, which resembles the real-world human cardiac system.

The obtained MAPE value of sysBP, diaBP, MAP, and HR using the ANN algorithm is 13.9%, 13.3%, 13.9%, 15.3% respectively, for cluster 1 and 19.1%, 18.8%, 18.1%, 19.1%, respectively, for cluster 2, which shows a comparatively low performance.

4) AI-ENHANCED CLOSED LOOP VIRTUAL VALIDATION OF DECISION MODEL AND CARDIAC DIGITAL TWIN MODEL

We used the outputs of the infusion rate decision model and the cardiac digital twin model for the closed-loop demonstration. The initial 15-minute time series data of a test patient in cluster 1 was used as a starting point to forecast the BP and HR values. These outputs and previous time series data (BP, HR, infusion rate) were given as input to the infusion rate decision model. The model forecasted the next instant infusion rate, and we again gave this output and previous data (BP, HR, infusion rate) as input to the digital twin in a closed-loop manner. We used the Shannon

TABLE 4. Performance analysis of cardiac digital twin models of cluster 1 and cluster 2.

Performance Metrics	Cluster 1				Cluster 2			
	Sys BP	Dia BP	MAP	HR	Sys BP	Dia BP	MAP	HR
Mean MAPE	6.1	6.4	5.6	4.5	6.9	7.8	6.4	4.6
Mean R^2 Score	0.7	0.70	0.76	0.84	0.70	0.65	0.64	0.71
Mean MAE	6.8	3.9	4.48	3.6	7.8	4.56	5.03	3.93
Mean S.D of error	10	6.12	6.12	5.5	11.2	7.46	7.46	4.6
Mean RMSE	10.1	6.31	6.51	5.9	11.4	7.67	8.02	4.8

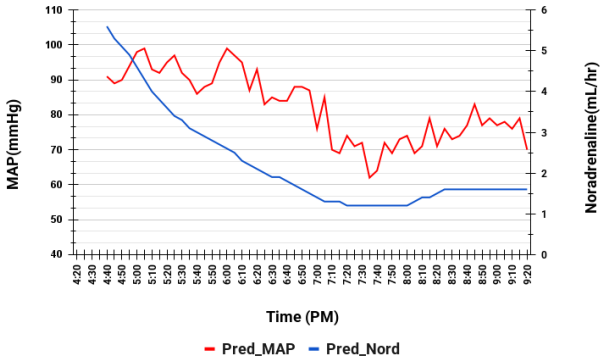

FIGURE 8. Closed-loop validation of digital twin and infusion rate decision models.

TABLE 5. Defined rule-based control logic of FLC.

MAP (mmHg)	Infusion Rate (mL/hr)
0 - 19 mmHg (Very low)	15 - 20 mL/hr (Rapid increase)
20 - 39 mmHg (Low)	10 - 14 mL/hr (Increase)
40 - 59 mmHg (Moderate)	3 - 9 mL/hr (Moderate increase)
60 - 79 mmHg (Normal)	1 - 2 mL/hr (Stable)
80 - 99 mmHg (Moderate high)	0.5 - 0.9 mL/hr (Moderate decrease)
100 - 109 mmHg (High)	0.2 - 0.4 mL/hr (Decrease)
>110 mmHg (Very high)	0 - 0.1 mL/hr (Rapid decrease)

entropy of BP and HR to introduce complexity in digital twin predictions. Among the 31 patients, the calculated mean entropy value of BP is 4.5, and HR is 3.6. We added Gaussian random noise to the predictions by using the entropy values as the standard deviation. It resembled the real-world fluctuations of drug responses in the predictions.

Figure 8 shows closed-loop validation of drug response (MAP) and noradrenaline infusion.

