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Artificial Neural Network Model Estimating the Initial Dose of Propofol Used in General Anesthesia

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Abstract: The right dosing of drugs has a pivotal role in anesthesia. In preoperative anesthesia, an anesthesiologist calculates the doses of hypnotic drugs according to the patient's factors implements them in the clinical setting in the form of an initial and continuation dose. In this study, the initial dose of hypnotic agent propofol (mg) was estimated using a multilayer feed-forward artificial neural network (MNN) structure, assuming no premedication or additional medication was used. The factors of age (year), weight (kg), height (m) and concomitant diseases have constituted the inputs of the proposed predictive network. The data set for this study consisted of 299 patient samples and was created by expert anesthesiologists. Many ANN models designed with different hyperparameters were tested to find the best estimator, and the results were recorded. According to the obtained results, the best estimator has estimated the initial dose of propofol with success rates over 92%. Thanks to this model, it has been proven that the initial doses of potentially anesthetic drugs can be calculated by ANN so that the application can be considered as an aid to anesthesiologists.

Keywords: Multilayer neural network; Propofol; Initial dose estimate

Genel Anestezide Kullanılan Propofolün Başlangıç Dozunu Tahmin Eden Yapay Sinir Ağları Modeli

Öz: Anestezide ilaç dozunun doğru hesaplanması çok önemli bir rol oynamaktadır. Preoperatif anestezide, bir anestezi uzmanı, hipnotik ilaçların dozlarını hastanın faktörlerine göre hesaplamakta ve bunları klinik ortamda bir başlangıç ve devam dozu şeklinde uygulamaktadır. Bu çalışmada, hipnotik bir ajan olan propofolün başlangıç dozu (mg), premedikasyon veya ek ilaç kullanılmadığı varsayılarak çok katmanlı ileri beslemeli yapay sinir ağı (ÇKYSA) yapısı kullanılarak tahmin edilmiştir. Yaş (yıl), ağırlık (kg), boy (m) ve eşlik eden hastalık faktörleri önerilen öngörücü ağın girdilerini oluşturmuştur. Bu çalışma için veri seti 299 hasta örneği ile uzman anesteziстler tarafından oluşturulmuştur. En iyi tahmin ediciyi bulmak için farklı hiper parametrelerle tasarlanan birçok YSA modeli test edilmiş ve sonuçları kaydedilmiştir. Elde edilen sonuçlara göre, en iyi tahminci % 92'nin üzerinde başarı oranlarıyla propofolün başlangıç dozunu tahmin etmiştir. Bu model sayesinde, potansiyel anestezik ilaçların başlangıç dozlarının YSA tarafından hesaplanabileceği kanıtlanmıştır. Bu çalışmada, uygulamanın anesteziстleri asiste edebileceği önerilmektedir.

Anahtar Kelimeler: Çok katmanlı yapay sinir ağları; Propofol; Başlangıç doz tahmini

1. Introduction

Today, machine learning from artificial intelligence methods supports the solution of many problems in the field of health and plays an essential role in the advancement of this field. Studies in the field of health are described as an assistant to experts by providing convenience to problem

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solvers. Artificial neural networks (ANN), one of the methods of artificial intelligence and machine learning, is one of the most frequently used methods in health field studies [1].

ANNs work is similar to a single neuron in the brain based on the pattern recognition capabilities of the neural networks of the brain. The artificial neuron unit processes and decides the data by getting input from many external sources. ANNs do not require strictly structured experimental designs and can model the problem using historical or missing data. This feature makes ANNs a powerful tool for simulating various nonlinear systems [2]. Because of their capacity regarding prediction, pattern recognition, and modeling, ANNs have been used for problem-solving in many areas of medical and pharmaceutical research, including brain neural network modeling, analytical data analysis, drug modeling, protein structure and function, dosage optimization and manufacture [3]. In addition to these studies, ANN is a frequently used method in the evaluation of the therapeutic and toxic effects of drugs [4].

Considerable success has been achieved by using ANN in various applications in drug dose calculation problems. In a study, the use of neural networks to individualize the dose of cyclosporine in patients undergoing kidney transplantation has been proposed. To obtain the models, 32 patients and different factors were examined, and three models were applied with the formation of network communities (MNN, FIR neural network, Elman Repetitive Network). The patients were randomly divided into two groups: 22 patient training sets (364 samples), and the other 10 patients formed the test and validation sets (217 samples). It has been concluded that neural networks can be used to estimate both dose and blood concentrations of cyclosporine [5]. In another study, the estimation of gentamicin serum drug concentrations was made with neural networks. A hidden layer with 5 neurons fully connected to the input and output layers was used. It has been concluded that neural networks can be useful in predicting clinical pharmacokinetics of drugs [6]. In another application, neural network-based visual body weight and drug dosage estimation were made. A statistical model based on data in the medical database has been developed for weight estimation and 900 000 images created by labeling body parts were applied to this ANN model. Preliminary experiments with 69 patients showed an accuracy of nearly 90% [7]. Previously mentioned studies show that ANNs give promising results in drug dose and concentration estimation. Similar to these references, the initial dose of propofol, a hypnotic drug, could be estimated through this application using ANN. However, this application was not intended to estimate the maintenance dose of propofol or blood concentration. While these references prove that most pharmacological problems are solvable using ANNs, they do not include anesthesia applications. There are various specific studies regarding the dosage and administration management of anesthetic drugs.

