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Adaptive Neuro-Fuzzy Inference System Estimation Propofol Dose in Induction Phase During Anesthesia: A Case Study

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ABSTRACT

In this study, the anesthetic drug dose is estimated with respect to patients' physiological parameters. The most critical anesthetic drug, propofol is considered in this modeling. The intravenous propofol is one of the widely used for both induction and maintenance phases of anesthesia. According to a deep uncertainty estimation model, the adaptive neuro-fuzzy inference system is applied to estimate the safe dose of anesthetic drug. The propofol model is estimated based on the patients' physiological parameters (age, weight, height, and gender) and variables (blood pressure, heart rate, and depth of anesthesia) each time. The sensitivity analysis evaluates the validity of the estimation model. At the end, performance of the proposed estimation model is compared to that of the classical Pharmacokinetics-Pharmacodynamics (PK-PD) model and the data obtained from the patients undergoing surgery. The results showed that the Adaptive Neuro-Fuzzy Inference System (ANFIS) estimation model with accuracy of 0.999 reduces the total amount of propofol dose. The novelty of the proposed model in this paper lies in its estimation of the depth of anesthesia in induction separately from the maintenance phase independent of Bispectral Index (BIS). To validate our methodology, a real case study of Mashhad hospital in Iran has provided, resulting in a comprehensive discussion and managerial insights.

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NOMENCLATURE

DOA	Depth of Anesthesia	C_1	Drug concentration
ANFIS	Adaptive Neuro-Fuzzy Inference System	C*2*	Slow compartments drug concentrations
BIS	Bispectral Index	C*3*	Fast compartments drug concentrations
BP	Blood Presure	kij	Drug transfer from ith to jth compartment
HR	Heart Rate	$\dot{C}_e(t)$	Centeral compartment of effect site
PK	Pharmacokinetics	lbm	Lean Body Mass
PD	Pharmacodynamics	**Greek Symbols**	
$\mu_{A_j^i}$	Membership Function(MF)	Γ	curve slope

1. INTRODUCTION

The general anesthesia complexity process consists of analgesia, hypnosis, and neuromuscular blockade. The anesthesia administration is traditionally carried out by anesthetists, who, according to their experience and personal knowledge, decide on the dose of adequately initial bolus as well as the dose of anesthetic drug to maintain a proper relaxation level during the surgery. A basic requirement for a safe anesthetic is to make decision on the proper combination of the type and dose of drugs under the direct supervision of the anesthesiologist [1]. Propofol is considered as the most popular intravenous anesthetic agent having short duration of action and rapid onset in the induction and

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maintenance during the general anesthesia process [2]. However, the prediction accuracy models may be affected by the patients' parameters. A current review of pharmacokinetics and pharmacodynamics approaches to optimize the anesthetic drug administration was performed [3, 4]. In this pursuit, advanced mathematical techniques can be of superb value, for instance, robust PID control [5], fuzzy-type I/II [6, 7], propofol injection robot-assistant [8, 9] and target control infusion [10]. Some of the auto-drug delivery systems have widely used bispectral index monitoring [11, 12], as variables of control modeling to administer the propofol dose during the anesthesia. Although there are some limitations such as inadequate control in the induction phase, lack of the pysiological parameters of the patients anesthetized, and the variability of the patient situation during the model-based controllers process. Machine learning and artificial intelligence techniques are also highly applicable and suitable to modify prediction and estimation models by using real-time observed data from patients. Adaptive Neuro-Fuzzy Inference System (ANFIS), widely applied for estimation in many works [13-15].

It should be noted that auto-control anesthesia model and auto-injection system are depending on the patients' depth of anesthesia. Bispectral Index (BIS) is a dimensionless indicator to show the patients' depth of anesthesia during surgery [16]. Having an accurate model in the predictive controller is the main problem for the process under control. The prediction accuracy mainly depends on the parameters of the model. This study contributes to the estimation of the propofol dose according to the patient's real needs based on patient parameters of the existing case studies not having used BIS. Regarding the shortage of BIS in case hospitals and the urgent need to improve anesthesia management, this paper focused on estimating the drug dose without the use of BIS. In this study, a different approach is applied to design an adaptive estimator for computing the infusion propofol dose base on the actual patient status. This study aimed to present the newly developed system for clinical practice applying the propofol dose estimation model.

This paper focuses on regulating the depth of anesthesia (DOA) by estimating the proper dose of propofol as a hypnotic agent without the use of BIS. The proposed ANFIS estimation model under the direct supervision of an anesthesiologist compares the results from control monitoring tool guided (BIS) and the PK-PD model in terms of clinical feasibility and accuracy. This model may allow surgeons or anesthesiologists to validate the model results or contribute to fine-tuning.

In this regard, the models are not dependent on BIS data, especially when the system is affected by multiple related patient parameters. To practically assess the propofol dose estimation model on the patients' depth of anesthesia, a real case study was carried out in Mashhad hospitals in Iran. To deal with the uncertainty of the proposed model, an integrated neural network with the fuzzy inference system was proposed as an ANFIS model. It deals with uncertain data when training and designing a model to estimate the drug dose according to the patient's real needs in the presence of multiple related events. The proposed estimation model aims to optimize anesthesia drug dose to diminish the total drug dose usage, minimize surgical costs, and reduce recovery time.