In this figure, the red line shows the MAP predictions from the digital twin model, and the blue line shows the corresponding infusion rate predictions from the decision model. The MAP variations are labeled on the primary Y axis, and the corresponding infusion rates are on the secondary Y axis. The target MAP range of this patient is 60 to 80 mmHg. Initially, the predictions from the digital twin showed that the patient had hypertension, and then our infusion rate decision model frequently reduced the infusion rate (from 4:40 PM to 8:20 PM) and maintained the MAP in the target range. From 8:25 PM to 9:20 PM, the infusion rate predictions remained the same, which prevented the sudden drop of MAP below the target range. Throughout this 5-hour virtual validation, we did not find any hypotension (for continuous 15 minutes) or hypertension (for continuous 30 minutes) to count as a dosage error based on the criteria defined in Table 1.

B. FLC AND PK-PD CLOSED LOOP VALIDATION

A PK-PD patient model was used for validating the output from the FLC. For designing the PK-PD model, we assumed certain control parameters and designed a patient profile. The assumed PK-PD parameters for a test person are:

- Demographics (Age: 72, weight: 83 Kg, male patient)
- E_{max} = 25 mmHg
- EC_{50} = 0.5 mg per mL
- V_d = 7 L
- Ke_{base} = 0.2 per minute
- Noradrenaline concentration = 0.1 mg per ml
- Drug absorption time = 5 seconds
- Drug distribution time = 100 seconds
- Drug metabolism time = 175 seconds
- Drug response time = 20 seconds

The range of the membership function is defined based on test patient ground truth data collected from the ICU. Table 5 shows the control logic of the FLC for various BP conditions. To start the closed-loop automation, we gave the ground truth MAP value to the FLC. The FLC calculated the optimum infusion rate, and this output was given to the PK-PD model. The PK-PD model calculated the MAP value for the given infusion rate, and this process continued in a closed-loop manner. Figure 9 shows the closed-loop validation of the FLC and PK-PD models. In this figure, the red line shows the MAP output from the PK-PD model, and the blue line shows the noradrenaline rate from the FLC. The MAP variations are labeled on the primary Y axis, and the corresponding infusion rates are on the secondary Y axis. In this demonstration, the infusion rate reduces with an increase in the MAP values, which is clinically significant. However, this PK-PD represents an average patient model that does not fully capture complex hemodynamics, and the

TABLE 6. Comparison of PID, FLC, and AI-Based Methods for controlled drug delivery.

Performance Metrics	PID [27], [49]–[52]	FLC [27], [49], [51], [52]	Proposed Method
RMSE of MAP (mmHg)	16.99 ± 7.4 [49]	13.44 ± 5.45 [49]	6.5 (cluster 1) and 8.02 (cluster 2)
MAE of MAP (mmHg)	15.7 ± 7.7 [49]	12.1 ± 5.5 [49]	4.48 ± 6.1 and 5.03 ± 7.4
Dosage error duration	High (trial-and-error tuning) [52]	Observed for >30 minutes	Observed for <30 minutes
Personalization	Generic (same logic for all patients) [27], [50]	Generic (same logic for all patients) [27]	High (trained on patients data)
Adaptability to BP change	Limited (fixed control algorithm) [27], [50]	Limited (fixed rules) [27]	High (learns and adapts)
Clinical efficiency	Requires manual adjustments [27], [50], [51]	Requires manual adjustments [27], [51]	Optimized dosing
Workload	High [27]	High [27]	Low
Response time	Slower (fixed logic) [27], [52]	Slower (rule-based) [27], [52]	Faster (real-time optimization)
Data requirement	Only at initial stage	Only at initial stage	Large amount of data needed
Frequency of dosage change	Low (fixed algorithm) [27], [49]	Low (rule-based algorithm) [27], [49]	High (automated control)
Drug consumption	High or Low (chances of dosage errors) [27]	High or Low (chances of dosage errors) [27]	Optimized dosage