Today, the use of ANN in anesthesia applications is quite common due to its reliability, achieving correct results, and applicability. In a study, a linear predictive model and a local learning predictive model based on the lazy learning algorithm were used to implement a predictive model of the bispectral index (BIS), which can measure the patient's level of awareness based on the variation of hypnotic drugs (remifentanil and propofol). The 1069 training set was created with data recorded by anesthesiologists during surgical operations. The results have proved in most cases that lazy learning performs better than the linear model [8]. In another study, an artificial neural network model was developed to predict the hypnotic effect of propofol based on common clinical parameters, and 270 patients with a physical condition of the American Society of Anesthesiology (ASA) 1 or 2 were included in this study. As a result of the study, the predictive results of neural network models prevailed over the results of the clinician [9]. In other studies; recurrent neural network (RNN) was proposed to estimate the nonlinear model of the anesthetic drug response and monitor the dynamic change of dose-response [10]. Also, the plasma concentration of remifentanil based on the Elman neural network has been estimated [11]. Various studies are available for estimating the depth of anesthesia with ANN. In some of these studies, features were extracted from

the EEG signal using methods such as discrete wavelet transform (DWT), empirical mode decomposition (EMD). Then, the extracted features were used as input data of ANNs to estimate the depth of anesthesia. As a result of these studies, it has been concluded that ANN solely can predict the BIS index in deep anesthesia [12] [13]. In another study, ANN was used to classify the EEG signal according to different anesthetic drugs [14]. E-Nose System has been developed for anesthetic dose level estimation. The system was among the studies supported by TUBITAK within the scope of the project with a 95% success rate for anesthetic dose level applied to a patient in surgical operations [15]. The purpose of this application was not to estimate the depth of anesthesia unlike references [8], [12], [13]; therefore, the BIS index was not used as a parameter for the formed ANN model. This application estimates the initial dose of propofol calculated by the anesthesiologist's preoperative estimation. It does not require the feature extraction process used in reference [12] and [13], successful outcomes were obtained by using the raw data set prepared by the expert. Likewise, this application did not aim to predict the hypnotic and dose effects of propofol, unlike references [9] and [10]. The MNN structure was used to estimate the starting dose of propofol, and it solved the problem with over 92% test results, while no other ANN structure has been studied yet. Similar to the method used in reference [9], patient samples with 1, 2, 3, and 4 physical status, according to ASA, were used to include the patient's preoperative accompanying disease in the data set used in this application.

Apart from these studies, ANN was used for mechanical control of drug delivery in many applications. To optimize drug management during anesthesia, automatic drug administration is recommended by closed-loop systems. Closed-loop systems can decide on their own and try to achieve a predetermined goal [16]. It is ubiquitous to use control methods such as Fuzzy Logic (FL) [17], ANN [18], PID [19] in closed-loop systems that can control propofol dose or concentration. Unlike previously mentioned references, no automatic drug delivery device was used in this application. The initial drug dose, which was not controlled by a closed-loop technology device, was estimated by the expert per the variable factors of patients.

In this application, the ANN model is proposed for estimating the initial dose of propofol, the most commonly used hypnotic agent in general anesthesia, without premedication and additional medication. Propofol is an anesthetic drug that is implemented intravenously, with the right dose without side effects, but could cause serious harm in overdose or wrong dose implementation. When calculating the initial dose of anesthesia, expert anesthesiologists decide the correct dose by evaluating the patient's physical factors and concomitant diseases [20]. In a study, the FL method was used to calculate the initial propofol dose values close to the results of the experts were obtained [21]. In this study, it is demonstrated that the ANN method is more effective than the FL method and gives more accurate results to experts for the prediction of initial propofol dose.

2. Methodology

2.1. Artificial Neural Networks

By using the data generated by brain functions, ANNs are a field of machine learning that can learn events, make connections, classification, and generalizations between events. The main task of ANNs is to identify possible outputs that may correspond to the inputs given. ANNs can create their conclusions from the examples and can make generalizations on similar topics. ANNs has brought innovations by introducing non-algorithmic, adaptive, parallel programming techniques to computer science, and are distinguished from traditional algorithms with some basic features. ANNs can be used to realize functions such as estimation, classification, data association, data filtering, diagnosis, and interpretation in applications of industrial, financial, military, healthcare fields. The type of network suitable for a problem varies according to the characteristics of the problem and the network type. In general, MNN networks provide more accurate results in prediction problems,

LVQ, and ART networks provide more successful outcomes in classification problems, Hopfield and Boltzmann Machine systems provide more successful results in data association problems [1].

The design of ANNs alters entirely depending on the problem and the designer. ANN hyperparameters are variables that determine the network structure and how the network is trained. The hidden layer and unit number, learning speed, learning rate, data set, network weight initial values, momentum coefficient, epoch number, and, activation functions constitute the hyperparameters of ANN. The values of these hyperparameters are determined by the designer depending on the solution requirements of the problem and the experience of the designer. An ANN needs samples to learn and can only work with examples containing numerical information. These samples constitute the data set. The training data set, on the other hand, is used to complete the training phase. After the training stage, the network undergoes testing and validation stages to test the validity of the results according to the expected values, and the validation data set is used to test the validity of the model. Another feature of ANNs is that they can work with missing information through producing results to new samples despite missing data, which indicates that they have error tolerance as well. ANNs exhibit superior features than traditional algorithms such as working with missing information and having error tolerance. In ANNs, information is stored in a distributed form and learning occurs when the network's weight connections change correctly. Hence, the network is challenging to interpret, and the behavior of the network cannot be explained. In addition to these features, ANN's have difficulties such as being dependent on hardware, lack of a set of rules for the design of the network structure, and representation of the problem to the network [22].

2.1.1. Multilayer Neural Network

If nonlinear relationships exist in a problem, MNN is generally a favorable solution. In general, an MNN structure consists of an input layer, a hidden layer or layers, and an output layer, which are interconnected and contain a varying number of neurons, as shown in Figure 1.