In this paper, the main objectives are summarized below:

- Appling the estimation model of the depth of anesthesia in the absence of BIS according to the previous work;
- Proposing a propofol dose estimation based on the DOA of real patients without the BIS monitoring;
- Considering uncertainty of patients' parameters in training and designing model by applying ANFIS to estimate propofol dose during the induction and maintenance separately.
- Introducing a multi-parameter decision-making system to anesthesiologist to tackle the challenges in anesthesia administration.

The rest of this paper is organized as follows. The research methodology is presented in section 2. Section 3 provides a comprehensive analysis of the results. The managerial implications are discussed in section 4. Finally, the concluding remarks are recommended for future work in section 5.

2. METHOLOGY

As a case study, an Iranian care public hospital was adopted in this study. As mentioned, this paper focuses on the anesthetic drug dose and the hypnosis control problem. The level of unconsciousness and hypnosis cannot be directly measured by the use of Bispectral Index (BIS), which is commonly used for indirect measurement. The patient's vital signs correlated with hypnosis are derived from the electroencephalogram (EEG) signals [16]. BIS is a dimensionless index that measures the level of unconsciousness with values ranging from 100 to 0 (100 = awake, 0 = no brain electrical activity). In general anesthesia, a BIS signal varies from 40 to 60. The problem in the closed-loop controller is calculation or estimation of the optimal drug dose during anesthesia for maintaining the patient's unconsciousness at an adequate level. A well-designed system must be able to refuse any disturbances (surgical stimulus, blood loss, etc.) during surgery. Generally, a value of 50 is considered as a set point appropriate for the surgical procedure [16]. Since there was limited access to BIS in our case study, DOA was monitored based on previous work [17]. Monitoring of DOA provides the feedback signal port with a laptop connection. Software

was hosted on the laptop to implement the algorithm of closed-loop control. Figure 1 represents a patient diagram in the operating theater for the closed-loop system to estimate the propofol dose per patient. In the pre-anesthesia phase, the patients' initial physiological parameters and information were collected. Then, the types of anesthesia and anesthetic drug as well as the dose of drug were determined by the anesthesiologist and the surgeon.

Data were collected on the patient's preparation before the surgery from the induction phase of anesthesia that begins with the injection of an estimated dose of propofol. An automatic propofol injection pump was connected to the patient based on the depth of anesthesia in such a way that anesthesia was administered by either the required amount of propofol injection into the patient's body or the stopped injection. About 5 to 7 minutes after the induction phase, patients entered the maintenance phase. This process is a closed-loop control system that injects the necessary propofol based on the patient's actual needs using an automatic injection pump connected to the patient. The estimator controls the closed-loop to prevent system failures with an alarm module. Errors in connection or transmission between various devices refer to the low-quality signal of DOA alerted by this module. The DOA was continuously monitored by this program, the suppression rate, and the electromyogram. According to the signal values, the alarm module was activated by the controller to alert the anesthesiologist. Besides, stop mechanism injection for the DOA below a given value (40) and a bolus dose injection for the DOA excessively high value (60) are assigned in the closed-loop system as safety measures to prohibit eventual consciousness. Thus, the neuro-fuzzy estimator model was designed to predict and control the patient's propofol dose based on input data, monitoring the vital signs every minute. The propofol dose estimation model will result in safe anesthesia with the minimum amount of medication required by the patient.

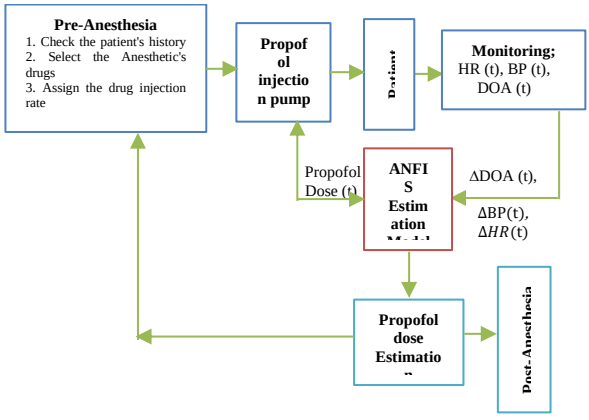

Figure 1. ANFIS model Propofol dose estimater

2. 1. Patient Model The model of the patient explains the relation between drug effect and drug infusion rate through a neuro-fuzzy inference system. On the one hand, the estimative model should be able to meticulously predict the dynamic responses of patients to the rate of infusion. On the other hand, it must not be complicated to avoid time-consuming calculation. In this model, the reaction of the patient undergoing anesthetic to the propofol dose is simulated and estimated based on the patient's needs using artificial intelligence techniques.

In the estimation propofol dose model, the patients' physiological parameters enter the model as inputs. The components of inputs are height, weight, age, gender, heart rate (HR), blood pressure (BP), type of surgery, surgery duration based on surgeon approval, and the depth of anesthesia (DOA). The proposed model structure is shown in Figure 2. The training model begins with the input data given to the system based on the actual data of patients during the operation. The single output of the model is the propofol dose estimated based on the patient's real needs every minute. The paper provides a training model in the induction phase, then models the maintenance phase according to the anesthesia process. The proposed model was finalized based on the propofol dose estimation for 5 to 7 minutes in the induction phase and during surgery in the maintenance phase. To validate the model, the results were compared with the real data and that the classical (PK-PD) model.

