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Optimization of Propofol Dose Estimated During Anesthesia Through Artificial Intelligence by Genetic Algorithm: Design and Clinical Assessment

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Abstract
This paper addresses the application of an adaptive neuro-fuzzy inference system (ANFIS) to assign the optimal dose of propofol as a vital anesthetic drug considering patient needs. The purpose of this research was to explore the factors that influence the propofol dosage needed to sedate patients. This paper estimates the drug dose to regulate the depth of anesthesia by administrating propofol. In this regard, two artificial intelligence approaches; a feedforward neural network and ANFIS are applied to predict the propofol dose. Introducing an estimator to control automatically might provide remarkable advantages for the patient in reducing the risk for under- and over-dosing. The suggested estimations are compared with results extracted from the classical model revised method and then evaluated patients undergoing surgery in a Mashhad's hospital to identify a research innovation. The propofol doses are optimized using a genetic algorithm. Sensitivity analysis methods are used to test the estimator using a collection of patient models consisting of some populations. Finally, during anesthesia, an optimal dose estimator allows for a rapid period of induction with reasonable overshoot and adequate disturbance rejection results. The novelty of this study is in estimating without using Bi-spectral Index signal and also there is a significant reduction in anesthesia costs by optimizing the drug dose. The results of the optimization model show a 14.06% saving of propofol dose with MSE 5.3×10^{-6}.

Keywords Propofol dose optimization · Feedforward neural network · ANFIS · Genetic algorithm · Anesthesiologists

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1 Introduction

Anesthesiologists strive to create an adequate equilibrium of patient analgesia and muscle relaxation while utilizing a number of induction instruments and prescribing a mixture of anesthesia medications during the procedure to preserve patient physiology parameters. While utilizing a combination of hypnosis and analgesia to achieve optimum sedation is an essential aspect of critical care medicine, due to inter-patient pharmacological variability, medication dosage instructions in the surgery room often result in under/over-sedation, which may contribute to increased mortality and morbidity [1, 2]. The complexity of the process of general anesthesia has been made up of the combined results of hypnosis, analgesia, and muscle relaxation components where each of these functions is controlled through a specific medication. Generally, the administration process is carried out by anesthetists, who, in accordance with their personal experience, determine the initial blouse of drug doses as well as the number of maintenance doses adequately to provide an adequate and safe depth of anesthesia (DOA) level during the surgery. Anesthesiologists struggle with regular evaluations while often choosing to confront difficult issues throughout crucial circumstances. Assisting with an anesthetist's daily functions can reduce stressful situations and, as a result, improve patient safety. So, in a medical study, anesthesiologists should have ample scope of anesthesia and analgesia to maintain patients' well throughout medical procedures. Ergo, a well-balanced drug administration has been needed. Model simulation or automatic control of anesthesia throughout surgery could result in improved patient safety by managing inter-patient variability [3, 4]. Recently, the implementation of drug dosing feedback control issues in the presence of BIS has received a lot of interest [5–11].

In general anesthesia, close loop structures proved the highly beneficial outcomes in the drug used to diminish, which implies safety and rapid recovery time in the post-anesthesia phase, more robust performance with less over/under dosing episodes [7, 9, 12]. Propofol is considered the most common intravenous (IV) anesthetic agent used for induction and maintenance of general anesthesia with fast onset and short duration of action, suitability for titration, sedative-hypnotic, amnestic, and anti-emetic properties. The administration of propofol guiding has been incorporated into automatic injection and advisory displays in some models [13–17].

Typically, simulation methods are mainly used in drug delivery systems and massive molecules that have been updated. Modeling has long been used in the traditional drug delivery method to assist formulation design based on preclinical experiments [18, 19]. Many study reports and book reviews have been published on the recent development of analysis in drug distribution, with an emphasis on pharmacokinetics and pharmacodynamics (PK-PD) systems for estimating plasma time-course and effect site of concentration, as well as the relationship between drug effect and concentration [13–15, 20–23].

These models are more widely used in purpose-regulated infusion systems, Target Controlled Infusion (TCI), which optimize propofol administration to achieve constant drug concentrations in plasma or at an effect-site [8, 9, 24]. Eleveld and et al. (2018) was designed TCI to test the propofol hypothesis in order to compare with manual infusion in shorter recovery time [20] and Mu compared manual infusion propofol and TCI in children. TCI systems deeply rely on PK-PD models by similar physiological characteristics of patients [8, 25]. So, surgeons must be aware of the model application for demographic support and might have to update models with different patients (adults, pediatrics, and obesity patients).

Artificial intelligence has been used in many areas of medicine, most prominently diagnostic applications in the healthcare system and anesthesia. Hatib et al. and Martinoni et al.

used machine learning to regulate systems and automate the application of neuromuscular blockade. Mendez et al. assessed the suggested controller in simulation and the operating room with patients undergoing surgery utilizing fuzzy predictive control methods under anesthesia [26]. The findings of these studies demonstrated that these systems utilized drug pharmacokinetic prediction to enhance infusion control [27, 28]. The first propofol dosage was calculated with 92% accuracy by Sivari et al. using a multilayer feed-forward artificial neural network structure. Hashimoto et al. explored the implications of artificial intelligence for clinical anesthesiologists within its limits, as well as the role of clinicians in further developing artificial intelligence for application in clinical care [29]. Previous research based on the artificial intelligence implementation in anesthesia has relied on the anesthetic depth estimation device or BIS, and they also have a restriction on the number of parameters and modalities.

The contribution of this research is to focus on monitoring the depth of anesthesia in complete intravenous anesthesia utilizing the hypnotic agent propofol to refine propofol administration to meet the requirements of the particular patient and thereby increase protection and outcomes. The key distinction between this analysis and elsewhere is that the current control system requires one to use both the induction and maintenance phases in the controller's closed-loop control methodology, instead of only the maintenance process without BIS. In the previous work, the depth of anesthesia is estimated by avoiding BIS monitoring applying an artificial intelligence approach and machine learning [11, 30]. Besides that, the adaptive neuro-fuzzy inference scheme (ANFIS) and feedforward neural network have been used to test and assess the viability of a closed-loop system for robust regulation of propofol infusions based on the most significant pharmacological characteristics of propofol using artificial intelligence methods. Genetic algorithms (GAs) were eventually used to evaluate the correct values for the estimation propofol dose. During the induction and management of anesthesia, propofol infusion was managed in a closed-loop, which facilitated clinically necessary system behavior. This study aims to introduce this new artificial model into clinical practice and try contrasting its precision and clinical feasibility to BIS-guided, effect compartment regulated propofol administration titrated by the anesthesiologist during ambulatory gynecological procedures under close supervision of an anesthesiologist.

The remaining section of the paper is set out as follows. To have a problem outline, we explain procedures and the patient anesthetic model in Sect. 2. The sensitivity analysis and discussion in Sect. 3 explain the computational results. Section 4 outlines the results and makes proposals for potential studies.

2 Experimental Methods

This paper focuses on the propofol dose as an anesthetic drug and the problem of hypnosis control by applying artificial intelligence systems modeling during surgery in induction and maintenance phases. The current study intends to look at patient behaviors that might influence the amount of propofol needed to sedate them. The Iranian care public hospitals were carried out in this study as a case study. The proper selecting of an optimum combination of the anesthetic drug is one of the main decision-making processes for an anesthesiologist to deliver safe anesthesia. Anesthesia drugs for induction or maintenance would come in the form of a gas or vapor (inhalation anesthesia) or an injectable (intravenous anesthesia). Intravenous medications are injected directly into a vein and are usually used in the induction phase whereas injectable anesthesia induction is quicker and easier than inhaled drugs.

During induction, maintenance, and sedation, propofol is frequently used as the hypnotic component of full intravenous anesthesia [31]. Since in the cases study propofol applied to sedate during surgery, in this work propofol is considered to estimation models. To do this, feed-forward perceptron networks with hidden layers and neuro-fuzzy inference system (ANFIS) trained by real data from a case study to estimate the propofol dose. To validate the estimation models, results are compared with the classic model (PK-PD model), and data-driven by BIS under the anesthesiologist's conservation and sensitivity analysis are applied. The Genetic Algorithm optimizes the propofol dose estimated based on the patients' real needs owing to physiological characteristics.