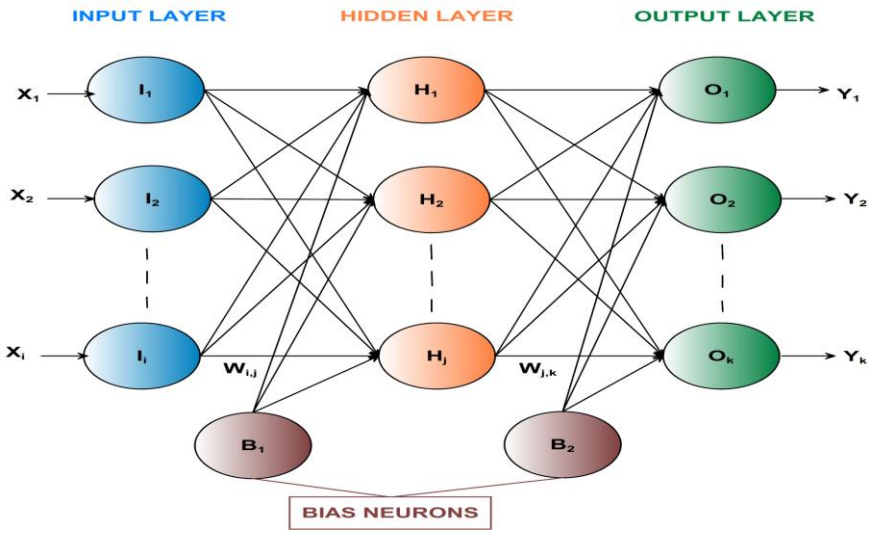

Figure 1. Three Layer MNN Structure

The generalized delta rule (GDR), which is based on the supervised learning strategy and developed by Rumelhart and McClelland is used in MNN [23]. The MNN training consists of two stages; feedforward calculation and backpropagation calculation [24]. The feedforward calculation is a stage where the output in the network is calculated. This stage begins with the presentation of examples to an input layer. The total input (TI) to the neurons in the hidden layer is calculated by multiplying incoming inputs by weights. The total input calculation of the j^{th} neuron in the hidden

layer of a feedforward network (TI_j^H) is given in (1). The total input calculation of each hidden layer and an output layer of the network is calculated in this way again. The product of the bias value and bias weights are also added to the total value in (1) (β_j^H). The bias value is always one and allows the activation function to be shifted to the right or left.

$$TI_j^H = \sum_{i=1}^{n} X_i^I W_{ij} + \beta_j^H \quad (1)$$

Total input values coming to the neurons of the hidden layer are passed through the activation function and the outputs of the neurons of the hidden layer are obtained. In MNN, derivative activation functions are used for the backpropagation of the error. The commonly used activation function is the sigmoid function given in (2). Y in Eq. (2) represents the output of the j^{th} neuron in the hidden layer (Y_j^H). The outputs of neurons in each hidden layer and the output layer are obtained by passing the activation function.

$$Y_j^H = \frac{1}{1+ e^{-(TI_j^H + \beta_j^H)}} \quad (2)$$

In the backpropagation calculation, error values of the neurons of the output layer are found by taking the difference of the output values of the network (output) and the expected output values (target). The error values found are distributed across the network's weight values so that the next iteration is aimed at reducing the error. Calculation of the error value of the k^{th} neuron of the output layer is given in (3). While calculating the total error for the output layer, the error value of each neuron is squared so that the total value is not zero.

$$\text{error}_\text{k} = \text{target}_\text{k} - \text{output}_\text{k} \quad (3)$$

The total error is distributed to the neurons that caused the error so that the error is minimized. Derivative activation functions are used in the calculation of error values distributed to neurons. The new weight value is found by adding the amount of change to the previous weight value. In any t iteration, the amount of change in the weight of the link that connects the j^{th} neuron in the hidden layer to the k^{th} neuron in the output layer and the new weight value are given in Eqs. (4) and (5), respectively. The learning coefficient (λ) given in (4) offers how much the error distributed to the k^{th} neuron (δ_m) will affect the change of new weights. The big learning coefficient increases instability. The momentum coefficient (α) gives how much the amount of change calculated in the previous iteration will affect the transformation of new weights and ensures that the network is not caught at a local optimum point during training.

$$\Delta W_{jk}^H(t) = \lambda \delta_k Y_j^H + \alpha \Delta W_{jk}^H(t-1) \quad (4)$$

$$W_{jk}^H(t) = W_{jk}^H(t-1) + \Delta W_{jk}^H(t) \quad (5)$$

This process is repeated in changing the weights between hidden layers or between a hidden layer and the input layer. Thus, the network learns as the correct weight values are obtained with each updated weight change. All of the processes given in this section are repeated until learning is completed. Passing the network through these processes for the first sample is called an iteration. Showing all samples to the network once is called an epoch. The number of epochs gives how many times all samples will attest to the network [25].

3. Implementation

In this application, the initial propofol dose was estimated using a neural network model in mg, without premedication and additional medication. Expert anesthesiologists created the data set used

in the ANN model with 299 patient samples. Generally, the factors that an anesthesiologist considers when calculating the initial dose of the drug are; the patient's age, weight, height, and concomitant diseases. The data set consists of, five columns and 299 rows, with the inclusion of age (year), weight (kg), height (m), concomitant disease, and propofol initial dose (mg). In the dataset, four columns, age, weight, height, concomitant disease represent the input values of the model, and one column, initial propofol dose represents the output value of the model. Since the ANN can only use numerical data, concomitant diseases are represented in the data set used in practice as shown in Table 1, after doctors created the data set.

In the digitization of concomitant diseases as given in Table 1, the system that the American Anesthesiologists Association (ASA) classifies patients according to the physical health status of patients before surgery was used. Anemia disease is classified as ASA 2 according to the ASA system, but the numerical value of Anemia disease was defined as 1.5 in the data set. The dose of the drug is calculated exceptionally determining a higher value in patients with anemia because of the difficulty of connecting the drug in the blood compared to regular patients [20].

Table 1. Representation of Concomitant Diseases in the Data Set

1	1.5	2	3	4
Healthy	Anemia	Chronic Bronchitis	Hypovolemia	Unstable Angina
		Hypertension	Stable Angina	Organ Failure
		Diabetes	Advanced Diabetes	Shock
		Obesity	Limited Heart or Lung Function	Advanced Heart or Respiratory Failure
		Emphysema	Latent Heart Failure	Unstable Angina

In the implementation of the application, a program was written in the MATLAB language and thanks to this program, the best efficiency of the performance criteria used was determined by changing the hyperparameters such as network models, hidden layer numbers, neuron numbers, training algorithms, and network type. In the evaluation of network models, Nash-Sutcliffe efficiency coefficient (NSEC) [26], correlation coefficient (R) [27], index of agreement (IOA) [28], root mean square error (RMSE) [29], mean absolute error (MAE) [30], mean percentage error (MPE) [31] respectively performance criteria given in Eqs. (6), (7), (8), (9), (10), (11) were used.

