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Hybrid model for the ANI index prediction using Remifentanil drug and EMG signal

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Abstract

With the aim to control and reduce the pain of patients during a surgery with general anesthesia, one of the main challenges is the proposal of safe an optimal and efficient methods of drugs administering. First step to achieve this goal is the proposal and development of right indexes that correlate satisfactory with analgesia. One of this index gives the most hopeful results is the Analgesia Nociception Index (ANI). The present research work deals the ANI response of patients during surgeries with general anesthesia with intravenous drug infusion. The main aim is to predict the ANI signal behavior regarding of the analgesic infusion rate. To do that, a hybrid intelligent model is developed, using clustering and regression techniques based on artificial neural networks and support vector regression. The proposal was validated with a dataset of surgeries real cases of patients undergoing general anesthesia. The achieved results attest for the potential of the proposed technique.

Keywords ElectroMyoGram signal (EMG) · Analgesia Nociception Index (ANI) · Multi-layer perceptron (MLP) · Support vector regression (SVR)

1 Introduction

Supplying the proper dose of drug in patients undergoing general anesthesia has become an important challenge in medicine. Anesthesiologist must control the level of hypnosis, analgesia and muscle relaxation during surgery. As a general rule, they evaluate the state of patients by means of clinical signs and then decide whether increasing or decreasing the corresponding drug dose manually. Nowadays, different automatic controllers have been proposed in order to adapt the drug titration automatically. Specifically, automatic control of hypnosis has been widely researched [1, 2]. However, the automatic control of analgesia is still a problem to face. Closed-loop control strategies are based on the use of a feedback variable. Nevertheless, the absence of a feedback variable capable of measuring the analgesic state of patient has become the main problem for the automation.

Traditional methods have been based on the evaluation of the autonomic reactions [3]. Currently, new monitors and sensors [4, 5] have been proposed in order to measure analgesia [6]. Among the different possibilities, the Analgesia Nociception Index (ANI), developed by Mdoloris Medical Systems, is supposed to be designed to optimize drug delivery in the analgesic process. It is able to compute an index that ranges from 0 to 100 in order to quantify the parasympathetic activity in patients undergoing surgery. Previous successful results have been reached when using the ANI to guide analgesic delivery [7–9]. However, more research is needed in order to validate the Analgesia Nociception Index as a measure of analgesia.

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On the other hand, not only the presence of a feedback variable, but also the availability of a mathematical model is necessary when trying to automate the analgesic process. Despite of hypnosis, where pharmacokinetic/pharmacodynamics models have been widely studied [10–12], analgesic models for patients are still a challenge for experts. In this sense, proposing a model able to relate the drug infusion of analgesic with the ANI index would make the automation of analgesia easier.

This work is based on the techniques used in [13], where a hybrid model was created for predicting the ElectroMyoGram signal (EMG) and Bispectral index signal (BIS), taking into account different variables involved in the surgery. For this research, the hypothesis is that the ANI index is correlated, not only to the infusion rate of analgesic, but also to the EMG as a measure of the painful surgical stimuli. Then, the objective is to predict the ANI in terms of EMG and Remifentanil rate. Understanding this index, as well as the variables involved would let the development of new strategies applied to the analgesia control. Specifically, the availability of a model able to predict a wide time horizon would let the application of predictive control strategies.

For the ANI prediction, many different methods can be considered. The accepted regression methods are typically based on multiple regression analysis techniques, that are very usual in applications in different fields [14–16]. However, these methods have limitations and do not provide a good performance [15, 17, 18]. In order to increase this feature, many new proposals have been developed. These proposals are based on soft computing techniques, both simple or hybrid [19, 20]. As it is shown in [21–25] these techniques improve the first ones mentioned above.

This study implements a global model to predict the ANI signal from the EMG signal and the Remifentanil infusion rate. Two regression methods (ANNs, artificial neural networks, and SVR, support vector regression) and different configurations were verified to select the best one based on the lowest mean squared error (MSE) reached.

This paper is structured in the following way. After the present section, the case of study is described. Then, the model approach and the tested algorithms taken into account in the research are shown. The results section shows the best configuration achieved by the hybrid model. After the results, the conclusions and future works are presented.