2.1 Drug Administration

Without any premedication, every one of the patients was given general anesthesia. Continuous pulse oximetry, electrocardiography, invasive blood pressure, and neuromuscular blockade were both developed in the operating room. Before receiving propofol, each person was given a standardized dosage of fentanyl (2 g/kg) or a target-controlled infusion of remifentanil (3 mg/mL). The propofol infusion was begun at 2000 mg/h and continued until the patient lost consciousness. In all cases, the total dose of propofol given before LOC was reported. Where needed after the loss of consciousness, Rocuronium was provided, and the propofol infusion rate was reduced to 6 mg/kg/h (LBW in patients with a BMI of 35 kg/m^2). Propofol infusion was driven by BIS values between 40 and 60 during surgery. Propofol and remifentanil infusions were stopped at the end of treatment, and Sugamadex 2 mg/kg was given to reverse neuromuscular blockade. The overall dosage and duration of propofol injection, the total dose of opioid, and the time it took for the patient to regain consciousness after the propofol was stopped were all documented. The appendix contains all of the patient's records.

2.2 Data Collection

Demographic details (gender, age, weight, height, and depth of anesthesia [DOA]) was obtained from medical reports, as well as information on the diagnosis, method of treatment, the total length of the radiological test, the initial dose of propofol, additional doses of propofol and injection times, and total dose of propofol administered. This procedure is carried out in an Iranian hospital in Mashhad. Data were automatically registered at a resolution of 1 data point per 5 s and saved to the computer's hard drive for further processing and evaluation. The demographic and clinical Patients' information data from the study hospital in Iran are summarized in Tables 1 and 2.

MATLAB™ software was used to code the model that allows for the collection and synchronization of data derived from the various monitors used to assess drug effects.

Remark 2.1 Thirty patients were monitored, and only 13 patients with no chronic or underlying disease were chosen to estimate the model. To evaluate comparisons, we utilized this model to investigate data from patients in surgical theaters in real case clinics, with the same number of instances as the Ionescu dataset [32].

Table 1 Demographic Patients' information data

	Closed-loop control (n = 13) [32]	Manual-control (n = 13)
Age (year)	37.8 ± 4.5	53.5 ± 5.0
Gender (F = female, M = male)	9 M, 4 F	7 M, 6 F
Weight (kg)	169.0 ± 5.9	169.9 ± 5.5
Height (cm)	64.7 ± 8.7	74.2 ± 8.0

Table 2 Clinical Patients' information data

	Closed-loop control (n = 13) [32]	Manual-control (n = 13)
Induction time (s)	66 ± 25	49 ± 9
Propofol dose until LOC (mg)	91 ± 22	117 ± 15
BISLOC	73 ± 11	98 ± 9
Duration of anesthesia from start until stop propofol infusion (s)	1013 ± 191	1068 ± 250
Total propofol used (mg)	261 ± 68	391 ± 64
BIS at stop propofol administration	46 ± 5	51 ± 11
Ce $_{PROP}$ at stop propofol administration	3.1 ± 0.8	4.5 ± 0.7

2.3 Propofol Dose Estimation Model

The artificial intelligence (AI) methodology is already successfully extended to extremely nonlinear structures, where the simulation of the system has been found to be significantly simplified. Even though mentioned method seems to have serious potential in various areas in artificial intelligence, the frequent use of these methods such as neural networks theory is in the area of estimation systems. It should be seen as a preliminary phase before going on to a more sophisticated pharmacologic analysis, such as a population-based approach using mixed-effects modeling techniques. The feed-forward neural network with a hidden layers approach allows the implementation of highly complex structures for which an effective mathematical model is inaccessible. To summarize, we used an FFNN with two hidden layers and an ANFIS simulation system with prospective validation to investigate the relationship between propofol dose estimation and the amount of the dose injected to patients during surgery and sedative effects in patients undergoing surgery. Figure 1 depicts the inputs and a single output data set used to design the feedforward neural network for each experiment in this study.

The Adaptive Neuro-fuzzy Inference System (ANFIS) is a fuzzy logic-based modeling technique that describes the relationship among variables using a non-restricted mathematical context without making any assumptions about the mathematical association. ANFIS has the advantage of being a data-driven method that does not depend on a mathematical model to monitor the relationship between anesthetic drugs and response-effect.

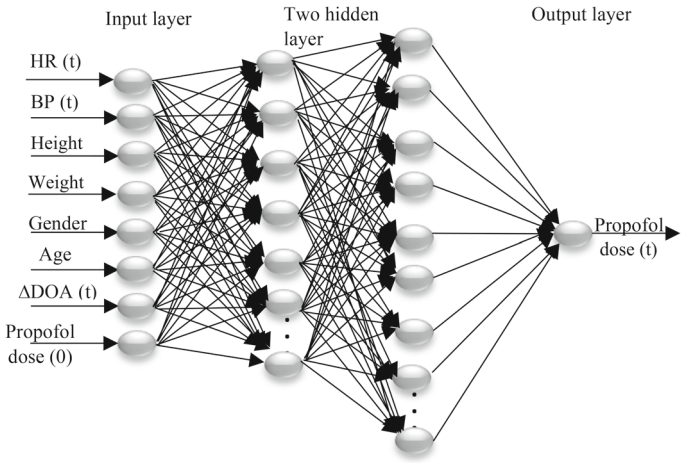


Fig. 1 The inputs and output of the Propofol dose estimation model by two-hidden layer feedforward neural network

We attempted to prospectively validate the ANFIS model in a new set of data to strengthen our conclusions, and we obtained comparable results. This suggests that the model is being used with confidence to calculate propofol doses in this form of therapy and patients. The Fuzzy Logic Toolbox in MATLAB is being used to identify clusters of input-output training results.

To effectively model data behavior, a Sugeno-type fuzzy inference method with the minimum possible rules is built from cluster knowledge. The rules are self-divided in terms of the fuzziness of each data cluster. The FCM (fuzzy c-means) clustering method was improved by Bezdek [33]. It is commonly used in pattern detection. This process causes a single piece of data to belong to several clusters. FCM divides n vector, 1, 2…, Xi = n collection into c fuzzy set and checks for the cluster center of every group while keeping the cost function of dissimilarity measure to a minimum. The 91 data sets collected from real patients undergoing surgery that were utilized to train the proposed model are shown in Fig. 3. The ANFIS-SCM model parameters are shown in Table 3. The SCM method was used to evaluate the cluster center of all results. The total of subtractive centers would have been used to generate automatic membership functions and classify them within measurements. A total of 78 rules were obtained for the ANFIS-SCM model. The ANFIS-SCM model's performance was analyzed using a patient dataset and the indices root mean square error (RMSE), MSE, d_α, and R2.

Figure 2 illustrates the inputs and a single output data set used in this analysis to design the ANFIS-SCM model for each experiment.

To make the estimation model of propofol dose using artificial intelligence techniques, according to the patients' data, a specific amount of the data must be selected to train the model, then it should be validated and tested. Based on the 7 variables of each patient, the total number of data for training is 91, which of these numbers is approximately 70% for training, 20% validation, and the rest was used for testing. Table 4, represents this information of estimation modeling.