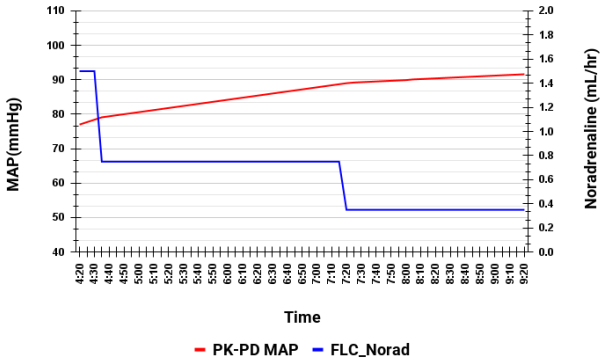

FIGURE 9. Closed-loop validation of FLC and PK-PD patient model.

outputs show a smooth curve that does not resemble the real-world MAP variations.

V. DISCUSSION

A major challenge of precision medicine in cardiac care is the control of the infusion rate of inotropes for sudden BP fluctuations. Our study proposes an advanced AI method and compares it against a conventional FLC method for the closed-loop control of a single inotrope. In the AI-enhanced method, we considered intracohort variability by clustering patients and personalizing the noradrenaline infusion. Clustering patients using the LSTM autoencoder method increases the chance of grouping patients having similar properties in BP and infusion patterns. Developing a digital twin model and an infusion rate model for each cluster further enhances the accuracy of personalized treatment. Using the infusion rate decision model, we frequently changed the noradrenaline rate, and the digital twin model forecasted the corresponding drug response. While adding Shannon entropy to drug response predictions, the digital twin resembled the real-world BP fluctuations. During the closed-loop demonstration, both AI models showed the best performance to optimize drug consumption and reduce dosage errors. This transition from manual infusion adjustment to AI-aided automation could help reduce the workload of clinicians. We demonstrate the potential for personalized drug control using data-driven AI models.

The major findings that we report in this paper are:

- Utilizing intracohort variability enhances the performance of both the infusion rate decision model and the cardiac digital twin model.
- Data-driven infusion rate decision models outperformed the conventional FLC methods.
- The digital twin model has the potential to capture the dynamic and complex nature of the cardiac system better than the conventional PK-PD patient model, although this requires much more experimentation and research.
- Combined closed-loop use of the infusion rate decision model and digital twin model shows acceptable performance, which further increases the possibility of using infusion rate decision models in real-world clinical settings.

The conventional rule-based FLC outputs the noradrenaline rate based on the given MAP value. Our experiment on a test patient shows that there is a variation in infusion rate after a certain BP range. However, the frequency of infusion change is low compared to the AI method, and we cannot generalize these FLC rules to the whole population. From patient to patient, the demographics and the infusion rate decision will vary, and we need to personalize the control algorithms to adapt to intracohort variability. The PK-PD model that we used in this study is a single-compartmental model, and it is designed based on certain assumptions in demographics, drug concentration, and distribution. Therefore, it doesn't resemble the actual physiological complexities of a patient. Hence, this mathematical patient model is not suitable to validate the actual drug response of a patient.

Table 6 shows the comparative performance analyses of conventional methods with our proposed AI method. With the limitations of conventional control methods, our proposed AI-enhanced drug delivery highlights the importance of digital twin technology and decision models for noradrenaline control.

While dealing with inotropes such as noradrenaline, vasopressin, and adrenaline together, their drug-drug interaction needs to be considered. In that case, the algorithm should control all drugs simultaneously and sometimes needs to switch between the inotropes or stop some inotropes on time to avoid dosage errors. Additionally, to improve the performance of AI models, we have to increase the sample size by considering various patient subgroups, such as neonates, adults, and geriatrics.

In our proposed method, we have only two clusters having different patient properties. Moving forward, we expect that with much larger patient cohorts, there would be multiple clusters (with similar or moderately different properties) that would enable us to experiment with dynamic cluster assignment strategies. The use of fuzzy based clustering methods would enable a smoother control system, signaling when switching between different cluster states.