2. 2. Patient Data The data were collected from patients of an Iranian hospital whose informed consent was fully obtained before the operation. Data collection was done by observing anesthetized patients during surgery. According to the healthcare unit protocols, ethical authorization was needed to monitor the patients' physiological data. After receiving official approval to observe patients under surgery in the operating room of the study hospital, the patients were tracked in all stages from pre-anesthesia to post-anesthesia. Before surgery, the surgeon consulted with the cases, all of them were

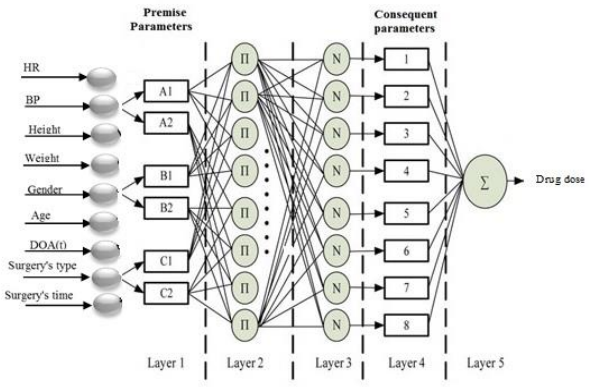

Figure 2. ANFIS propofol estimation model

elective surgery patients. In pre-anesthesia, patients' parameters of age, gender, height, weight, BP, HR, and level of consciousness were recorded. According to the case history and operation type in pre-anesthesia, the surgeon assigned the approximate operation time. Therefore, the anesthesiologist determines the average drug dose through consulting the surgeon.

Concerning the protocol of medical, standard monitors including pulse oximetry, noninvasive blood pressure, and ECG were daily used. In pre-anesthesia, an intravenous catheter was placed in the patient's arm. Depending on the analgesic requirements, the remifentanil was injected (0.25 mcg/kg/min) just before the induction phase. As long as the patient's hemodynamic status became stable, the clinicians maintained the injection rate .

2. 3. Estimation Model by Adaptive Neuro Fuzzy Inference System (ANFIS) ANFIS is far more intricate than fuzzy inference systems, not accessible by all their options. In ANFIS modeling, the data are first examined under fuzzy (clustering). Next, the data are trained using fuzzy inference of Sugeno or Takagi-Sugeno-Kang and then the error is reduced by the fuzzy rules of IF-THEN and functions of membership. The Sugeno type of fuzzy inference system is created from cluster information using a minimum number of rules to well model the behavior of data. The rules are self-divided regarding the fuzzy qualities of each data cluster. To train the ANFIS model, derivative-based algorithms such as backpropagation utilize each node with differentiable functions. Input parameters are Age, Height, Weight, and Gender. The variables are described in Table 1.

A predefined structure is formed where the related parameters determin each membership function (MF). Then, a learning algorithm adjusts these parameters to the N-sample data set. The Takagi-Sugeno Kang fuzzy rules in the fuzzy inference system are described for ANFIS as follows [17]:

TABLE 1. Patient inputs/ output variables

Inputs Variables	
Blood pressure at t	$BP(t)$
The differential Blood pressure at t	$\Delta BP(t)$
Heart rate at t	$HR(t)$
The differential Heart rate at t	$\Delta HR(t)$
The Depth of Anesthesia at t	$DOA(t)$
The differential the Depth of Anesthesia at t	$\Delta DOA(t)$
Drug Dose	D_s
Outputs Variables	
The differential the Depth of Anesthesia at t	$\Delta DOA(t+i)$

$$R_i: if\ x\ is\ A_i,\quad then\ y = f_i(x) = \sum_{j=1}^{n} a_{i,j}x_j + a_{i,o} \tag{1}$$

$A_i = \{A_i^1, A_i^2, \dots, A_i^n\}$, represent the sets of fuzzy and $a_{i,j}, j = 0, 1, \dots, n$ shows the outcom of the parameters. The system output at the *t* stage will be:

$$\hat{y}_t = \frac{\sum_{i=1}^{K} \mu_{A_i}(x_t) f_i(x)}{\sum_{i=1}^{K} \mu_{A_i}(x_t)} \tag{2}$$

$$E_t = \frac{1}{2}(\hat{y}_t - y_t)^2 \tag{3}$$

The specifications of the ANFIS model are illustrated in Table 2. These results are obtained using all 9 inputs, 4 hidden layers, and a single output. The estimation model is trained based on the patients' data.

2. 4. PK-PD Method The classic model defines the relationship between the drug infusion rate and the drug effect by the pharmacokinetics-pharmacodynamics (PK-PD) model.

Pharmacodynamics (PD) explains the relationship between the site concentration effect of the drug and its clinical effect, while pharmacokinetics (PK) describes the drug effect on the body by the infusion rate, drug distribution, and drug elimination. A schematic diagram is represented in Figure 3.