$$NSEC = 1 - \frac{\Sigma(Q_O - Q_S)^2}{\Sigma(Q_O - \acute{Q}_O)^2} \tag{6}$$

$$R = \frac{\Sigma(Q_O - \acute{Q}_O)(Q_S - \acute{Q}_S)}{\sqrt{\Sigma(Q_O - \acute{Q}_O)^2 \Sigma(Q_S - \acute{Q}_S)^2}} \tag{7}$$

$$IOA = 1 - \frac{\Sigma(Q_O - Q_S)^2}{\Sigma(|Q_S - \acute{Q}_O| + |Q_O - \acute{Q}_O|)^2} \tag{8}$$

$$RMSE = \sqrt{\frac{\Sigma(Q_S - Q_O)^2}{N}} \tag{9}$$

$$MAE = \frac{\Sigma|Q_O - Q_S|}{N} \tag{10}$$

$$\text{MPE} = \frac{\sum^{\frac{|Q_O - Q_S|}{Q_O}}}{N} * 100 \quad (11)$$

Q_O used in these formulas represents the observed data, Q_S represents the simulated data and N represents the total number of test sets. Performance criteria are the criterion of predictive success, which gives the statistical relationship between the observed data and the simulated data. NSEC efficiency is between -∞ and 1, R efficiency is between +1 and -1, and IOA efficiency is between 0 and 1. When NSEC, R, IOA criteria are close to 1, it shows that there is excellent compatibility between the observed data and the simulated data. RMSE, MAE, MPE measure the error of the model, and it is preferred to have small values.

Table 2 shows the success rates for the test results according to the performance criteria of the models created with varying hyperparameters. Since the performance results of models with three or more hidden layers are lower than the results given in Table 2, this article has not included results of models with three or more hidden layers. The models exhibited in Table 2 were created using feed-forward MNN, and Bayesian Regularization (BR) [32] and Levenberg Marquardt (LM) [33] algorithms were used in the training of the models. The LM algorithm minimizes the mean square error, while the BR algorithm minimizes the weighted sum of square errors and square weights. The LM algorithm is one of the fastest backpropagation algorithms, although it requires more memory than other training algorithms. The BR algorithm is used to prevent over-training of the network.

Table 2. Performance Criteria Results of Network Models with Varying Hyperparameters

Hidden Layer Size	1						2					
Training Algorithm	BR			LM			BR			LM		
Neuron Numbers	10	20	40	10	20	40	10	20	40	10	20	40
NSEC	0,888	0,894	0,892	0,902	0,896	0,880	0,893	**0,908**	0,896	0,893	0,886	0,858
R	0,944	0,946	0,946	0,952	0,949	0,943	0,945	**0,957**	0,947	0,947	0,946	0,933
IOA	0,969	0,971	0,970	0,973	0,972	0,969	0,971	**0,977**	0,971	0,972	0,970	0,964
RMSE	16,117	15,674	15,835	15,060	15,496	16,652	15,750	**14,565**	15,515	15,695	16,245	18,145
MAE	11,559	11,288	11,445	11,171	11,791	12,456	11,157	**9,470**	10,884	11,330	12,313	13,927
MPE	11,131	10,842	11,072	10,654	11,481	11,683	10,918	**8,771**	10,470	10,464	11,770	13,194

Therefore, it keeps the training subset of small datasets as large as possible and does not use the validation subset. 10, 20, and 40 values were assigned to the neuron numbers of each hidden layer. Training, test, and validation data were created by dividing them into indices. The validation data set has not been established in models that have undergone training with the BR algorithm in Table 2.

Mean square error MSE value [34], has been considered as the performance criterion of the MNN model created for the application, unlike the above performance criteria. MSE formula is given in Eq. 12. MSE provides information on how far the estimates spread from one data sample to another and how far the average estimated value is.

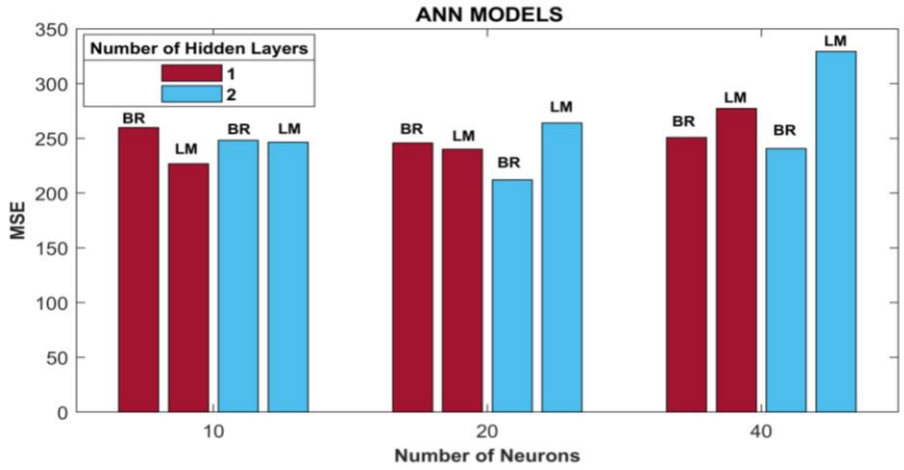

Figure 2. MSE Values of ANN Models

A small MSE value is a preferred choice as it shows that data values are scattered closely around the average estimated value.

$$MSE = \frac{1}{N}\sum_{i}^{N} error_i^2 \quad (12)$$

The MSE values of ANN models given in Table 2 combined with varying hyperparameters are shown in Figure 2. The model highlighted in Figure 2 and Table 2 with different colors clearly shows the requirements of the model that should be used for problem-solving. As shown in Figure 3, this selected model has four layers, two hidden layers, each hidden layer has 20 neurons, and is trained with the BR algorithm. During the training process with the BR algorithm, the data set created with 299 patients was divided into two sets, training, and testing. The selected model has given the best performance values among the models combined with varying hyperparameters and the test MSE value of the model is 212.139.