Table 3 The ANFIS-SCM estimation model of the Propofol dose specifications

Parameter	Description
The type of membership function	Gaussian
The output membership function	Linear
The nodes (number)	187
The number of linear variables	454
The number of nonlinear parameters	46
The parameters (total number)	900
Total number of data pairs for training	84
The total number of data pairs tested	12
The total number of fuzzy rules	78

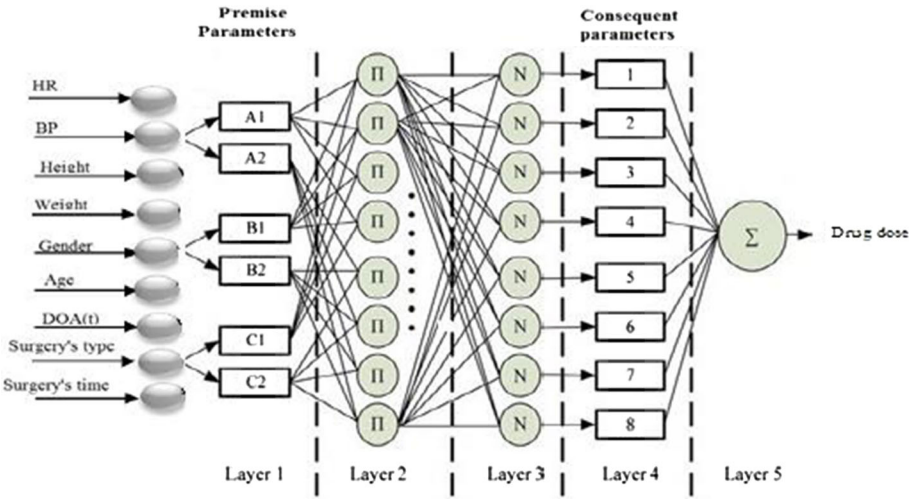


Fig. 2 The inputs and output of the Propofol dose estimation model by ANFIS

Table 4 The number of samples data of the estimation models

Data	Patient input data's number	Training data (70%)	Validate data (20%)	Test data (10%)
Input	91	63	18	10
Output	91	63	7	21

2.4 PK Modeling Analysis

The usage of physiology-dependent pharmacokinetic modeling for drug delivery, uptake, and distribution models is attracting scholarly interest [34], and it provides comprehensive results based on replicating biological system elements [35]. Understanding the time courses of drug

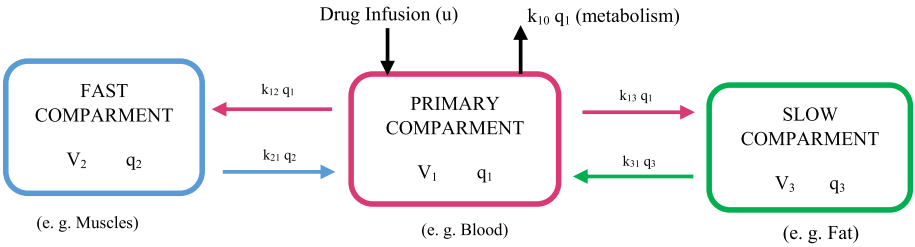


Fig. 3 The three-compartmental PK model of patient

concentration following the administration of various formulations, as well as quantifying the dose-concentration relationship, requires PK modeling. Compartmental modeling is widely used to characterize PK [21, 36]. The PK curve with multi-exponential decay is defined by a two- or three-compartment model. Pharmacodynamics model PD refers to the relationship between medication concentration and the consequence of a patient's pharmacology. The propofol effect-site concentration and BIS values were calculated using the following sigmoidal inhibitory maximal effect in the statistical PK models:

$$BIS_{effect} = BIS_{baseline} \times \left(1 - \left(\frac{I_{max} \times C_e^{\gamma}}{C_{e50}^{\gamma} + C_e^{\gamma}}\right)\right) \tag{1}$$

where BIS_{effect} is the value of BIS, $BIS_{baseline}$ means the value before propofol injected, I_{max} is the maximum inhibitory drug effect on the BIS value, and Ce denotes the propofol impact-site concentration, C_{e50}^{γ} denotes the propofol effect-site concentration required to achieve 50% of the BIS possible drug effect, and defines the steepness of the effect-site concentration. Figure 3 illustrates a patient's three-compartmental PK model, which was included in this research.

The three-compartmental model is generally stated as follows:

$$\begin{aligned} q_1(t) &= -(k_{10} + k_{12} + k_{13})q_1(t) + k_{21}q_2(t) + k_{31}q_3(t) + u(t) \\ q_2(t) &= k_{12}q_1(t) - k_{21}q_2(t) \\ q_3(t) &= k_{13}q_1(t) - k_{31}q_3(t) \end{aligned} \tag{2}$$

where $q_1(t)$[mg] represents the amount of drug in the central blood compartment over time. The quantity in the peripheral fast compartment, which includes well-perfused body tissues including muscles and tendons, is denoted by $q_2(t)$[mg]. The amount in the slow dynamics compartment, which includes weakly perfused bodily tissues including fat and bones, is expressed as $q_3(t)$[mg]. The parameters kij are constants that express the amount of mass flow from the ith to the jth compartment, except for k10, which represents the drug's elimination rate (metabolism), and u(t)[mg/min], which is the drug's infusion rate into the plasmatic circulation and thus it is the input of the model.

2.5 PD Modeling Analysis

PD simulation analyses the time course of a drug's pharmacological results, taking into consideration the drug's mechanism of activity as well as significant rate-limiting stages in the system's biology [37]. The association between medication concentration and therapeutic impact is quantified using PD models. The key processes of drug activity are captured by PD

models, which include direct impact and indirect action models. Particularly in comparison with PK, compartmental models are used to explain PD, and complex PD models are generated by merging simple models [38]. The PD parameters were measured with appropriate precision.

A first-order delay-free function links the drug concentration in the central compartment to a fictitious volume defined as the effect-site compartment in pharmacodynamics:

$$C_e(t) = K_{1e}C_p(t) - K_{e0}C_e(t) \tag{3}$$

where C_e indicates the concentration of the effect site. The existence of this compartment is prompted by a lag time between the concentration of blood plasma and its clinical impact. The effect-site compartment is believed to be quite tiny. As a result, the effect-site rate transfer constant will be nearly equal to the elimination rate:

$$K_{1e} \cong K_{e0} \tag{4}$$

The corresponding transfer function is:

$$PD(s) = \frac{C_e(s)}{C_p(s)} = \frac{K_{e0}}{s + K_{e0}} \tag{5}$$

Thus, the concentration in the effect compartment may be determined from drug metabolism, which is defined by the parameter ke0 [min^{-1}], which represents the time constant of equilibration between the plasma concentration and the corresponding drug effect. Its value is evaluated in the literature [32] as follows:

$$K_{e0} = 0.459 \tag{6}$$

The relationship between plasma drug concentration and clinical impact may then be stated mathematically using a nonlinear sigmoid function, often referred to as the Hill function, which represents the BIS, a dimensionless variable normalized between 0 (isoline) and 100 (totally awake and alert):

$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + C_{e50}^{\gamma}}\right) \tag{7}$$

C_e(t) is the propofol concentration in the brain (g/ml) in the Hill equation. E0 represents the patient's initial status (awake and un-medicated), which is usually set to 100. The drug dosage maximum effect is expressed by E_{max}, and the drug concentration at 50% of the maximum effect is represented by EC_{50}, which shows the patient's response to drugs. The slope of the curve is γ. Throughout anesthesia, the set-point is 50, with levels between 40 and 60 providing an appropriate degree of relief. Based on the experimental nonlinear relationship [39, 40], the BIS variable will refer to the impact of C_e, and the drug concentration (t) in the patient.

The baseline value is a patient that is awake and has not been offered any drug, denoted by E_0 and assigned the value 100. The entire benefit of the opioid injection is used in E_{max}. The EC_{50} explains the patient's exposure to the medication and represents the drug concentration at 50% of the best impact, as well as the steepness of the curve.

2.6 Genetic Algorithms Optimization

Genetic algorithms were used to find the best propofol dose estimator so they would vouch, at least in a stochastic sense, that an optimal solution is reached (at the cost of potentially

high computational effort, which isn't a concern for the problem at hand). Since conducting multiple studies takes time, money, and ANFIS simulation model of this method was created data that has been collected in the lab, and the effects of various parameter and variable values on propofol dose were estimated. The ANFIS model's findings showed strong precision, which is consistent with MSE 5.3×10^{-6}. Besides, our proposed model estimates the optimal propofol dosage for healthy sedation during surgery and rehabilitation, which is consistent with experimental findings. According to these findings, the ANFIS estimated is used as a fitness function in the Genetic algorithm to refine the model. The worst-case integrated absolute error for all patients has been chosen as the expense feature to be reduced. Intelligent systems are built on the idea that the natural world is more complex than a set of straightforward mathematical interactions could describe. Natural systems are complex, unreliable, and disruptive, and the purpose is to deal with high-order nonlinear systems.