The three-compartmental general model is:

$$\begin{aligned} \dot{C_1}(t) &= -[K_{10} + K_{12} + K_{13}].C_1(t) + K_{21}.C_2(t) + K_{31}.C_3(t) + u(t)/V_1 \\ \dot{C_2}(t) &= K_{12}.C_1(t) - K_{21}.C_2(t) \\ \dot{C_3}(t) &= K_{13}.C_1(t) - K_{31}.C_3(t) \end{aligned} \tag{4}$$

The drug concentration is represented by C_1 [mg/l]. Muscle and fat are the circumferential compartments that model the drug replacement of the blood with fine and weak sporadic tissues of the body. C_2 and C_3 correspond to the slow and fast equilibrating circumferential compartments drug concentrations. The iterative drug

TABLE 2. The ANFIS model specifications

Parameter	**Description**
Number of nodes	316
Number of linear parameters	1040
Number of nonlinear parameters	40
Total number of parameters	1072
Number of training data pairs	98
Number of testing data pairs	6
Number of fuzzy rules	142

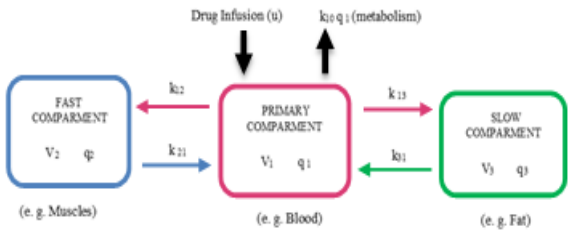

Figure 3. The three-compartmental PK model of patient

transfer from *i*th to *j*th compartment is defined by *kij* (*i*=1, 2, 3), $i \neq j$, and k_{10} implies the drug iteration elimination in the central compartment. The rate of the analgesic drug injection into the central compartment is defined by $u(t)$ [mg/min] [2, 17]. The relevance between drug concentration and the effect of a patient's pharmacology is referred to as PD. The mathematical PD-models are:

$$BIS(t) = E_0 - E_{max} \cdot \frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + EC_{50}^{\gamma}} \quad (5)$$

Observing the effect of drug on the patient, the variation of BIS values may depend on the effective C_e, drug concentration by the experimental non-linear Eq. (5) [6-8], named the Hill-Curve in the PD model. In the Hill equation, $Ce\ (t)$ is the concentration of propofol (μg/ml) in the brain. E_0 expresses the patient's initial state (awake, without medication), which is normally considered to be 100. E_{max} represents drug dose maximum effect, and EC_{50} is the concentration of drug at 50 percent of the maximum effect indicating the medication sensitivity of the patient. The γ shows the curve slope. The set point during anesthesia is 50, with a sufficient level of relaxation provided by values between 40 and 60. Considering the medication effect observed in the patient, the BIS values can relate to the C_e effect and the concentration of the drug (t) based on the experimental nonlinear relationship [9, 17]. To predict the propofol dose using the equations of the PK-PD model, the patients' data were applied and the results were compared with the output of the proposed model.

3. RESULTS AND DISCUSSION

In this study, a single output of the model based on the nine input data in every experiment was applied to design and model the ANFIS estimator, presented in Table 1. The results of estimation model illustrate that the intelligent system can strongly estimate the propofol dose. Therefore, a neuro-fuzzy inference system as well as the ANFIS estimation model was applied in this study. The obtained outcome was compared with that of the PK-PK model and the real data. From the proposed model results shown in Table 3, it can be infered that ANFIS had a better performance on modeling.

TABLE 3. The result of propofol dose estimation by ANFIS model in the induction phase

Induction Time (min)	Real Data	ANFIS-estimated Propofol Dose	ANFIS error
1	1.6	1.6001	0.0001
2	1.6	1.6001	0.0001
3	1.6	1.6	0
4	1.6	1.601	0.001
5	1.6	1.6	0
6	1.6	1.6	0
7	1.6	1.6	0

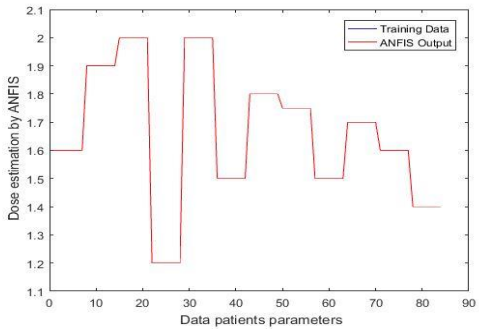

Figure 4. Propofol dose estimation model by ANFIS

Since ANFIS combines a neural network and a fuzzy system to apply experts' knowledge, learning phase implements a more powerful model.

Figure 4 shows the estimation model of propofol dose using a neuro-fuzzy system.

3. 1. ANFIS Estimation Model vs PK-PD Model

Different indicators were used to validate the proposed model, evaluating the error rate and estimating the model accuracy. These evaluation indicators were accuracy, d_α, reliability, MSE, and RSME. The proposed estimation model was compared with the classical PK-PD model and the real values of patients during surgery. Table 4 represents the comparison results of of these indicators between models.