VI. CONCLUSION

The major challenges in the inotropic infusion process include pre-programmed infusion, limitations of fixed control algorithms, complex hemodynamics, and intracohort variability in drug responses. Due to the complex variations of the BP, conventional controller algorithms cannot adapt to them. We introduce an AI-enhanced closed-loop infusion method for the controlled delivery of noradrenaline. To incorporate intracohort variability into the model, we clustered patients and designed cluster-specific cardiac digital twins and infusion rate decision models using the LSTM network.

Our AI-enhanced closed-loop control method demonstrates satisfactory performance in controlling patient BP in the target range while ensuring optimized drug delivery. The output of the digital twin model resembled real-world BP variations to a large extent and was used to validate the infusion rate prediction model. The proposed AI models outperformed conventional FLC combined with the PK-PD models, thereby demonstrating the potential use of such models in infusion control systems as well as the utilization of digital cardiac twins for in vitro validation studies. Moving forward, more patient samples with varying drug infusion conditions are required to generalize cluster-specific AI models that can handle complex drug-drug interactions as well.

APPENDIX

FUZZIFICATION AND DEFUZZIFICATION OF FLC

Fuzzy logic controllers are used in various control system applications. It is a rule-based control system that has three main control processes, such as fuzzification, the inference engine, and defuzzification. In our FLC design, there are seven rules that show seven different BP conditions and the corresponding noradrenaline rates that were suggested by the clinician. We defined the rules based on the sample data of a test patient. In our FLC control algorithm, there are

- Fuzzy Variables: Input (MAP) and output variables (Infusion rate)
- Fuzzy Set: Contain variables with linguistic values such as very low, low, moderate, high, very high, etc.
- Membership function: Each of the 7 ranges of fuzzy variables (MAP and infusion rate) is represented by membership functions. In our case, we used a triangular membership function, which is computationally efficient and allows for a precise mapping of input to output values.

TABLE 7. Fuzzification process containing defined fuzzy sets for various MAP conditions.

Rule	Patient Condition	MAP (mmHg)	Fuzzy Set of Input
1	Dangerous low MAP	0-19	Very low
2	Severe hypotension	20-39	Low
3	Moderate hypotension	40-59	Moderate
4	Target MAP	60-79	Normal
5	Moderate hypertension	80-99	Moderate high
6	Severe hypertension	100-110	High
7	Dangerous high MAP	>110	Very high

The process of converting the crisp input variable (MAP) to a fuzzy set is called fuzzification. Table 7shows the fuzzification process to maintain MAP.

After fuzzification the next phase is the inference engine, which is a rule evaluation stage. Fuzzified inputs (fuzzy sets) are passed through predefined fuzzy rules. In our case, it consists of seven rules that relate inputs to outputs using if and then conditions. The fuzzy rules are applied to the current patient condition based on the MAP value, and it evaluates which rule is activated and determines the corresponding output fuzzy sets. The fuzzy output set is the linguistic values of the noradrenaline rates. The seven rules are listed below.

- Rule 1: If the patient's MAP is in the range of 0-19, then a rapid increase of infusion rate should be performed.
- Rule 2: If the patient's MAP is in the range of 20-39, then an increase in infusion rate should be performed.
- Rule 3: If the patient's MAP is in the range of 40-59, then a moderate increase in the infusion rate should be performed.
- Rule 4: If the patient's MAP is in the range of 60-79, then they are in stable condition, and we maintain the suitable infusion rate.
- Rule 5: If the patient's MAP is in the range of 80-99, then a moderate decrease in the infusion rate should be performed.

TABLE 8. Defuzzification process containing defined output fuzzy sets for various MAP conditions.