2 Case of study

Data for the analysis were obtained from fifteen patients scheduled for cholecystectomy surgery at the Hospital Universitario de Canarias. All patients included received an informative document about the study and an informed consent was signed. A Total IntraVenous Anesthesia with Propofol and Remifentanil (hypnotic and analgesic drugs, respectively) was performed. Drugs were manually delivered according to the anesthesiologist criteria using two intravenous Graseby 3500 pumps. For the control of hypnosis, BIS monitor was used as a guidance variable. Propofol dose was changed in order to obtain an adequate level of hypnosis, with a BIS target of 50. On the other hand, Remifentanil dose was adjusted depending on autonomic reactions and the presence of surgical events. During the surgery, ANI index as well as EMG signal and Remifentanil rate (mcg/kg/min) were automatically registered with a sample time of 5 s using a laptop via RS232 interfaces. Although ANI was registered, this information was not visible for the clinician to avoid conditioning their decisions based on traditional clinical parameters. In patients undergoing anesthesia, it is supposed that the ANI level will vary depending on the concentration of Remifentanil and the external disturbances that will be considered taking the EMG information into account.

The studied problem could be represented as shown in Fig. 1.

Fig. 1 Case of study. Input/output representation

3 Model approach

The model approach used in this research is shown in Fig. 2. In this figure, two of the model inputs are measured signals (Remifentanil drug—Remi- and the ElectroMyoGram—EMG-) and the third input represents feedback of the predicted Analgesia Nociception Index—ANI. As the model is used to predict the future value of ANI, the inputs are the actual and the 4 previous values of the signals; and the output is the predicted ANI value at the next 40 s.

The time values that appear in Fig. 3 are the real surgery time; but as the acquisition system uses a sample time of 5 s, the model uses the 4 previous value to predict the value in the next 8th instant. These previous values allow the intelligent model to predict the signal including the dynamic on the process.

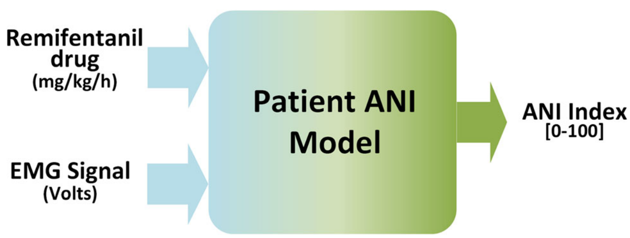


Fig. 2 Model approach

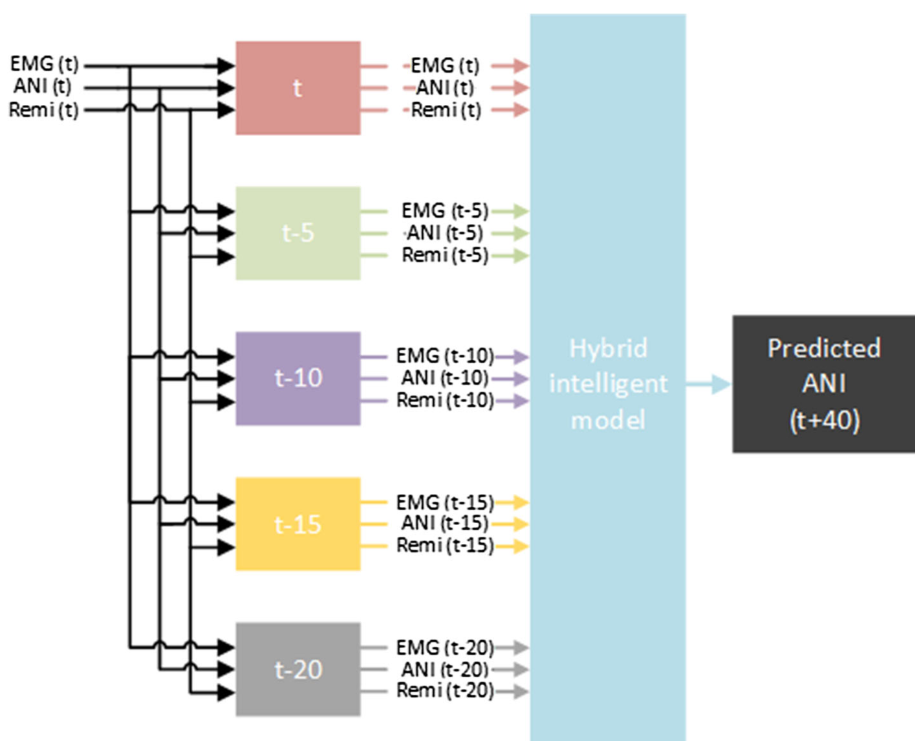
Moreover, Fig. 4 shows the internal layout of the hybrid intelligent model. Each internal model is selected to achieve the best global results, then, the training phase is taking into account all the different clusters and the different regression algorithms used (and its configuration).