TABLE 4. The comparison of estimation model with real patients' data and PK-PD model in the induction-maintenance phases

Estimation / Method	Propofol dose (induction- maintenance)				
	Accuracy	d_α	Reliability	MSE	RMSE
PK-PD	0.966	0.951	0.95	0.002	0.043
BIS	0.975	0.98	0.99	0.003	0.055
FFNN	0.989	0.999	1	0.001	0.101
Fuzzy	0.953	0.999	1	0.002	0.043
ANFIS	1	1	1	5.3×10^{-6}	0.002

3. 2. Sensitivity Analysis To do sensitivity analysis of the parameters affecting the model, two different senarios were considerd. In each run of the model, by omitting parameter/s of the input data, the final output of the ANFIS model was acquired. The model was also compared with the classical PK-PD method and BIS values to investigate the effect of input on estimating the propofol dose. In first senario, one input parameter was removed and then the model was trained. The outcome was compared with the final output and the estimation results by removing the relevant parameter from the actual values. The results are shown in Figures 5-8, by removing a model input parameter. It is noteworthy that the results were obtained after 20 times implementation of a neuro-fuzzy inference system in MATLAB.

Figure 5 shows the patients' variables and parameters to estimate the required propofol dose in the absence of Age with high accuracy. Therefore, it doesn't have a remarkeable effect on the drug dose

Figure 6 indicates acceptable accuracy of propofol dose estimation without height, so it does not have a considerable effect on the drug dose. Figure 7 shows the gender alone doesn't have a significant effect on the drug dose. Figure 8 shows that there is a significant difference between the actual and the estimated amount of propofol dose in the absence of the weight parameter. As shown by the figures, it is observed that the patient's age has a significant effect on the propofol dose estimation, which

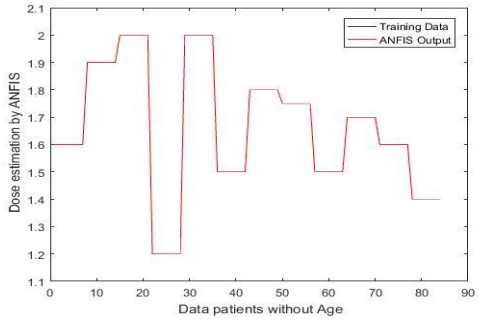

Figure 5. Propofol dose estimation without Age

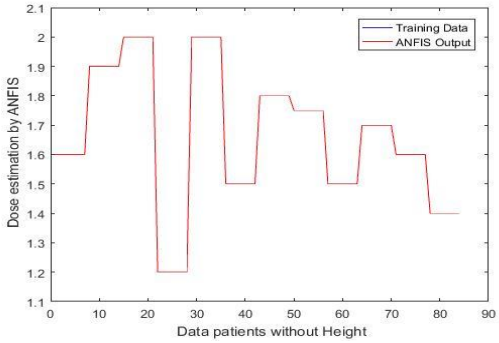

Figure 6. Propofol dose estimation without Height

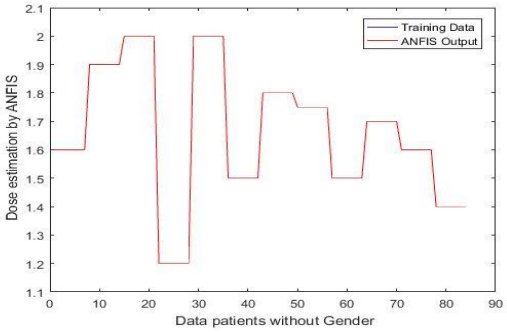

Figure 7. Propofol dose estimation without Gender

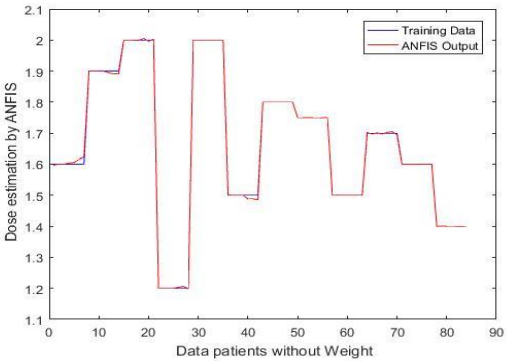

Figure 8. Propofol dose estimation without Weight

can also be affected by the patient's weight compared to other parameters.

Another noteworthy point in the propofol dose estimation is that the patient variables including HR, BP, and DOA in each time should not be omitted in the training model under no circumstances. Otherwise, the estimation results indicate a high error in the absence of vital physiological variables. The results of the sensitivity analysis of parameters affecting propofol dose estimation using ANFIS are summarized in Table 5.

In the second scenario of sensitivity analysis, we examined the effect of patient parameters on the estimation of propofol dose by simultaneous removal of two parameters. The results are shown in Figures 9 to 14.

TABLE 5. The sensitivity analysis of propofol dose estimation parameters by ANFIS

Estimation / Model Parameter	ANFIS				
	Accuracy	d_α	Reliability	MSE	RMSE
Age	1	1	1	3.59×10-4	0.0099
Weight	1	1	0.99	4.52×10-4	0.067
Height	1	1	1	9.29×10-4	0.0031
Gender	1	1	1	3.62×10-4	0.0019
Age	1	1	1	3.59×10-4	0.0099

Figure 9 shows the patients' variables and parameters estimate the required propofol dose in the absence of Age-Gender with accepetable accuracy by slight differences in the drug dose estimation.

Figure 10 represents the patients' variables and parameters estimate the required propofol dose in the absence of age-height with some errors. Therefore, these parameters have a significant effect on the drug dose estimation.

Figure 11 indicates the patients' variables and parameters to estimate the required propofol dose in the absence of height-gender with accepetable accuracy. Therefore, these parameters have a minor effect on the drug dose estimation. Figure 12 shows high differences from the actual data in the absence of age-weight . So, these parameters have a significant effect on the drug dose estimation.