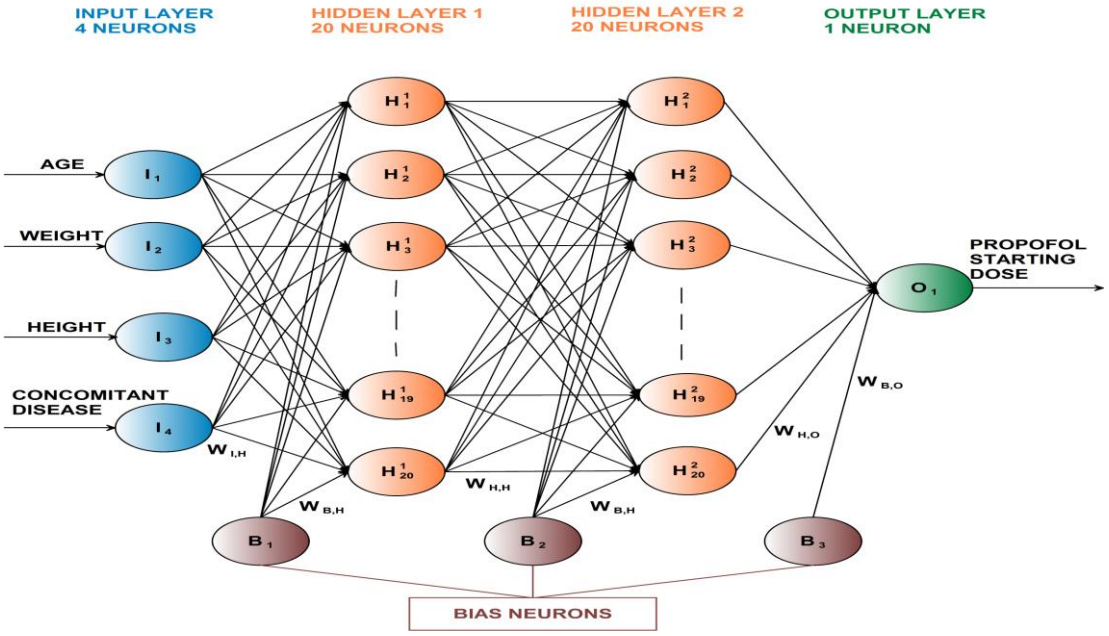

Figure 3. ANN Model Used in Application

4. Simulation and Results

In the study, it has been aimed to estimate the initial propofol dose commonly used in general anesthesia with ANN, which is the sub-branch of machine learning. A program has been written

through which the network model with the best efficiency of performance criteria has been selected for the prediction of the initial propofol dose. This model has four layers, two hidden layers, each hidden layer has 20 neurons, and has been trained with the BR algorithm. In the simulation stage, the data set was divided into three sub-sets, training, testing, and validation, to measure model accuracy and improve performance efficiency. The data set was created with 299 patients, 70% of the data set was used for training, 15% for testing, and 15% for validation and divided into indices. Thus, the performance values of the selected model have increased statistically; in other words, its success in estimation has been increased. Figure 4 shows the relationship between observed data and simulated data according to the test and validation results of the model. Figure 4 clearly shows that the simulated data takes values close to the observed data, which is valid for both the test stage and the validation stage.

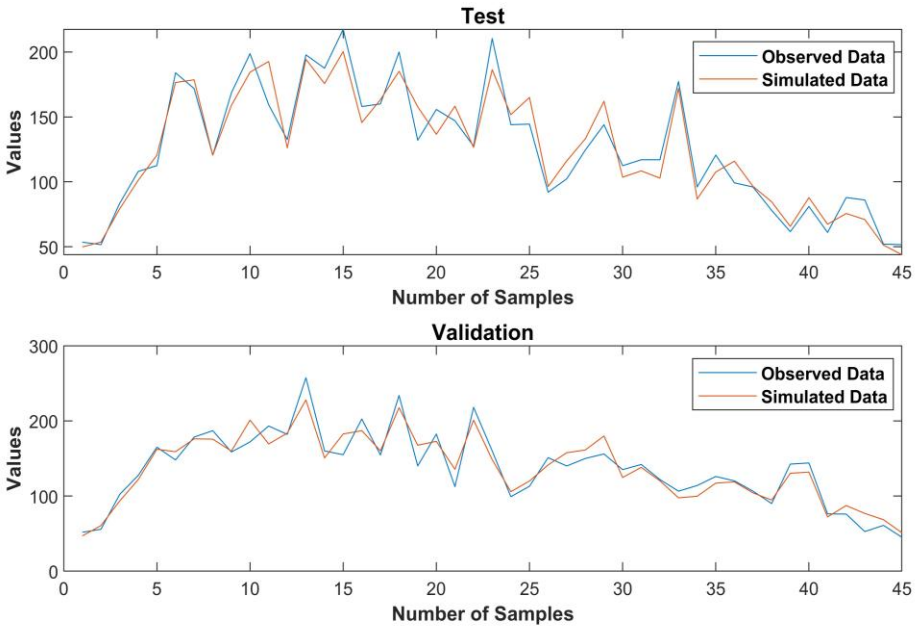

Figure 4. The Relationship Between Observed Data and Simulated Data

First, the trained network is randomly tested for estimation using this trained network model, then confirmation tests are performed to verify the validity of the model. According to the network performance graph in Figure 5, the test set error and validation set error to have similar properties. The network has undergone training with a total of 33 epoch and 6 validation controls. It showed the best test performance with 152.4362 MSE and the best validation performance with 194.2141 MSE in the 27th epoch. The latest mean square error of the model is small and showed the best network performance value in test performance with 152.4362 MSE.

Regression graphs of the application are given in Figure 6. Regression graphics are graphs that give linear regression values between network outputs and corresponding targets. They show the relationship between the outputs of the network and the goals. The R-value is an indication of the relationship between outputs and targets. In the regression graph, if R = 1, then there is a completely linear relationship between outputs and targets. If R is close to zero, then there is no linear relationship between outputs and targets.

According to the regression graphs in Figure 6, it proved model validity with regression values are above 92% for all trained, approved, tested, and general experimental studies.