Rule	Patient Condition	Fuzzy Set of Output	Infusion Range
1	Dangerous low MAP	Rapid increase	15-20
2	Severe hypotension	Increase	10-14
3	Moderate hypotension	Moderate increase	3-9
4	Target MAP	Stable	1-2
5	Moderate hypertension	Moderate decrease	0.5-0.9
6	Severe hypertension	decrease	0.2-0.4
7	Dangerous high MAP	Rapid decrease	0-0.1

- Rule 6: If the patient's MAP is in the range of 100-110, then a decrease in infusion rate should be performed.
- Rule 7: If the patient's MAP is >110, then a rapid decrease in infusion rate should be performed.

In our case, there is one specific rule for a particular condition. After selecting the rule and output fuzzy set, the defuzzification process starts. During this phase, the fuzzy output sets (noradrenaline rates) selected from the inference engine are converted into crisp values.

Table 8 shows the defuzzification phase of various patient conditions. We used the centroid defuzzification method to find the final output of FLC. This method gives the center value of the noradrenaline range (mL/hr) for each patient condition.

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REFERENCES

[1] S. Hunter, E. Manias, and J. Considine, "Nurse management of noradrenaline infusions in intensive care units: An observational study," *Austral. Crit. Care*, vol. 37, no. 1, pp. 58–66, Jan. 2024.

[2] J. Rinehart, S. B. Lee, B. Saugel, and A. Joosten, "Automated blood pressure control," in *Proc. Seminars Respiratory Crit. Care Med.*, Aug. 2020, vol. 42, no. 1, pp. 47–58.

[3] N.-M.-Z. Bakkar, A. F. El-Yazbi, F. A. Zouein, and S. A. Fares, "Beat-to-beat blood pressure variability: An early predictor of disease and cardiovascular risk," *J. Hypertension*, vol. 39, no. 5, pp. 830–845, 2021.

[4] R. K. Pathinarupothi and E. Rangan, "Discovering vital trends for personalized healthcare delivery," in *Proc. ACM Int. Joint Conf. Pervasive Ubiquitous Comput., Adjunct*, Sep. 2016, pp. 1106–1109.

[5] R. Darniss, V. S. Nair, and A. R. Devidas, "An IoT based vitals monitoring system for babies in neonatal intensive care unit," in *Proc. IEEE 10th Region 10 Humanitarian Technol. Conf. (R10-HTC)*, Sep. 2022, pp. 130–135.

[6] C. Beaudart, M. Witjes, P. Rood, and M. Hiligsmann, "Medication administration errors in the domain of infusion therapy in intensive care units: A survey study among nurses," *Arch. Public Health*, vol. 81, no. 1, p. 23, Feb. 2023.

[7] V. S. Nair, R. K. Pathinarupothi, and T. Madathil, "Personalized algorithms and techniques for development of a smart infusion pump for ICU," in *Proc. IEEE 8th Int. Conf. Converg. Technol. (I2CT)*, Apr. 2023, pp. 1–7.

[8] A. Sasmal, P. Arora, and A. D. Roy, "A retrospective observational study on impact of medication errors and its severity in a tertiary care teaching hospital in India," *Int. J. Health Sci. Res.*, vol. 13, no. 5, pp. 143–155, May 2023.

[9] J. Alteren, M. Hermstad, L. Nerdal, and S. Jordan, "Working in a minefield; nurses' strategies for handling medicine administration interruptions in hospitals, -a qualtiative interview study," *BMC Health Services Res.*, vol. 21, no. 1, pp. 1–10, Dec. 2021.

[10] E. S. Kirkendall, K. Timmons, H. Huth, K. Walsh, and K. Melton, "Human-based errors involving smart infusion pumps: A catalog of error types and prevention strategies," *Drug Saf.*, vol. 43, no. 11, pp. 1073–1087, Nov. 2020.

[11] R. Ibarra-Pérez, F. Puértolas-Balint, E. Lozano-Cruz, S. E. Zamora-Gómez, and L. I. Castro-Pastrana, "Intravenous administration errors intercepted by smart infusion technology in an adult intensive care unit," *J. Patient Saf.*, vol. 17, no. 6, pp. 430–436, 2021.