Figure 13 represents the patients' variables and parameters to estimate the required propofol dose in the absence of Weight-Gender with some errors. Therefore, these parameters have a significant effect on the drug dose estimation.

Figure 14 indicate that age and weight are the two parameters with the highest effect on prescribing propofol. The results indicate that age and weight have the highest effect on prescribing propofol, are consistent with those of classical model and BIS values [3, 12, 17].

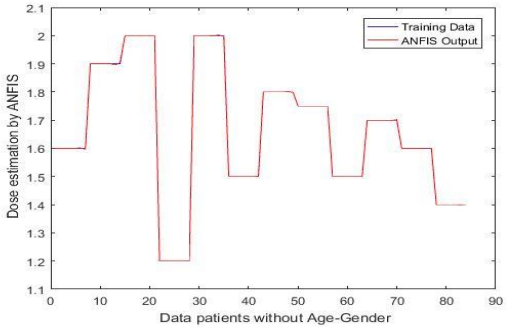

Figure 9. Propofol dose estimation without Age- Gender

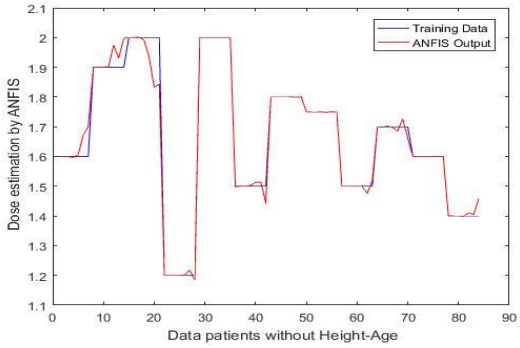

Figure 10. Propofol dose estimation without Age- Height

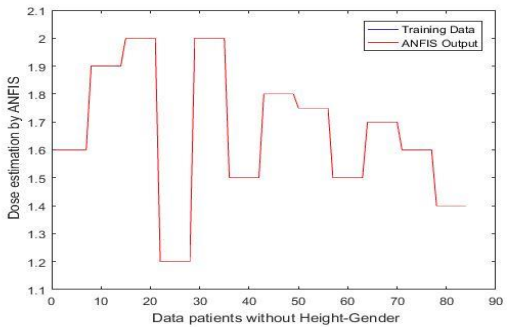

Figure 11. Propofol dose estimation without Height- Gender

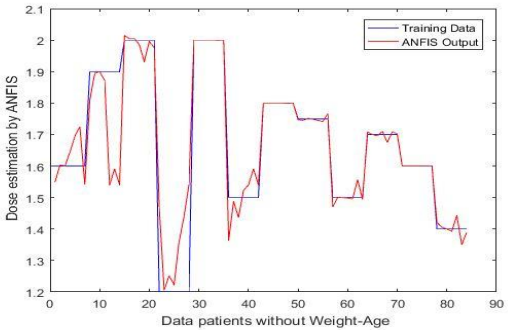

Figure 12. Propofol dose estimation without Age- Weight

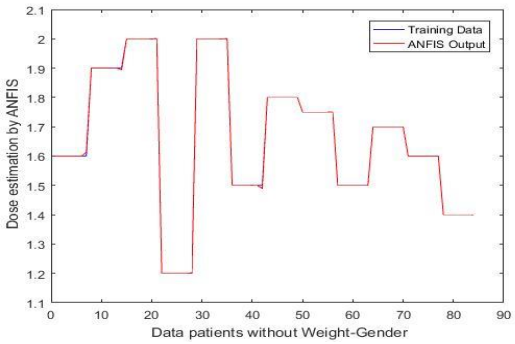

Figure 13. Propofol dose estimation without Weight- Gender

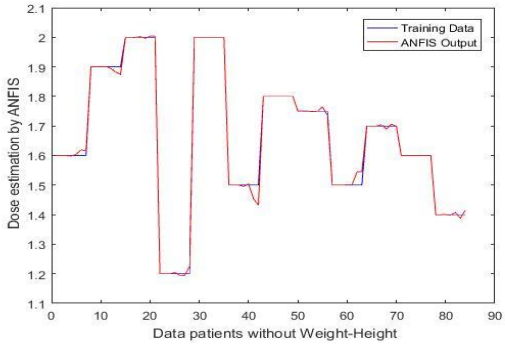

Figure 14. Propofol dose estimation without Weight- Height

4. MANAGERIAL IMPLICATIONS

This paper presents a model for estimating the anesthesia drug dose to cope with possible major anesthesia administration problems, the over/under dosing, propofol wastage in anesthesia, patient's long stay in the hospital, and postoperative complications. This study is motivated by the necessity for safe anesthesia and pain relief in post-anesthesia in hospitals. Since observing data in the operation room needs entry authorization and there is limited number of patients available concerning their historical data. We applied the artificial intelligence techniques to deal with imprecise data for estimation. This neuro-fuzzy training and designing modeling provides enough flexibility regarding input data. The observation of all physiological parameters of the patients at pre-anesthesia, under surgery, and even post-anesthesia stages is of importance for estimating sufficient drug dose. The rationale behind is evident as follows. Each patient reacts differently and his/her parameters may differ from others. In order to satisfy all anesthesiologists' expectations and overcome arising problems from the injected drug, the model was trained based on the patients' parameters to estimate the real dose of propofol needed to be injected. This estimation model aims to compensate for the shortage or limit the surplus of the propofol dose while making reduction in propofol wastage and recovery time. Accordingly, the anesthesiologists prescribe a safe anesthesia delivery during the surgery and post-surgery if the process is managed without the unexpected problems so that every critical situation is predicted directly by the nearest monitoring alarms. This means that the existing anesthesia prediction models have limitation that can just control the parameters which are monitored during surgery.