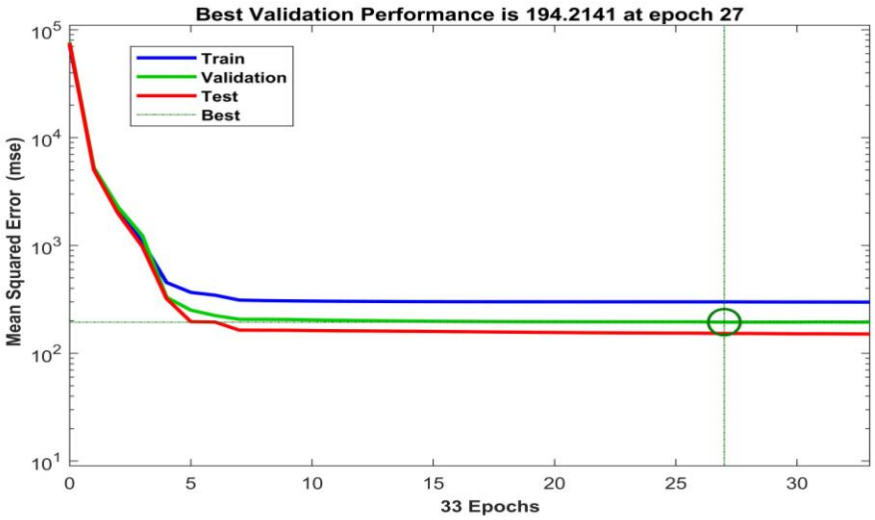

Figure 5. Best Performance Values

The success and validity of a network model can be evaluated by looking at performance criteria and regression values. Table 3 shows the MSE and R values of the training, testing, and validation results of the network model were used for the solution of the problem. 70% of the data set created with 299 patients was used for training, 15% for testing, and 15% for validation, and the data set was divided into indices. According to Table 3, the validation and test R values are above 92% and the MSE values prove the validity of the network.

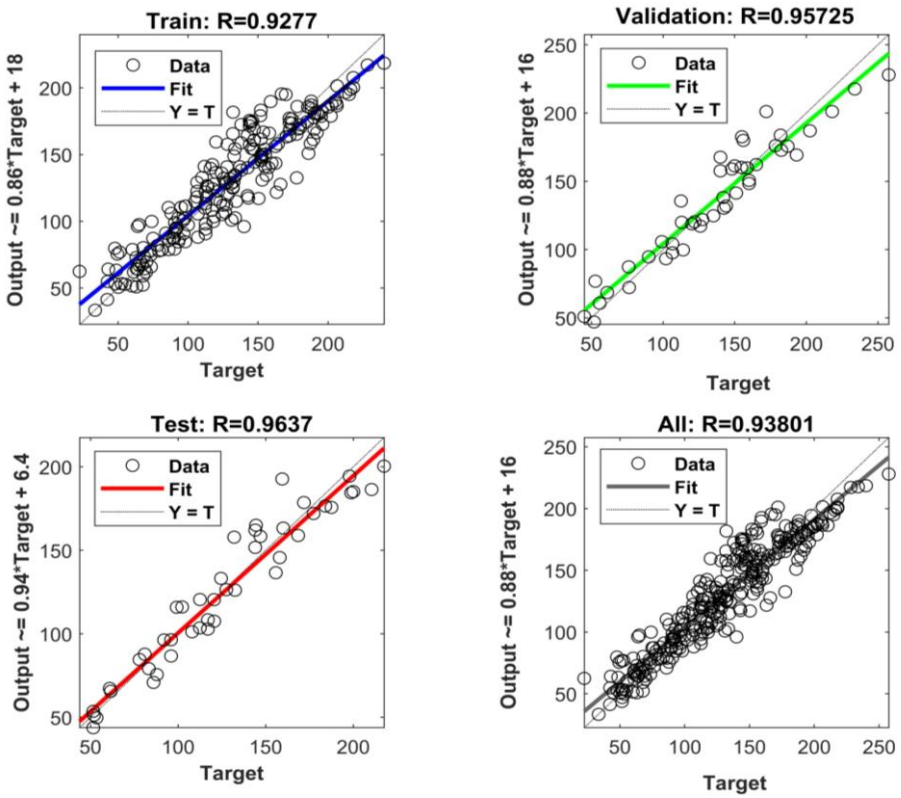

Figure 6. Regression Graph of ANN Model

In a study on the same subject, the FL method was used to estimate the propofol starting dose. In Table 4, FL and ANN results of some samples from the test dataset are compared. The results given

in Table 4 are simulated in Figure7. With the FL method, values close to the values given by the experts are estimated, but ANN errors are lower.

Table 3. MSE and R Values of ANN Model

	Performance (MSE)	**Regression (R)**
Train	299.6617	0.9277
Validation	194.2141	0.95725
Test	152.4362	0.9637
All	261.6340	0.93801

With this study, it is observed, according to Table 4 and Figure 7 that in the modeling of the problem with the ANN method, more success was achieved than the success achieved with the FL method.

Table 4. ANN and FL Results of Application

Age (year)	**Weight (kg)**	**Height (m)**	**Concomitant Disease**	**Propofol Starting Dose (mg)**	**ANN Results (mg)**	**ANN Errors**	**FL Results (mg)**	**FL Errors**
6	19.7	1.17	Anemia	68.9	70.7433	-1.8433	59.1	9.8000
13	47	1.53	Healthy	117.5	116.7514	0.7486	138.18	-20.6800
23	79	1.67	Diabetes	158	157.4331	0.5669	162.74	-4.7400
34	101.3	1.85	Advanced Heart Failure	151.9	149.7927	2.1073	151.95	-0.0500
48	62	1.56	Anemia	155	153.9265	1.0735	133.3	21.7000
58	50	1.62	Shock	75	89.4186	-14.4186	87.5	-12.5000
68	50	1.59	Hypovolemia	100	93.9359	6.0641	108.5	-8.5000
69	50	1.65	Chronic Bronchitis	125	126.4206	-1.4206	112.5	12.5000
80	62	1.7	Organ Failure	93	96.0043	-3.0043	88.04	4.9600
99	51.6	1.66	Unstable Angina	51.6	55.9725	-4.3725	68.112	-16.5120
						ANN MSE		**FL MSE**
						28.4705		169.9060

An error histogram is a visualization of errors between observed data and simulated data. The error values given by the histogram show how different the predicted values differ from the target values. The histogram given in Figure 8 was created using the results in Table 4. According to this histogram, FL and ANN errors are divided into 20 different groups between -19.62 and 20.64 values. While FL errors spread over a wide range of error groups, ANN errors accumulated in a narrow range between -4.788 and 5.807 groups. Thus, for this study, the predictive power and accuracy of the ANN method are effectively revealed.