This form is regarded as an appropriate performance index in process control since its reduction means a decrease in both the increase period and the overshoot percent in general. In anesthesia, a quick transient response without a significant overshoot is deemed adequate in the induction process, and the DOA estimator is held as near to the target value as possible in the maintenance phase. The set-point following and disruption exclusion tasks both had their optimization challenge that had to be solved separately. This makes for a separate investigation of the medication dosage estimator's optimal results in the two phases of the anesthesia paradigm. The value of 391 ± 64 [mg/min] was calculated using the maximum rate of a normal medical pump and the propofol hypnotic medication concentration. This finding suggests that using AI techniques can be advantageous. Only during the induction process of anesthesia is the DOA estimator calibrated for the set-point following task used. The controller parameters are transferred to the disturbance rejection optimum ones until the target is accomplished and the DOA is stabilized around the set-point for a predefined time period. There must be a bump-free switching process between the two estimators.

In the induction step, it is clear that the load disruption tuning results in a long time period where the control variable saturates, resulting in oscillatory behavior. When the medication dose estimation parameters are used for a purpose other than the one for which they were optimized, the need for the AI methodology is shown in Table 5. The use of disturbance rejection tuning for set-point monitoring tasks, in particular, results in a significant loss of efficiency.

Survival of the fittest and recombination are the two most significant heuristics in GA. The former chooses the best chromosomes to produce a more likely next generation, while the latter tries to find stronger outcomes by combining chromosomes in a new generation. The crossover and mutation operators help us to create new combinations in the new generation's output. The crossover and mutation operators help us to create new combinations in the new generation's output. GA is a stochastic optimization approach that, no matter how long it takes, will eventually arrive at a solution. However, it is not possible to say that it would solve all problems precisely because it was motivated by design, and has solved complex problems by its implementation. The explanation for this is that, first and foremost, the problem we're simulating does not happen normally, and second, we don't have the same amount of time and energy as nature. As a result, to decide the best input variables that yield the smallest particles, this analysis uses the ANFIS model as a fitness function for GAs. Table 6 shows the effects of such an optimized method. To optimize the estimation propofol dose, the model runs 20 times to reach the desired anesthesia depth of 50. Therefore, the results obtained for the patient reach the desired depth by injecting the 1.549 [mg/min] propofol dose, which is generally considered to be injectable 2 [mg/min] for each period and overall we see a significant decline in total dose usage.

Table 5 The characteristics of the genetic algorithm

Factors	Dose estimation model
Population size	91
Early population (chromosomes)	10
Crossover	0.8
Mutation	0.4
Fitness function	ANFIS estimation model
Max Iteration	200

In this work, based on the set-point of the depth of anesthesia and taking into account the physiological characteristics and the real needs of the patients, the required propofol is determined and optimized. Figure 9 shows the diagrams of the genetic algorithm in achieving the optimal dose of propofol in 5 steps of the target value in 200 iterations.

3 Discussion and Results

The findings of this paper are being compared to many of those generated via other methods. The same group of patients was analyzed previously in [8], whereby model predictive control methods were being used. The findings for the induction phase indicate that the existence of data-driven estimators is needed for AI estimators to perform better other controllers/predictors (as the induction phase provided by AI techniques is faster and more accurate than that provided by a controller with a very similar maximum overshoot). Proof of performance degradation for ANFIS as compared to FFNN and the PK-PD method backs this up. In [6], our ANFIS algorithm outperforms the PID controller and the fractional-order controller in the induction process (although the latter has been tested on a different set of patients). Assessing the findings in [2, 7], where a model predictive controller and an internal model control approach are contrasted, leads to the same finding. As compared to the findings provided in [8, 9, 24, 41–43] the output obtained with our estimator is greater.

It's worth noting that we've used a basic phase signal as a disturbance to make evaluating the estimator's disturbance rejection output simpler. When reviewing the data, nevertheless, it is possible to assume that the data taken with ANFIS explicitly tuned for this assignment is completely compatible with that achieved using other methods. By use of a disturbance rejection estimator for a set-point monitoring mission, in specific, results in a significant loss of output. The findings show this kind of intelligent device is capable of accurately modeling propofol doses. In the recent research, a Feedforward neural network and ANFIS were used such that the findings from the latter might be comparable to those from the previous.

The results of the simulations described in Table 6 demonstrate that ANFIS achieves better modeling results. This is because any one of these intelligent systems seems to have its series of flaws, which we want to address by integrating them into soft computing. ANFIS is a hybrid of a fuzzy system and a neural network that aims to build a more accurate model by combining simulation with expert knowledge.

Considering Fig. 4, both models have the ability to estimate the actual dose of the drug. ANFIS estimation model has shown high accuracy in contrast to real patients' dose usage.

Table 6 Result of the Propofol dose estimation through the FFNN and ANFIS

Induction time (min)	Real data	FFNN-estimated propofol dose	FFNN error	ANFIS-estimated propofol dose	ANFIS error
1	1.6	1.6981	0.0981	1.6001	0.0001
2	1.6	1.7683	0.1683	1.6001	0.0001
3	1.6	1.6934	0.0934	1.6	0
4	1.6	1.5561	0.0225	1.601	0.001
5	1.6	1.5775	0.0373	1.6	0
6	1.6	1.6373	0.0373	1.6	0
7	1.6	1.7283	0.1283	1.6	0

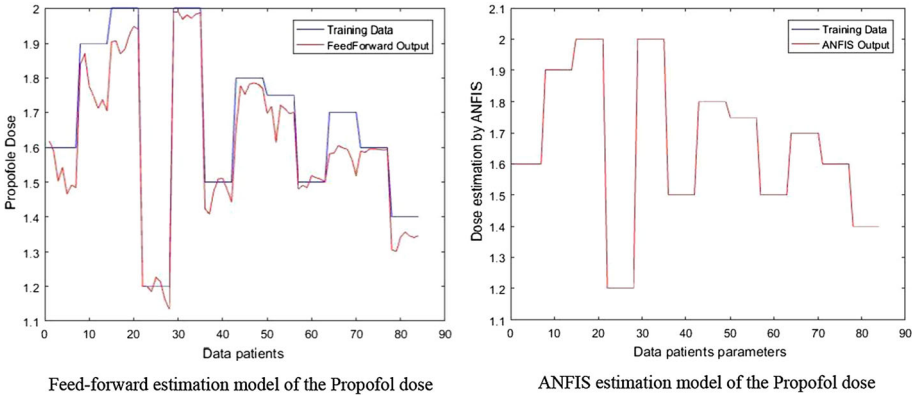


Fig. 4 The Propofol dose estimation through the FFNN and ANFIS

3.1 Sensitivity Analysis

The findings of the model's sensitivity analysis might well be interpreted as being more adaptive to certain parameters than others [44]. By eliminating input from the training model, the sensitivity analysis was submitted to the test. When evaluating the outcomes of various approaches, the most applicable statistical indexes to choose the right network architectures are normally sufficient for the model's output evaluation [45]:

$$RMSE = \sqrt{\frac{1}{n}\sum_{d=1}^{n}(x_d - \widehat{x}_d)^2} \tag{8}$$

$$R^2 = 1 - \frac{\sum_{d=1}^{n}(x_d - \widehat{x}_d)^2}{\sum_{d=1}^{n}(x_d - \bar{x}_d)^2} \tag{9}$$

where $\widehat{x}_d$ represents the computed value by the model, x_d denotes the observed value, and $\bar{x}_d$ constitutes the average of n observed data set. A model with $R^2 \in [-1,1]$ values and $RMSE \in [0,1]$ and respectively close to 1 and 0 may be chosen as the best option.