[12] R. Sharma, K. K. Deepak, P. Gaur, and D. Joshi, "An optimal interval type-2 fuzzy logic control based closed-loop drug administration to regulate the mean arterial blood pressure," *Comput. Methods Programs Biomed.*, vol. 185, Mar. 2020, Art. no. 105167.

[13] S. P. Tharimela and M. E. Harikumar, "Modelling of syringe infusion pump control system using FOPID controller," in *Proc. 4th Int. Conf. I-SMAC (IoT Social, Mobile, Analytics Cloud) (I-SMAC)*, Oct. 2020, pp. 1123–1129.

[14] A. Kumar and R. Raj, "Design of a fractional order two layer fuzzy logic controller for drug delivery to regulate blood pressure," *Biomed. Signal Process. Control*, vol. 78, Sep. 2022, Art. no. 104024.

[15] N. Paolino, M. Schiavo, N. Latronico, M. Paltenghi, and A. Visioli, "PK/PD model based design of PID control for closed-loop anesthesia," *IFAC J. Syst. Control*, vol. 27, Mar. 2024, Art. no. 100247.

[16] T. T. Thomas, S. Nithin, P. Sivraj, and K. Guruvayurappan, "Design of an embedded controller for next generation low cost insulin pump," in *Proc. Int. Conf. Inventive Res. Comput. Appl. (ICIRCA)*, Jul. 2018, pp. 200–204.

[17] L. Rachaputi, J. Yerramelli, K. P. Rajesh, and P. Ratnakaram, "Performance analysis of hexapod leg with different controllers," in *Proc. 6th Int. Conf. Commun. Electron. Syst. (ICCES)*, vol. 2, Jul. 2021, pp. 139–145.

[18] D. S. Vamsi, U. M. Krishna, and M. Nithya, "Performance analysis of PID controller for path planning of a quadcopter," in *Proc. 2nd Int. Conf. Power Embedded Drive Control (ICPEDC)*, Aug. 2019, pp. 116–121.

[19] T. E. Baum and E. N. Brown, "Theoretical development of a closed-loop system for blood pressure control," in *Proc. Amer. Control Conf. (ACC)*, May 2021, pp. 672–677.

[20] A. Joosten, J. Rinehart, P. Van der Linden, B. Alexander, C. Penna, J. De Montblanc, M. Cannesson, J.-L. Vincent, E. Vicaut, and J. Duranteau, "Computer-assisted individualized hemodynamic management reduces intraoperative hypotension in intermediate- and high-risk surgery: A randomized controlled trial," *Anesthesiology*, vol. 135, no. 2, pp. 258–272, 2021.

[21] K. Sasaki, T. Kawada, H. Matsushita, S. Yokota, M. Kakuuchi, A. Yokoi, Y. Yoshida, H. Morita, K. Sato, T. Nishikawa, A. P. N. Kutter, Y. Kataoka, J. Alexander, K. Saku, T. Ishikawa, and K. Uemura, "Computer-controlled closed-loop norepinephrine infusion system for automated control of mean arterial pressure in dogs under isoflurane-induced hypotension: A feasibility study," *Frontiers Veterinary Sci.*, vol. 11, May 2024, Art. no. 1374356.

[22] P. Grant and O. Naesh, "Fuzzy logic and decision-making in anaesthetics," *J. Roy. Soc. Med.*, vol. 98, no. 1, pp. 7–9, Jan. 2005.

[23] R. J. Hill, P. F. Innominato, F. Lévi, and A. Ballesta, "Optimizing drug infusion schedules towards personalized cancer chronotherapy," *bioRxiv*, vol. 2019, Jul. 2019, Art. no. 688606.

[24] S. Parihar, P. Shah, R. Sekhar, and J. Lagoo, "Model predictive control and its role in biomedical therapeutic automation: A brief review," *Appl. Syst. Innov.*, vol. 5, no. 6, p. 118, Nov. 2022.