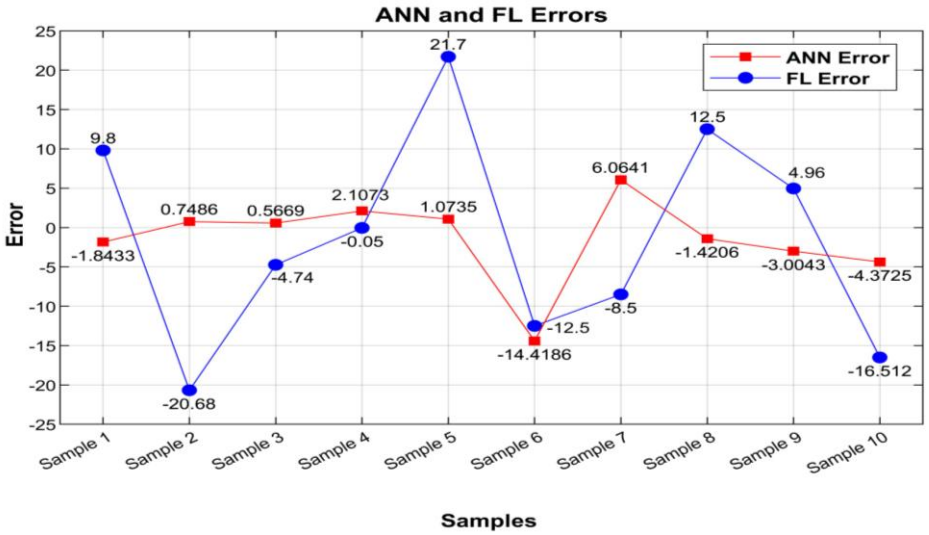

Figure 7. ANN and FL Errors Simulation

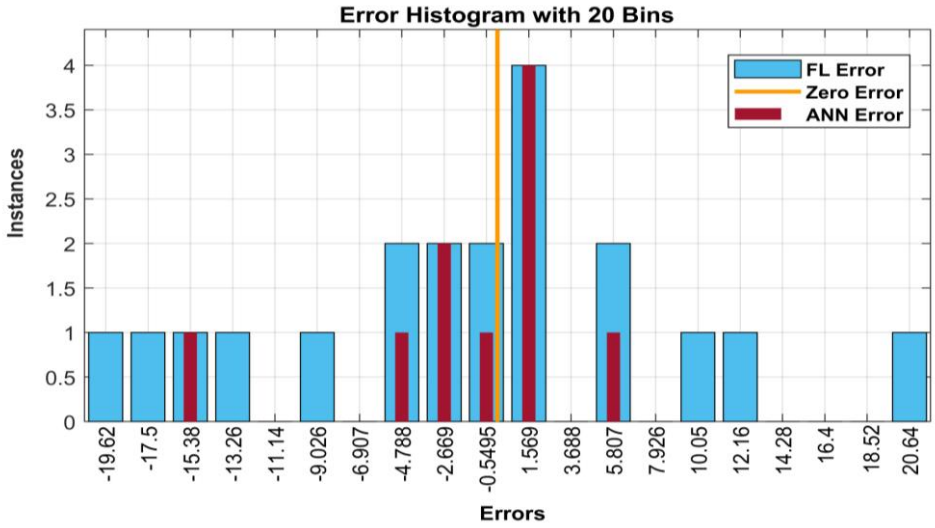

Figure 8. Error Histogram of ANN and FL Errors

5. Conclusion

This application has distinct differences from previous anesthesia applications. In this application, an automatic drug delivery device was not used and the initial drug dose was estimated, which a closed-loop technology device did not control. The specialist himself calculated according to the variable factors of the patients. This application can only estimate the initial dose of the drug and not the continuation dose of the drug, assuming no premedication and no additional medication is used. For this application, the most commonly used hypnotic agent, propofol, is used in general anesthesia and a general model that calculates for other anesthetic drugs is not created.

This application is a specific study proving that ANNs can calculate the starting dose of anesthetic drugs like a specialist and confirmed that the ANN method could be used in future studies to estimate the starting dose of the desired anesthetic drug. The ANN model used for estimation has realized the prediction of the initial propofol dose with successful results. The results have potentially proven that propofol can help determine the starting dose, thereby reducing the workload of specialists as an assistant to anesthesiologists.

Modeling of health applications with ANN is increasing day by day and ANN's success in the health field is proven. With this study, a new one has been added to ANN's applications in the field of health, thus increasing the contribution of engineering studies to the field of health. In the future, the workload of many healthcare professionals will be reduced with the increasing use of artificial intelligence technologies such as this study, which has proven its success.

References

[1]. Buscema M., Massini G., Breda M., Lodwick W.A., Newman F., Asadi-Zeydabadi M., Artificial neural networks, Stud. Syst. Decis. Control, 2018, 131: 11–35.

[2]. Mhatre M., Siddiqui F., Dongre M., Thakur P., A Review paper on Artificial Neural Networks: A Prediction Technique, Int. J. Sci. Eng. Res., 2017, 8: 1–3.

[3]. Sutariya V., Groshev A., Sadana P., Bhatia D., Pathak Y., Artificial Neural Network in Drug Delivery and Pharmaceutical Research, Open Bioinforma, 2014, 7: 49–62.

[4]. Basile A.O., Yahi A., Tatonetti N.P., Artificial Intelligence for Drug Toxicity and Safety, Trends Pharmacol, 2019, 40: 624–635.