Willmott Index (d_α):

$$d_\alpha = 1 - \frac{\sum_{d=1}^{n} |\widehat{x}_d - x_d|^\alpha}{\sum_{d=1}^{n} \left(|\widehat{x}_d - \tilde{x}_d| + \left| x_d - \bar{x}_d \right| \right)^\alpha} \tag{10}$$

α may be either 1 or 2, so the value of two in this paper is chosen. The coefficient of the dimensionless boundary is d_α, ought to be1 for complete fit between observed and estimated values.

The important physiological parameters influencing the propofol dose were investigated during the modeling period. During the surgery, the physiological variables of both patients were analyzed and reported for the training model, and the impact of every parameter on the depth of anesthesia was evaluated. Table 7; Figs. 5 and 6 show the capacity of each parameter to estimate the propofol dose based on the real needs of patients.

During the modeling process, the significant physiological parameters influencing the propofol dose were investigated. During the surgery, the physiological variables of both patients were measured and recorded for the training model. Each parameter's impact on the depth of anesthesia has been evaluated. Table 7; Figs. 5 and 6 demonstrate each parameter's ability to estimate the propofol dose depending on the real needs of patients.

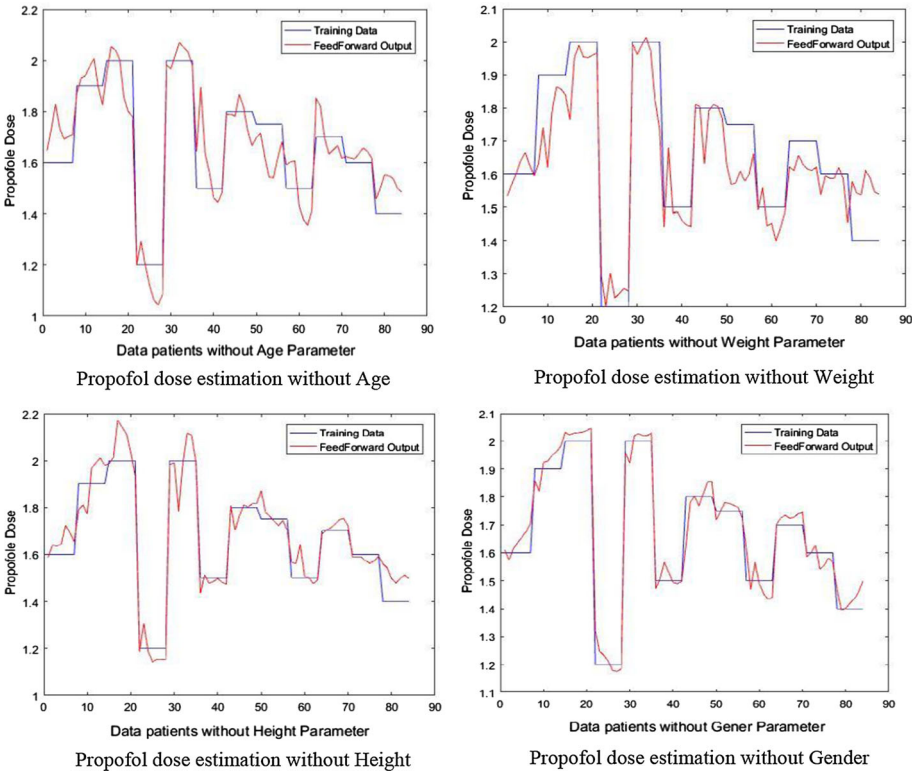


Fig. 5 A feed-forward neural network is used to perform sensitivity analysis and to measure the parameter's input effect on estimation

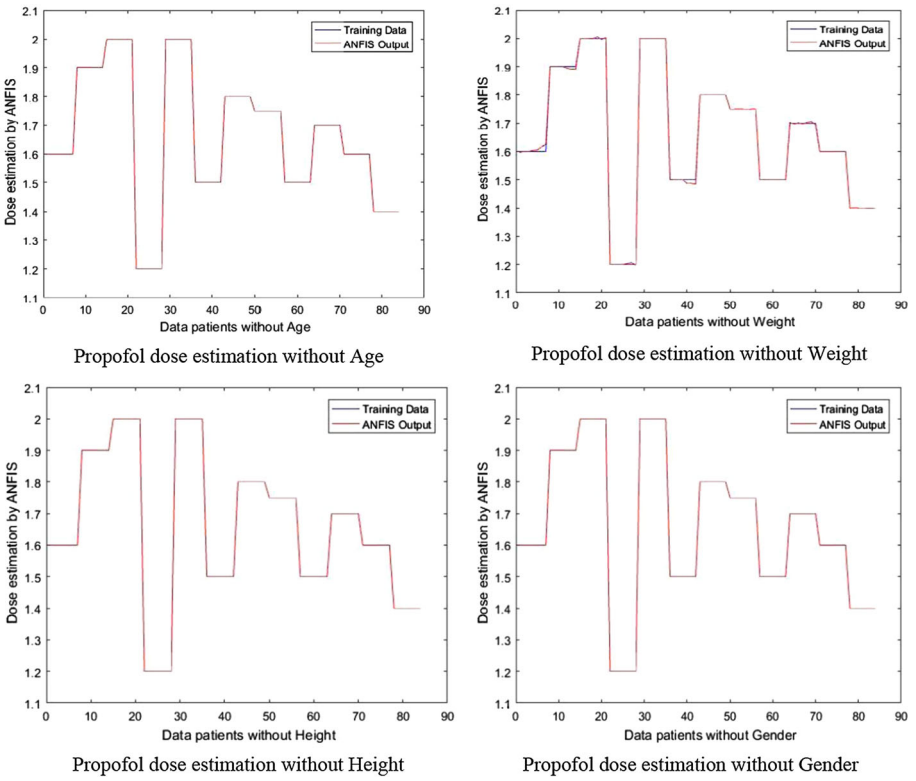


Fig. 6 ANFIS performed a sensitivity study and evaluated the parameter's input effect on estimation

According to the results of Table 7, the removing effect of one input parameter on the ANFIS model is presented in Fig. 6. The propofol dose estimation without Weight parameter compared to other parameters shows a minimal error in estimation.

Since propofol dosage is strongly affected by weight and age, these results are unmistakably related to the PK-PD model and data gathered from a single patient during surgery. Figures 5 and 6 display the most important input variables on propofol dose estimation using a feed-forward neural network and ANFIS modeling, as shown in the training data table, by removing one input parameter at a time.

Figures 7 and 8 demonstrate how to exclude two input parameters from the feed-forward neural network and ANFIS modeling to identify the two most influential input variables on dose estimation.

Figure 7 shows the weight and age have the greatest influence on drug prescription to estimate the dose of propofol. Since propofol dosage is highly influenced by weight and age, these findings are most definitely associated with the PK-PD model and evidence obtained from actual patients during surgery.

Age and weight provide the greatest influence on drug prescription to estimate the propofol dose, as seen in Fig. 8. Since propofol dosage is highly influenced by weight and age, these findings are most definitely associated with the PK-PD model and evidence obtained from real patients during surgery.