As can be seen in Figure 4, the estimation model is trained by patients' physiological parameters of age, weight, height, and gender and patients' variables of heart rate, blood pressure, and depth of anesthesia in every minute. The ANFIS model accurately estimates the propofol dose based on the patient's actual needs in comparison with the BIS data. The estimation model is then compared with real patient data and the PK-PD model in the induction and maintenance phases; the results are summarized in Table 5. According to the high uncertainty in the patient's parameters and the effect of drugs on the patient's body, in this study, propofol was considered as the only anesthetic drug neglecting the effect of drugs on each other. The majority of estimation models are designed under this assumption that there is only one drug and they neglect the effect of subsequent drugs.

5. CONCLUSION AND FUTURE WORKS

The results of this work can be compared with those obtained from the PK-PD model and real data of patients. The ANFIS estimation model proposed in this work is data-driven. Thus, the results obtained from propofol dose estimation in the induction and maintenance phases indicate that the presence of data is inalienable for the Artificial Intelligence (AI) estimator to outperform other predictors. ANFIS technique applied in the induction and maintenance phases is more accurate and faster than others. The estimation model with accuracy of 0.999 reduces the total amount of propofol dose. This result is supported by the performance of ANFIS estimator when compared to the PK-PD controller and real data results under the supervision of the surgeon and the anesthesiologist.

Making use of AI estimator, the propofol dose has been thoroughly modeled to regulate the depth of anesthesia during the surgery in this work. The importance of the data-driven estimation model has also been highlighted. Moreover, the role of the drug dose estimator in coping with the noisy signal has been addressed by applying AI techniques. The results of dose estimation show the accuracy of the model in determining the propofol dose in accordance with the real needs of the patient. Furthermore, this dose of anesthetics not only brings safe anesthesia but also minimizes risks of consciousness during surgery or delayed recovery by optimizing the amount of propofol dose. These results will be valuable in clinical trials and this method must be put into practice in hospitals. There are also some suggestions for future studies. The propofol dose optimization is an interesting topic for continuation of this work. The multi-period (pre-anesthesia, anesthesia and post-anesthesia) can be further considered to determine the propofol dose of the estimation model. The costs of drug wastage merits further investigation to be addressed using a cost reduction optimization model.

5. REFERENCES

1. Mu, J., Jiang, T., Xu, X., Yuen, V. and Irwin, M., "Comparison of target-controlled infusion and manual infusion for propofol anaesthesia in children", ***British Journal of Anaesthesia***, Vol. 120, No. 5, (2018), 1049-1055, DOI: 10.1016/j.bja.2017.11.102.
2. Zhang, J. and Huang, C., "Dynamics analysis on a class of delayed neural networks involving inertial terms", ***Advances in Difference Equations***, Vol. 2020, No. 1, (2020), 1-12, DOI: 10.1186/s13662-020-02566-4.
3. Van Den Berg, J., Vereecke, H., Proost, J., Eleveld, D., Wietasch, J., Absalom, A. and Struys, M., "Pharmacokinetic and pharmacodynamic interactions in anaesthesia. A review of

current knowledge and how it can be used to optimize anaesthetic drug administration", ***British Journal of Anaesthesia***, Vol. 118, No. 1, (2017), 44-57, DOI: 10.1093/bja/aew312.