[25] A. Maxim and C. M. Ionescu, "A model-based optimal distributed predictive management of multidrug infusion in lung cancer patient therapy," in *Computational and Mathematical Models in Biology*. Cham, Switzerland: Springer, 2023, pp. 235–256.

[26] A. Pawlowski, M. Schiavo, N. Latronico, M. Paltenghi, and A. Visioli, "Experimental results of an MPC strategy for total intravenous anesthesia," *IEEE Access*, vol. 11, pp. 32743–32751, 2023.

[27] R. Sharma, D. Singh, P. Gaur, and D. Joshi, "Intelligent automated drug administration and therapy: Future of healthcare," *Drug Del. Translational Res.*, vol. 11, no. 5, pp. 1878–1902, Oct. 2021.

[28] Y. Ilan, "Next-generation personalized medicine: Implementation of variability patterns for overcoming drug resistance in chronic diseases," *J. Personalized Med.*, vol. 12, no. 8, p. 1303, Aug. 2022.

[29] N. Paolino, M. Schiavo, N. Latronico, M. Paltenghi, and A. Visioli, "On the use of the eleveld PK/PD model for the design of PID control of anesthesia," *IFAC-PapersOnLine*, vol. 56, no. 2, pp. 3015–3020, 2023.

[30] J. Joachim, J. Cartailler, F. Vallee, T. Lefevre, J. Callebert, E. Gayat, and M. Lavielle, "Design of a pharmacokinetic/pharmacodynamic model for administration of low dose peripheral norepinephrine during general anaesthesia," *Brit. J. Clin. Pharmacol.*, vol. 90, no. 11, pp. 2861–2869, Nov. 2024.

[31] L. Zhang, H. Xie, Y. Wang, H. Wang, J. Hu, and G. Zhang, "Pharmacodynamic parameters of pharmacokinetic/pharmacodynamic (PK/PD) integration models," *Frontiers Veterinary Sci.*, vol. 9, Mar. 2022, Art. no. 860472.

[32] R. Sood and A. Anita, "Pharmacokinetic and pharmacodynamic modeling (PK/PD) in pharmaceutical research: Current research and advances," in *Software and Programming Tools in Pharmaceutical Research*. UAE: Bentham Science Publishers, Mar. 2024, pp. 153–169.

[33] P. Thamotharan, S. Srinivasan, J. Kesavadev, G. Krishnan, V. Mohan, S. Seshadhri, K. Bekiroglu, and C. Toffanin, "Human digital twin for personalized elderly type 2 diabetes management," *J. Clin. Med.*, vol. 12, no. 6, p. 2094, Mar. 2023.

[34] C. Meijer, H.-W. Uh, and S. E. Bouhaddani, "Digital twins in healthcare: Methodological challenges and opportunities," *J. Personalized Med.*, vol. 13, no. 10, p. 1522, Oct. 2023.

[35] A. Hult, I. Zholobova, E. Bäcklin, and P. Nydert, "Flow rate deviation in infusion pump: Infusion set defect enables pump malfunction and considerable accuracy deviation," *J. Infusion Nursing*, vol. 47, no. 1, pp. 30–35, 2024.

[36] L. B. DeRidder et al., "Closed-loop automated drug infusion regulator: A clinically translatable, closed-loop drug delivery system for personalized drug dosing," *Med*, vol. 5, no. 7, pp. 780–796, Jul. 2024.

[37] O. Atanda, J. West, T. Stables, C. Johnson, R. Merrifield, and J. Kinross, "Flow rate accuracy of infusion devices within healthcare settings: A systematic review," *Therapeutic Adv. Drug Saf.*, vol. 14, Jan. 2023, Art. no. 20420986231188602.

[38] M. D. S. Silva, J. L. Araújo, G. A. M. D. A. Nunes, M. F. F. Rosa, G. V. D. S. Luz, S. D. S. R. F. Rosa, and A. Piratelli-Filho, "Precision and reliability study of hospital infusion pumps: A systematic review," *Biomed. Eng. OnLine*, vol. 22, no. 1, p. 26, Mar. 2023.