Table 7 The sensitivity analysis of physiological patient's parameters of the propofol dose estimation

Estimation model parameter	FFNN					ANFIS				
	Accuracy	d_α	Reliability	MSE	RMSE	Accuracy	dα	Reliability	MSE	RMSE
Age	0.868	0.999	0.021	0.147	0.881	1	1	1	3.59×10^{-4}	0.0099
Weight	0.896	0.999	0.999	0.15	0.124	1	1	0.99	4.52×10^{-4}	0.067
Height	0.865	0.999	0.999	0.017	0.133	1	1	1	2.29×10^{-4}	0.0031
Gender	0.905	0.999	0.999	0.013	0.115	1	1	1	3.62×10^{-4}	0.0019

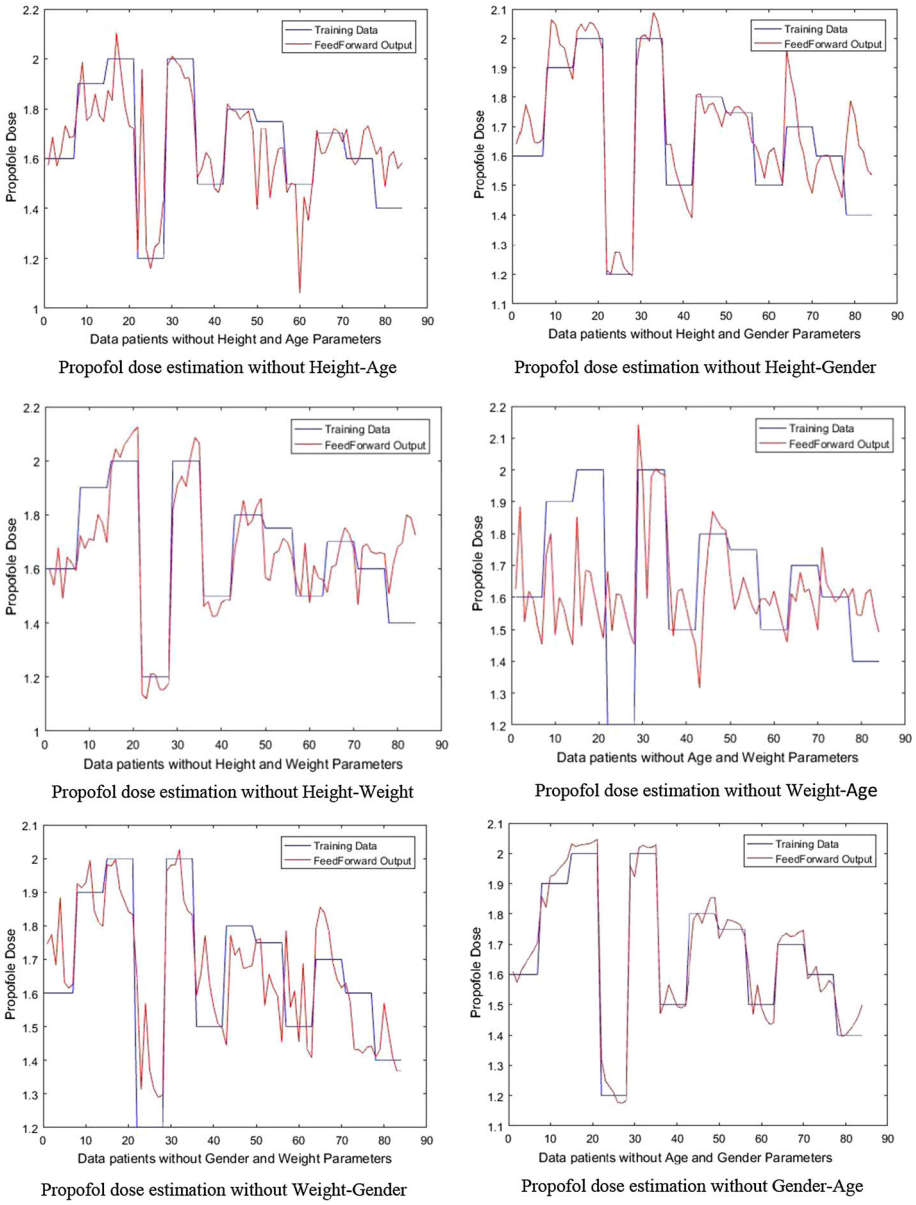


Fig. 7 Sensitivity analysis and measurement of the input impact on estimation without the use of two parameters

The results show that the age and weight parameters are the most effective factors in determining the dose of the drug. The results are validated by Miller's book [31], Araújo [21], and Nașcu [32] reference models and also confirmed by anesthesiologists in the studied hospitals.

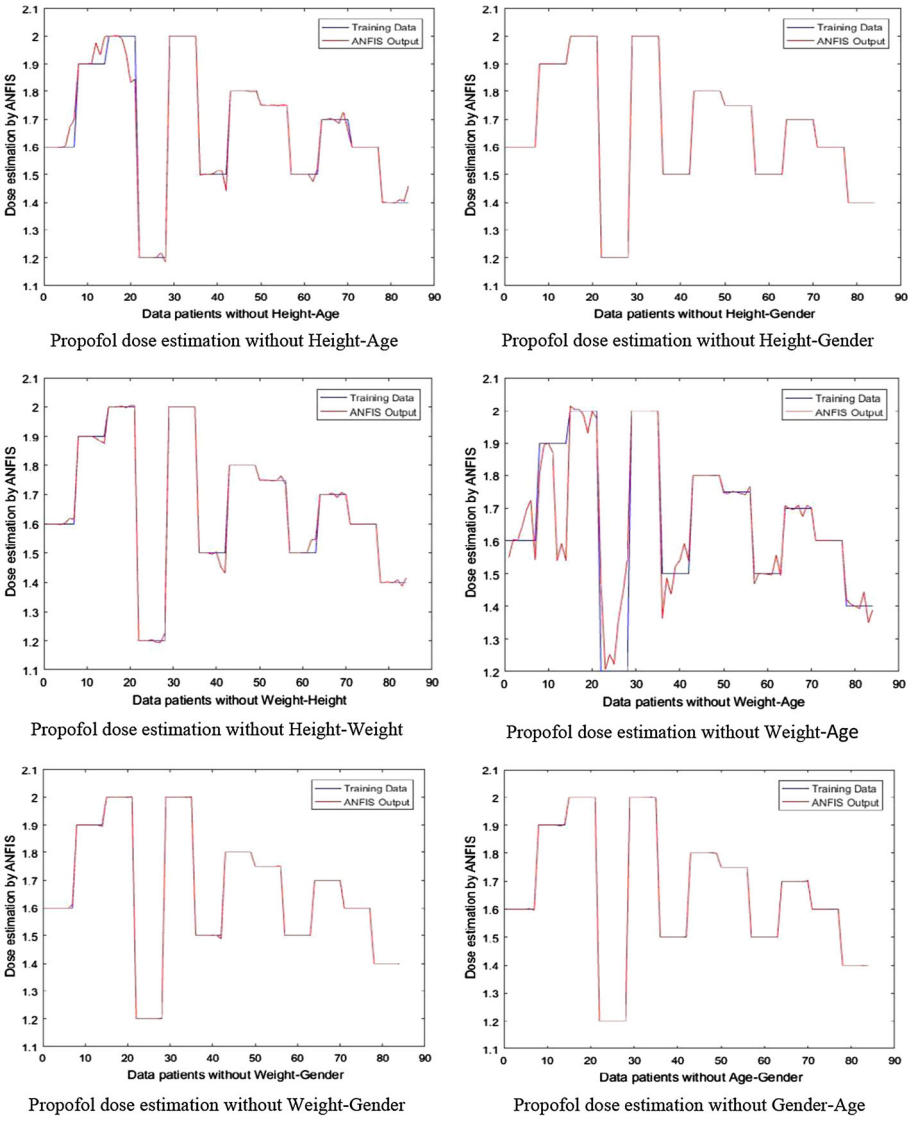


Fig. 8 Sensitivity analysis and assessment of the input impact on estimation without two parameters

3.2 Model Validation

To validate the propofol dose estimation models are compared with the PK-PD model as well as with the closed-loop system of propofol injection control. The results of the estimation models and their comparison with the others in Table 8 are given.

The ANFIS model has the highest accuracy of propofol dose estimation based on the patient's actual needs, according to the results of Table 8.