4. Sahinovic, M.M., Struys, M.M. and Absalom, A.R., "Clinical pharmacokinetics and pharmacodynamics of propofol", ***Clinical Pharmacokinetics***, Vol. 57, No. 12, (2018), 1539-1558, DOI: 10.1007/s40262-018-0672-3.
5. van Heusden, K., Soltesz, K., Cooke, E., Brodie, S., West, N., Gorges, M., Ansermino, J.M. and Dumont, G., "Optimizing robust pid control of propofol anesthesia for children; design and clinical evaluation", ***IEEE Transactions on Biomedical Engineering***, (2019), doi: 10.1109/TBME.2019.2898194.
6. Wei, Z.-X., Doctor, F., Liu, Y.-X., Fan, S.-Z. and Shieh, J.-S., "An optimized type-2 self-organizing fuzzy logic controller applied in anesthesia for propofol dosing to regulate bis", ***IEEE Transactions on Fuzzy Systems***, Vol. 28, No. 6, (2020), 1062-1072, doi: 10.1109/TFUZZ.2020.2969384.
7. Jin, W., Zucker, M. and Pralle, A., "Membrane nanodomains homeostasis during propofol anesthesia as function of dosage and temperature", ***Biochimica et Biophysica Acta (BBA)-Biomembranes***, Vol. 1863, No. 2, (2021), 183511, doi: 10.1016/j.bbamem.2020.183511.
8. Hsieh, M.-L., Lu, Y.-T., Lin, C.-C. and Lee, C.-P., "Comparison of the target-controlled infusion and the manual infusion of propofol anesthesia during electroconvulsive therapy: An open-label randomized controlled trial", ***BMC Psychiatry***, Vol. 21, No. 1, (2021), 1-10, doi: 10.1186/s12888-021-03069-6.
9. Lai, H.-C., Lee, M.-S., Lin, K.-T., Huang, Y.-H., Chen, J.-Y., Lin, Y.-T., Hung, K.-C. and Wu, Z.-F., "Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in robot-assisted radical prostatectomy", ***PloS One***, Vol. 15, No. 3, (2020), e0230290, doi: 10.1371/journal.pone.0230290 .
10. West, N., van Heusden, K., Görges, M., Brodie, S., Rollinson, A., Petersen, C.L., Dumont, G.A., Ansermino, J.M. and Merchant, R.N., "Design and evaluation of a closed-loop anesthesia system with robust control and safety system", ***Anesthesia & Analgesia***, Vol. 127, No. 4, (2018), 883-894, doi: 10.1213/ANE.0000000000002663.
11. Kodama, M., Higuchi, H., Ishii-Maruhama, M., Nakano, M., Honda-Wakasugi, Y., Maeda, S. and Miyawaki, T., "Multi-drug therapy for epilepsy influenced bispectral index after a bolus propofol administration without affecting propofol's pharmacokinetics: A prospective cohort study", ***Scientific Reports***, Vol. 10, No. 1, (2020), 1-9, doi: 10.1038/s41598-020-58460-2.
12. Araújo, A.M., Machado, H., de Pinho, P.G., Soares-da-Silva, P. and Falcão, A., "Population pharmacokinetic-pharmacodynamic modeling for propofol anesthesia guided by the bispectral index (bis)", ***The Journal of Clinical Pharmacology***, Vol. 60, No. 5, (2020), 617-628, doi: 10.1002/jcph.1560.
13. Samadi, F. and Moghadam-Fard, H., "Active suspension system control using adaptive neuro fuzzy (anfis) controller", ***International Journal of Engineering***, Vol. 28, No. 3, (2015), 396-401, doi: 10.5829/idosi.ije.2015.28.03c.08.
14. Lashkenari, M., KhazaiePoul, A., Ghasemi, S. and Ghorbani, M., "Adaptive neuro-fuzzy inference system prediction of zn metal ions adsorption by γ-Fe_2O_3/polyrhodanine nanocomposite in a fixed bed column", ***International Journal of Engineering***, Vol. 31, No. 10, (2018), 1617-1623, doi: 10.5829/ije.2018.31.10a.02.
15. Bahadori-Chinibelagh, S., Fathollahi-Fard, A.M. and Hajiaghaei-Keshteli, M., "Two constructive algorithms to address a multi-depot home healthcare routing problem", ***IETE Journal of Research***, (2019), 1-7, doi: 10.1080/03772063.2019.1642802.
16. Sigl, J.C. and Chamoun, N.G., "An introduction to bispectral analysis for the electroencephalogram", ***Journal of Clinical Monitoring***, Vol. 10, No. 6, (1994), 392-404, doi: 10.1007/BF01618421.
17. Jamali, N., Sadegheih, A., Lotfi, M., Wood, L.C. and Ebadi, M., "Estimating the depth of anesthesia during the induction by a novel adaptive neuro-fuzzy inference system: A case study", ***Neural Processing Letters***, (2020), 1-45, doi: 10.1007/s11063-020-10369-7.

Persian Abstract

چکیده

در این مطالعه، دوز داروی بیهوشی براساس نیاز واقعی بیمار و پارامترهای فیزیولوژیکی آن تخمین زده می‌شود. در بین داروهای بیهوشی داخل وریدی، پروپوفول یکی از پرکاربردترین حین جراحی در مرحله القاء و نگهداری بیهوشی بشمار می‌آید. با استفاده از تکنیک های هوش مصنوعی، دوز پروپوفول بر اساس نیاز واقعی تخمین زده می شود. در این مدلسازی، تخمینگر سیستم استنتاج عصبی- فازی تطبیقی برای محاسبه دوز دارو جهت ارائه بیهوشی ایمن بکار رفته است. مدل بر اساس پارامترهای فیزیولوژیکی بیماران واقعی حین عمل مانند (سن ، وزن ، قد ، جنس) ، فشار خون ، ضربان قلب و سطح هوشیاری بیمار، دوز پروپوفول را در مرحله القا تخمین می‌زند. عملکرد مدل برآورد پیشنهادی با مدل کلاسیک فارماکوکینتیک- فارماکودینامیک و داده‌های بدست آمده از بیماران تحت عمل جراحی مقایسه می‌شود. نتایج نشان می‌دهد که مدل برآورد سیستم استنباط عصبی فازی تطبیقی با دقت ۰.۹۹۹ مقدار کل دوز پروپوفول را به میزان قابل توجهی کاهش می‌دهد. نوآوری مدل پیشنهادی برآورد عمق بیهوشی بیمار در فازهای القاء و نگهداری جداگانه و مستقل از شاخص دوطیفی است. مدل پیشنهادی با مطالعه موردی از بیماران در بیمارستان مشهد- ایران جهت اعتبارسنجی ارائه شده است.