The dataset used in the training process was divided using K-fold cross-validation with tenfold. This type of cross-validation ensures more general parameters to calculate the error for each regression technique. Figure 5 shows the modeling process, this training repeats K times until all the training data are used with each algorithm. Once all the K-fold were trained, the error for each specific algorithm is calculate as shown in Fig. 6.

3.1 Dataset obtaining and description

The dataset has been obtained from 15 patients undergoing general anesthesia. The three variables used on this research (Remifentanil drug infusion rate, EMG and ANI) have been monitored during surgeries. A preconditioning stage was considered for the signals. The dataset is composed with the data of all patients, recording new set of values with a sample time of 5 s. The dataset was initially inspected visually to detect outliers. Additionally, missing measurements were recovered by performing simple interpolation on each data with its neighbors. The induction phase and the recovery phase were not considered in this study; only the maintenance phase of surgery has been

Fig. 3 Model approach with the timed variables indicated



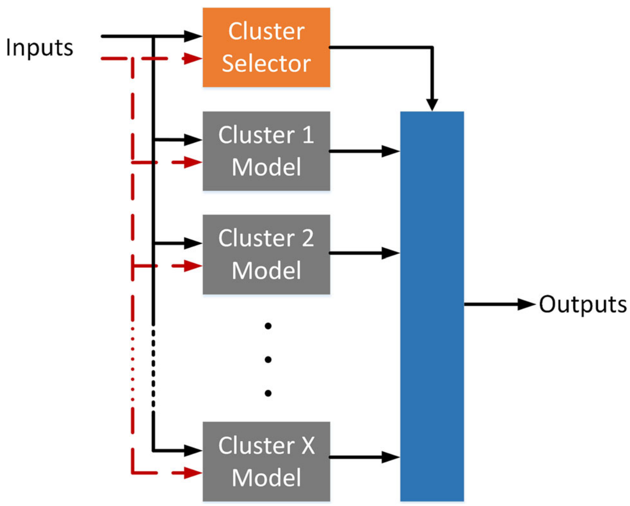


Fig. 4 Hybrid intelligent model

used. With the conditions exposed above, the employed dataset contains 19,441 samples.

The data registered for two patients were separate in the first processing step to perform the validation at the end of the modeling process; with this validation, the dataset was reduce until 17,356 samples. As the model predicts future signals, the dataset had to be prepared in a specific way, and the final dataset had 17,200 samples. The last 12 samples for each patient were not used, they do not have the future ANI signal to train the model.

3.2 Used techniques

In this section, the different regression algorithm used to achieved the final hybrid intelligent model are described. Different configurations for the intelligent regression techniques are tested. The best algorithm and its configuration is chosen based on MSE criteria, using 10 K-fold cross-validation to allow a more general measure than when hold-out is used. Moreover, as the hybrid intelligent model is divided internally in different clusters, a mean MSE (taking into account the number of samples in each cluster) of local model is used to compare the different clusters configurations.

3.2.1 Data clustering: the K-means algorithm

Clustering techniques make data grouping measuring the similarity between samples [26, 27]. These algorithms organize unlabeled data in groups; the samples within a cluster are similar to each other [26]. K-means is a frequently used clustering algorithm with square-error criterion, which minimizes the specific error function shown in Eq. 1.

$$e = \sum_{k=1}^{C} \sum_{x \epsilon Q_k} \|x - c_k\|^2 \quad (1)$$

where x new input vector, c_k centroid of cluster k.