Table 8 Evaluation of the effect of patient parameters on propofol dose estimation models

Estimation model method	Propofol dose (induction- maintenance)				
	Accuracy	d_α	Reliability	MSE	RMSE
PK-PD	0.966	0.951	0.95	0.002	0.043
Closed-loop sys.	0.975	0.98	0.99	0.003	0.055
FFNN-L2	0.989	0.999	1	0.001	0.101
ANFIS	1	1	1	$5.3 \cdot 10^{-6}$	0.002

3.3 Estimates of Performance Using k–Fold Cross-Validation (KCV)

The k–Fold Cross-Validation (KCV) process [31] is a useful resampling strategy because it is simple, effective, and trustworthy [31]. The data set D is first chunked into K disjoint subsets of the same size 3 m $\Delta =$ n/K. The KCV divides the training set into k parts, each one with l/k samples: k-1 parts are utilized as a training set, whereas the remaining one is used as a validation set. Let Tk represent the k-th such block, and Dk denotes the training set created by deleting the items in Tk from D. The cross-validation estimator is calculated by taking the average of the errors on test block Tk acquired after the training set is removed:

$$CV(D) = \frac{1}{K}\sum_{k=1}^{K}\frac{1}{m}\sum_{Z_i \in T_k} L(A(D_k),\, Z_i) \tag{11}$$

Cross-validation is frequently conducted using stratified random sampling, which implies that the class ratios in the individual subsets represent the proportions in the learning set. Cross-validation is often done 95 with various k-fold subsets to decrease the variance of the calculated performance measure (r times repeated k-fold cross-validation). However, Molinaro et al. demonstrated that such repeats only marginally decrease variance [32].

3.4 Bias Correction of K-Fold Cross-Validation

Burman [46] claims that the bias of K-fold cross-validation $CV_{N,K}$. The bias of K-fold cross-validation is as follows:

$$E(S_N) = \delta^2 + \frac{\delta^2}{N} \tag{12}$$

$$E(CV_{N,K} - S_N) = \frac{\delta^2}{(K-1)N} \tag{13}$$

Table 9 presents the findings after 1000 repetitions. Whenever K is small, bias-corrected variants of cross-validation outperform regular cross-validation [47, 48]. This is a natural assumption given that we are interested in bias correction of 5-fold or 10-fold cross-validation for large-size datasets.

The error of $CV_{N,K}$ offered the best estimate, according to the approved in [46]

Table 9 The K-fold cross-validation for estimates of prediction error

N	$E(S_N) = 0.721$	K = 5	K = 10	K = N
91	$E(CV_{N,K} - S_N)$	0.069	0.035	0.004

Table 10 The performance of propofol dose optimization model of genetic algorithm

Run no.	Running time (s)	DOA target	DOA estimated	GA error	Drug dose optimized
1	18.545	80	79.9678	0.0322	1.989
2	49.435	80	79.9988	0.0012	1.859
3	44.975	70	70.1222	0.1222	1.61
4	20.11	60	59.9055	0.0945	1.846
5	44.31	50	49.9341	0.0659	1.549

3.5 Dose Optimization

After estimating the dose based on the real needs of patients using feed-forward neural network and ANFIS estimation models, it is observed that the ANFIS neural-fuzzy network dose estimation model has the highest accuracy compared to the classical model and the actual values of patients. So, to optimize the propofol dose, we optimize the estimated dose value using genetic algorithms and compare the optimal values of the algorithm with the values obtained from the PK-PD model. Propofol dose optimization method Genetic algorithm in MATLAB software encoded and optimized by a personal computer with a 64-bit operating system, 1.8 GHz CPU Intel core i5-3337 (U), and 6 GB RAM It becomes. To summarize, 5 times the average of the total number of times the model is executed in the results of Table 10.

3.6 The Comparison Results

In this section, the proposed model presented in this paper (GA) is compared and discussed with other methods such as PK-PD and BIS. Table 11 depicts the best dose estimation using the classical model (PK-PD) and real data from BIS. Table 11 shows that the three factors, running time, propofol dose estimation, and depth of anesthesia estimation, have been compared in the three approaches described. It should be noted that the DOA estimating in the PK-PD technique is dependent on the BIS, therefore the data in this column is very similar to the BIS column, which is not written.

Table 11 shows that the GA optimization model takes much less time to run than the other two techniques. The speed of operation is required for the patient during anesthesia due to the nature of the anesthesia procedure. Tables 12 and 13 summarize the results of Table 11.

According to the BIS application, data is extracted and monitored every minute, therefore the value of 60 s remains constant throughout time. The time of 60 s in each period is deducted from the time of the other two techniques to obtain the amount of time increase or decrease, which is the same error between the BIS and data-driven from two methods, as shown in Table 12. It is worth noting that the absolute value of the error is obtained, thus the greater the number of differences, the higher the rate of dosage estimating.

Table 11 Comparison of GA method results with PK-PD and BIS methods

No.	GA			PK-PD Model			BIS		
	RT*	DE**	DOAE***	RT	DE	DOAE	RT	DE	DOAE
1	16.97	1.989	89.9678	18.54	1.990	–	60	2	90
2	19.87	1.859	79.9988	49.43	1.990	–	60	2	80
3	20.21	1.61	70.1222	44.97	1.990	–	60	2	70
4	20.20	1.846	59.9055	39.11	1.990	–	60	2	60
5	18.81	1.549	49.9341	44.31	1.990	–	60	2	50

*RT: Running time of GA optimization estimation model (The unit of time was considered seconds.)
**DE: Propofol Dose Estimation
***DOAE: The Depth of Anesthesia Estimation

Table 12 The Summary of the running time error of GA and PK-PD relative to BIS

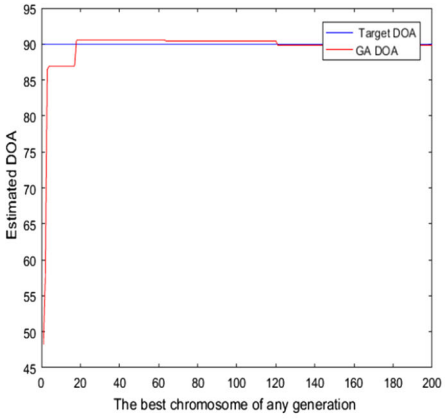
No.	GA $RT(error_{GA}) = \lvert RT_{BIS} - RT_{GA} \rvert$	PK-PD $RT(error_{PK-PD}) = \lvert RT_{BIS} - RT_{PK-PD} \rvert$
1	43.03	41.46
2	40.13	10.57
3	39.79	15.03
4	39.8	20.89
5	41.19	15.69
Av.	40.788	20.728

As a result, as shown in Table 12, the running time of dosage estimate utilizing artificial intelligence techniques and optimization by GA compared to the PK-PD yields significant results. Table 13 compares the BIS values to the estimation model proposed in this study and PK-PD.

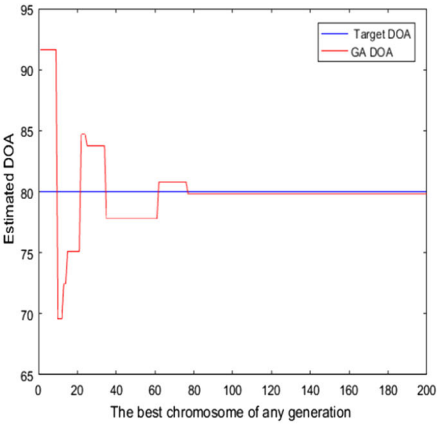
It is worthy to note that in the patients observed in an Iranian hospital, the number of propofol doses with a predetermined value of 2 units and at particular times was considered,

Table 13 The Summary of the dose estimation error GA and PK-PD relative to BIS

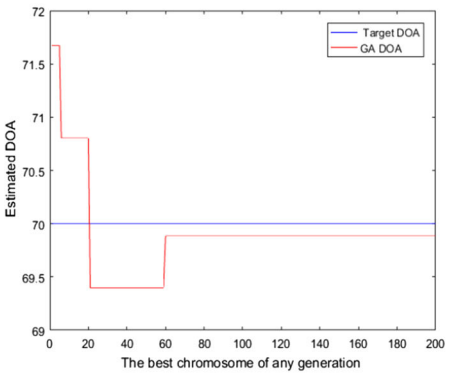
No.	GA $DE(error_{GA}) = \lvert DE_{BIS} - DE_{GA} \rvert$	PK-PD $DE(error_{PK-PD}) = \lvert DE_{BIS} - DE_{PK-PD} \rvert$
1	0.011	0.01
2	0.141	0.01
3	0.39	0.01
4	0.154	0.01
5	0.451	0.01
Av.	0.2294	0.001