[5]. Camps-Valls G., Porta-Oltra B., Soria-Olivas E., Martin-Guerrero J.D., Perez-Ruixo J.J., Jimenez-Torres N.V., Prediction of cyclosporine dosage in patients after kidney transplantation using neural networks, IEEE Trans. Biomed. Eng., 2003, 50: 442–448.

[6]. Brier M.E., Zurada J.M., Aronoff G.R., Neural Network Predicted Peak and Trough Gentamicin Concentrations, Pharm. Res. An Off. J. Am. Assoc. Pharm., 1995, 12: 406–412.

[7]. Pfitzner C., May S., Nüchter A., Neural network-based visual bodyweight estimation for drug dosage finding, in M.A. Styner, E.D. Angelini (Eds.), Med. Imaging 2016 Image Process., 2016, 97841Z.

[8]. Caelen O., Cailloux O., Ghoundiwal D., Alexander A., Real-time prediction of an anesthetic monitor index using machine learning, Artif. Intell. Med., 2011.

[9]. Lin C.S., Li Y.C., Mok M.S., Wu C.C., Chiu H.W., Lin Y.H., Neural network modeling to predict the hypnotic effect of propofol bolus induction., Proc. AMIA Symp., 2002: 450–454.

[10]. Sakuma Y., Kohno R., A Dynamic Model Estimation Scheme for Model Predictive Control of Anesthesia Using Recurrent Neural Network, in 2018 12th Int. Symp. Med. Inf. Commun. Technol., IEEE, 2018: 1–5.

[11]. Tang J., Cao Y., Xiao J., Guo Q., Predication of plasma concentration of remifentanil based on Elman neural network, J. Cent. South Univ., 2013, 20: 3187–3192.

[12]. Rabbani H., Mehri A., Ghanatbari M., Estimation the Depth of Anesthesia by the Use of Artificial Neural Network, in Artif. Neural Networks - Methodol. Adv. Biomed. Appl., InTech, 2011.

[13]. Sadrawi M., Fan S.Z., Abbod M.F., Jen K.K., Shieh J.S., Computational Depth of Anesthesia via Multiple Vital Signs Based on Artificial Neural Networks, Biomed Res. Int., 2015: 1–13.

[14]. Benzy V.K., Jasmin E.A., A Combined Wavelet and Neural Network-Based Model for Classifying Depth of Anaesthesia, Procedia Comput., 2015, 46: 1610–1617.

[15]. Saraoğlu H.M., Edin B., E-Nose System for Anesthetic Dose Level Detection using Artificial Neural Network, J. Med. Syst., 2007, 31: 475–482.

[16]. Neckebroek M.M., De Smet T., Struys M.M.R.F., Automated Drug Delivery in Anesthesia, Curr. Anesthesiol. Rep., 2013, 3: 18–26.

[17]. Hossein S., Khazaei M., Khomarlou Z.A., Geramipour H., Controlling the Depth of Anesthesia Using Adaptive Fuzzy Sliding Mode Control Strategy, Int. J. Mechatronics, Electr. Comput. Technol., 2015, 5: 2313–2326.

[18]. Moore B.L., Pyeatt L.D., Kulkarni V., Panousis P., Padrez K., Doufas A.G., Reinforcement learning for closed-loop propofol anesthesia: A study in human volunteers, J. Mach. Learn. Res.,2014, 15: 655–696.

[19]. Merigo L., Padula F., Latronico N., Paltenghi M., Visioli A., Optimized PID control of propofol and remifentanil coadministration for general anesthesia, Commun. Nonlinear Sci. Numer. Simul., 2019, 72: 194–212.
[20]. Pearl R.G., Clinical Anesthesiology, Anesth. Analg., 1992, 75: 650.
[21]. Sivari E., Civelek Z., Kahraman G., Genel Anestezide Kullanılan Propofolün Başlangıç Dozunun Bulanık Mantık ile Tahmini, El-Cezeri Fen ve Mühendislik Derg., 2019, 6(3): 808–816.
[22]. Jain A.K., Mao J., Mohiuddin K.M., Artificial neural networks: a tutorial, Computer (Long. Beach. Calif)., 1996, 29: 31–44.
[23]. Rumelhart L., Hinton D.E., McClelland G.E., A general framework for parallel distributed processing., in Parallel Distrib. Process. Explore. Micro Struct. Cogn. Vol. 1 Found., Cambridge, MA: Bradford Books/MIT Press., 1986.
[24]. Buscema M., Tastle W.J., Intelligent Data Mining in Law Enforcement Analytics, Springer Netherlands, Dordrecht, 2013.
[25]. Sathyanarayana S., A Gentle Introduction to Backpropagation, Numer. Insight, Inc Whitepaper., 2014, 1–15.
[26]. Nash J.E., Sutcliffe J.V., River flow forecasting through conceptual models part I — A discussion of principles, J. Hydrol., 1970, 10: 282–290.
[27]. Pearson K., VII. Note on regression and inheritance in the case of two parents, Proc. R. Soc. London., 1985, 58: 240–242.
[28]. Willmott C.J., On the Validation of Models, Phys. Geogr., 1981, 2: 184–194.
[29]. Hyndman R.J., Koehler A.B., Another look at measures of forecast accuracy, Int. J. Forecast., 2006, 22: 679–688.
[30]. Willmott C., Matsuura K., Advantages of the mean absolute error (MAE) over the root mean square error (RMSE) in assessing average model performance, Clim. Res., 2005, 30: 79–82.
[31]. Meade N., Armstrong J.S., Long-Range Forecasting: From Crystal Ball to Computer (2nd Edition)., J. Oper. Res. Soc., 1986, 37: 533.
[32]. Burden F., Winkler D., Bayesian Regularization of Neural Networks, in Methods Mol. Biol., 2008, 23–42.
[33]. Levenberg K., A method for the solution of certain non-linear problems in the least-squares, Q. Appl. Math., 1944, 2: 164–168.
[34]. Ziegel E.R., Lehmann E.L., Casella G., Theory of Point Estimation, Technometrics., 1999, 41: 274.