[39] R. Costa-Pinto, A. S. Neto, M. C. Matthewman, D. Osrin, G. Liskaser, J. Li, M. Young, D. Jones, A. Udy, S. Warrillow, and R. Bellomo, "Dose equivalence for metaraminol and noradrenaline—A retrospective analysis," *J. Crit. Care*, vol. 80, Apr. 2024, Art. no. 154430.

[40] P.-G. Chassot, P. Van der Linden, M. Zaugg, X. Mueller, and D. Spahn, "Off-pump coronary artery bypass surgery: Physiology and anaesthetic management," *Brit. J. Anaesthesia*, vol. 92, no. 3, pp. 400–413, 2004.

[41] (2019). *Hypertension in Adults: Diagnosis and Management*. [Online]. Available: https://www.nice.org.uk/guidance/ng136

[42] J. Yao, D. Liu, W. Huang, Y. Fang, Y. Yang, Y. Li, P. Liu, and X. Pan, "Increased variability of mean arterial pressure is associated with increased risk of short-term mortality in intensive care unit: A retrospective study," *Frontiers Neurol.*, vol. 13, Sep. 2022, Art. no. 999540.

[43] C. J. O'Hanlon, A. Sumpter, B. J. Anderson, and J. A. Hannam, "Time-varying clearance in milrinone pharmacokinetics from premature neonates to adolescents," *Clin. Pharmacokinetics*, vol. 63, no. 5, pp. 695–706, May 2024.

[44] M. Legrand and A. Zarbock, "Ten tips to optimize vasopressors use in the critically ill patient with hypotension," *Intensive Care Med.*, vol. 48, no. 6, pp. 736–739, Jun. 2022.

[45] C. Wan, C. Xie, L. Liu, D. Wu, and Y. Li, "A multi-scenario attention-based generative model for personalized blood pressure time series forecasting," 2024, *arXiv:2409.04704*.

[46] Y. Wahlquist, A. Gustafsson, and K. Soltesz, "Exploring the influence of patient variability on propofol target-controlled infusion performance," in *Proc. Eur. Control Conf. (ECC)*, Jun. 2024, pp. 3027–3032.

[47] A. Gustafsson, "Towards individualised anaesthesia: A comparison between target-controlled infusion and closed-loop control," Dept. Autom. Control, Sweden, Tech. Rep. TFRT-6217, 2023.

[48] B. Gholami, W. M. Haddad, J. M. Bailey, and W. W. Muir, "Closed-loop control for fluid resuscitation: Recent advances and future challenges," *Frontiers Veterinary Sci.*, vol. 8, Feb. 2021, Art. no. 642440.

[49] E. Estiri and H. Mirinejad, "Closed-loop control of fluid resuscitation using reinforcement learning," *IEEE Access*, vol. 11, pp. 140569–140581, 2023.

[50] J. M. Gonzalez-Cava, F. B. Carlson, O. Troeng, A. Cervin, K. van Heusden, G. A. Dumont, and K. Soltesz, "Robust PID control of propofol anaesthesia: Uncertainty limits performance, not PID structure," *Comput. Methods Programs Biomed.*, vol. 198, Jan. 2021, Art. no. 105783.

[51] H. H. Tang and N. S. Ahmad, "Fuzzy logic approach for controlling uncertain and nonlinear systems: A comprehensive review of applications and advances," *Syst. Sci. Control Eng.*, vol. 12, no. 1, Dec. 2024, Art. no. 2394429.

[52] M. Esmail Karar and A. Sayed A. Mahmoud, "Intelligent networked control of vasoactive drug infusion for patients with uncertain sensitivity," *Comput. Syst. Sci. Eng.*, vol. 47, no. 1, pp. 721–739, 2023.

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