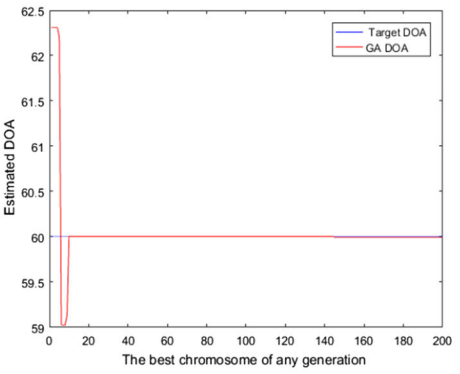
propofol dose optimization based on 90 set-point



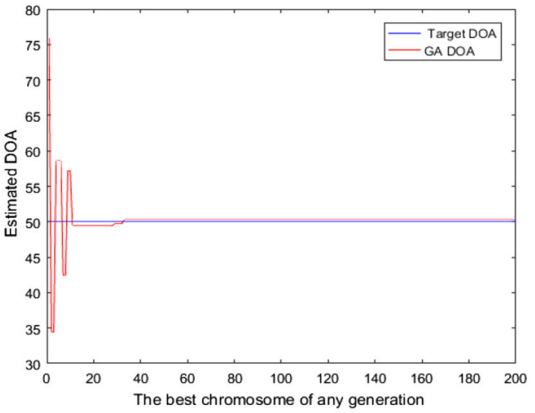
propofol dose optimization based on 80 set-point



propofol dose optimization based on 70 set-point



propofol dose optimization based on 60 set-point



propofol dose optimization based on 50 set-point at the end of the induction

Fig. 9 The GA results of propofol dose optimization during induction

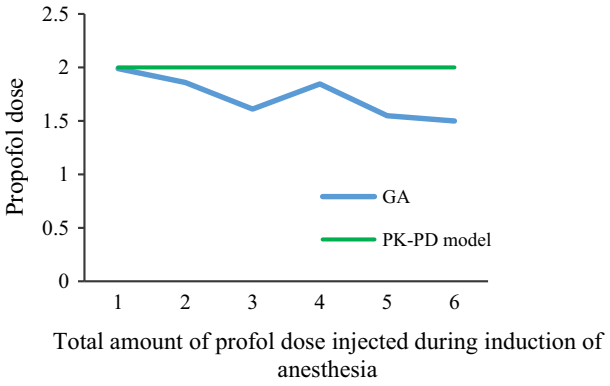


Fig. 10 The comparison of the optimization model of propofol dose injected to the patient

which was injected automatically. As a result, the goal of the propofol dosage estimating model is to be in accordance with the patient's needs, which differ from period to period, and the absolute value of the difference between these values is deducted from 2 in each period. The PK-PD considers the amount of propofol dose a constant value at all times, therefore the difference with the dose in the device in all periods is the same. According to Table 13, the propofol dose utilizing GA is obtained with significant results when compared to the PK-PD.

Figure 9 shows that the algorithm starts from a random point in repetition 170 with sufficient accuracy to reach the set depth of 50, at which point the automatic injection is stopped and the induction phase of anesthesia is over. The patient then enters the anesthesia maintenance phase, which should be kept at level 50 by monitoring vital signs and estimating the depth of anesthesia until the end of the operation.

By observing the graphs of the genetic algorithm, it is observed that the steps to reach the depth of anesthesia of the patient from 100 to the set-point of 50 are defined in 5 steps. The first step is to reduce the number to 20 and the next step is to reduce the number to 10 to reach the desired depth. For this purpose, by injecting propofol, the patient's depth is observed at any time and propofol is injected if necessary. The final results of optimizing the propofol dose estimation model with a genetic algorithm are shown in Table 14.

Considering Fig. 10, the amount of savings in estimating the dose of propofol compared to the existing model is quite obvious. The genetic optimization algorithm's speed is higher than the computational values of the classical model and shows significant savings in propofol dose determination. This saves time, speed, and accuracy in deciding whether or not to inject propofol. Ultimately, this decision will help the anesthesiologist make sure that the dose of propofol is exactly what the patient needs to inject to prevent over-or under-injection.

Figure 10, shows a comparison of the dose of propofol injected into the patient using the optimization algorithm compared to the classical model.

As can be seen in Fig. 11, the genetic algorithm has estimated the propofol dose in comparison with the PK-PD model and the actual values represent high accuracy and have optimized the estimation model well. Also, the estimated time of propofol dose using optimization algorithms in comparison with the classic PK-PD model is shown in Fig. 11.

Considering Fig. 11, we can conclude that the genetic algorithm shows a significant saving in estimating the dose of propofol. Therefore, it can be concluded that the genetic algorithm works much better in propofol dose optimization than the classical model, but the

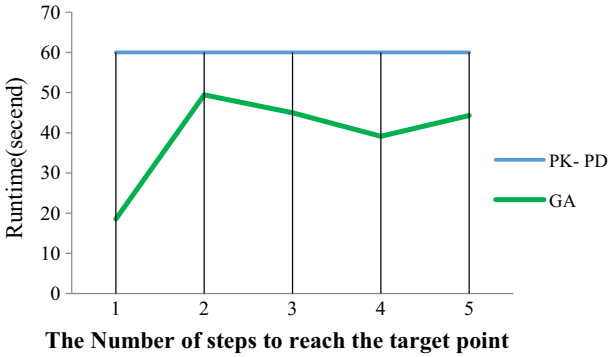


Fig. 11 Comparison of dissolution time using propofol dose optimization algorithms

Table 14 The summarizing the results of the propofol dose optimization algorithm

Optimization of the Propofol dose estimation	The average percentage of runtime savings	The average percentage of propofol dose savings	The average error in propofol dose estimation
Genetic Algorithm	$\frac{\sum RT(error_{GA})n}{RT_{BIS}} = \frac{\frac{\lvert RT_{BIS} - RT_{GA}\rvert}{RT_{BIS}}}{}$	$\frac{\sum DE(error_{GA})n}{DE_{BIS}} = \frac{\frac{\lvert DE_{BIS} - DE_{GA}\rvert}{DE_{BIS}}}{}$	$\frac{\sum DE(error_{GA})}{n}$
	0.21	14.06	0.06

optimization time in the genetic algorithm is significantly reduced. The final result of GA optimization is summarized in Table 14.

4 Conclusions and Future Works

In this paper, the usage of an AI estimator for propofol dosing to control the depth of hypnosis in general anesthesia is extensively examined. In specific, genetic algorithms were used to tune the Propofol dose estimator parameters to minimize the worst-case integrated absolute error in a patient group that is indicative of a large population. The significance of data-driven behavior has also been stressed. Furthermore, the function of the drug dose estimator in dealing with the noisy BIS signal has also been explored by using AI techniques to estimate the DOA and demonstrate the set-point monitoring output loss.

The findings suggest that every other improved control technique for controlling anesthesia should be compared to the ideal Propofol dose estimator since they can provide a fast induction period with reasonable overshoot and adequate disturbance rejection performance.

The results of MSE and the other error measures (RMSE, R2, and d_α) and physiological parameters sensitivity analysis, the dose optimization model revealed superior performance in contrast with to classical model (PK-PD) and the close-loop index. In future studies, other widely used anesthetics may be studied in potential experiments, and the dosage estimator method may be modeled based on anesthetic modifications to achieve the appropriate drug

dose. It could be analyzed and modeled to maximize the usage of sedatives during recovery, in addition to dosage optimization during anesthesia. In addition to dose optimization during anesthesia, it can also be investigated and modeled to optimize the use of sedatives in recovery.

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