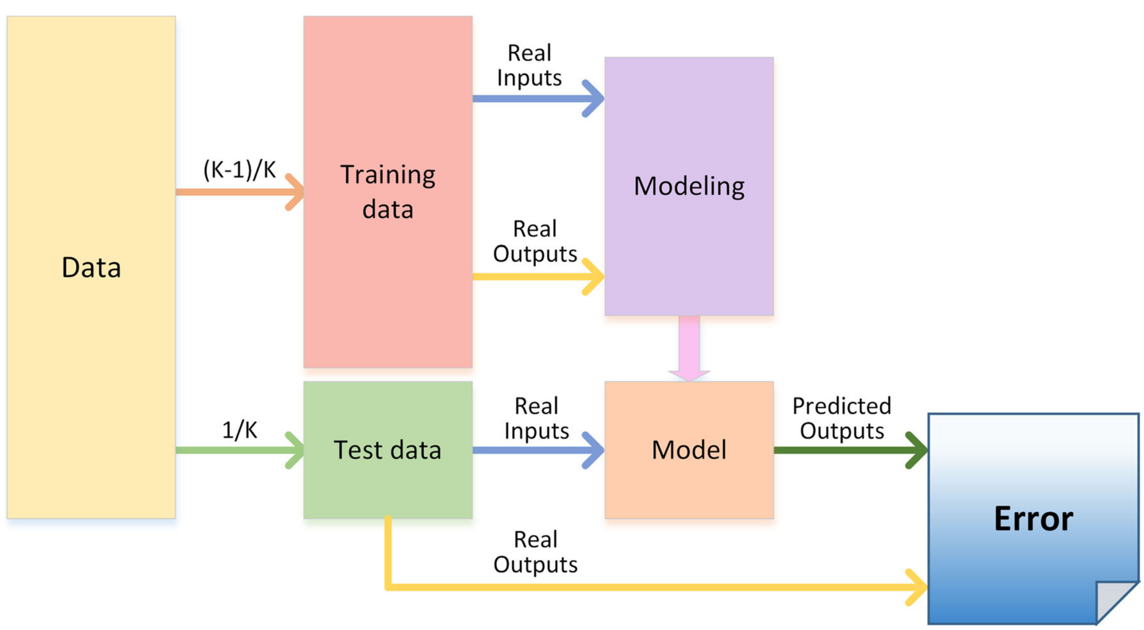


Fig. 5 Modeling process

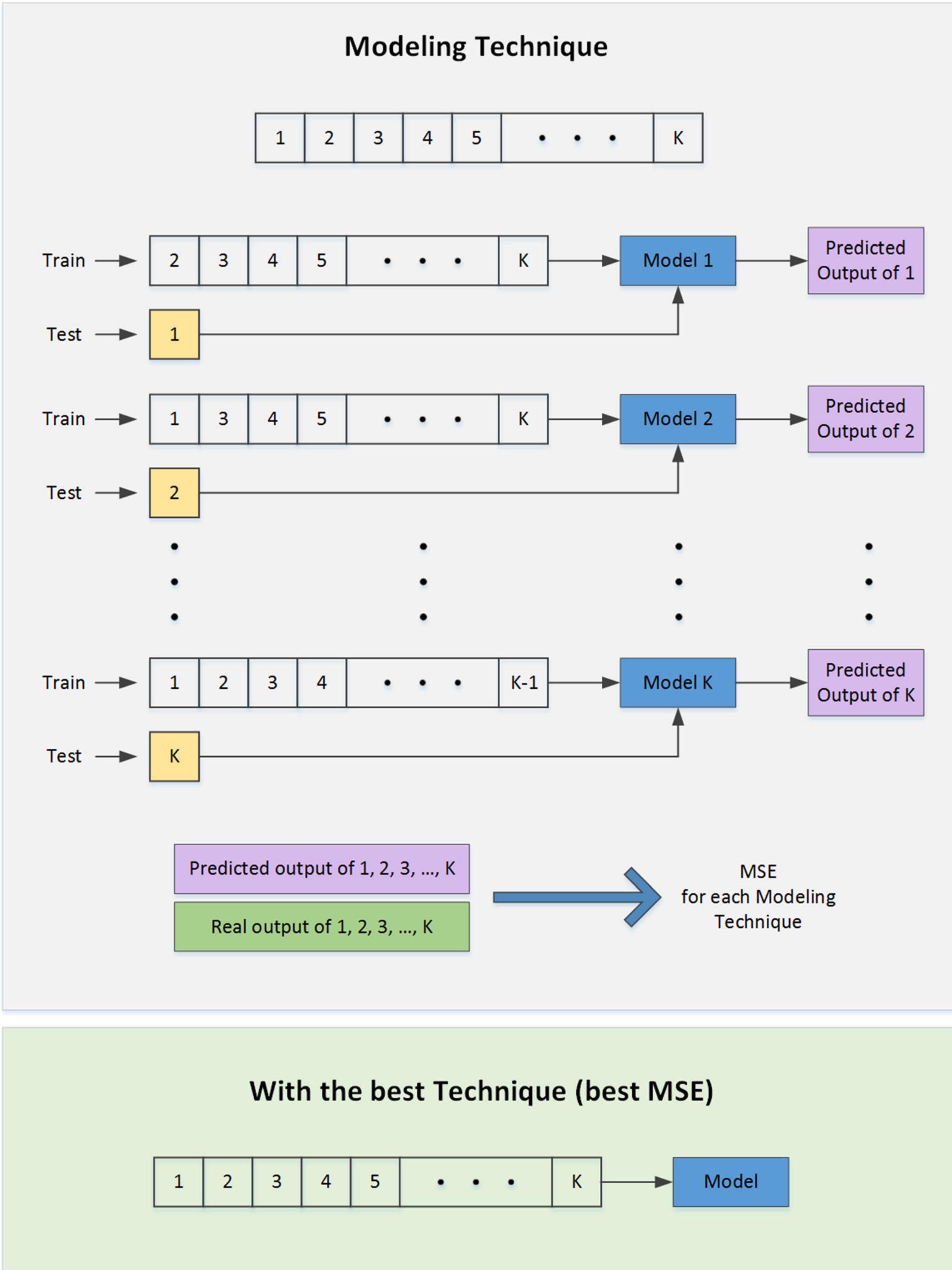


Fig. 6 *K*-fold training process

The obtained clusters depend on the initial centroids and on the K value (number of groups). The most critical election is the choice of K value because it needs certain knowledge of total clusters present in the data and, sometimes, it is extremely uncertain. The K-means clustering algorithm is computationally effective, it works well when the data are close to its cluster, the cluster is hyperspherical in shape and they are well-separated in the hyperspace.

3.2.2 Artificial neural networks (ANN), multi-layer perceptron (MLP)

A multi-layer perceptron is the most known feedforward artificial neural network [28, 29]. It is due to its simple configuration and its robustness. Despite of that, the ANN architecture must be carefully chosen in order to achieve satisfactory results. MLP is made of one input layer, one or more hidden layers and one output layer. The layers have neurons with an activation function. In a typical configuration, all layer neurons have the same activation function, but this is not a restriction. This function could be step, linear, log-sigmoid or tan-sigmoid.

3.2.3 Support vector regression (SVR), least square support vector regression (LS-SVR)

Support vector regression is based on the algorithm of the support vector machines (SVM) for classification. In SVR the data are mapped into a high-dimensional feature space F through a nonlinear plotting and linear regression is done in this space [30].

The least square algorithm of SVM is called LS-SVM (least square support vector machines). The solution estimation is obtained by solving a system of linear equations, and it is similar to SVM in terms of performance generalization [26, 31, 32]. The use of LS-SVM algorithm to regression is well-known as LS-SVR [33, 34]. In LS-SVR, the insensitive loss function is replace by a classical squared loss function, which makes the Lagrangian by solving a linear Karush–Kuhn–Tucker.

4 Results

As it was explained, the model was obtained using the current and previous values of the variables to predict the ANI signal in the next 40 s. To improve the prediction, a hybrid intelligent model is selected in this paper.

The MLP-ANN regression algorithm was trained for different configurations; always with one hidden layer, but the number of neurons in the hidden layer varies from 1 to 8. The activation function of this neurons was tan-sigmoid for all tests, and the output layer neuron had a linear activation function to perform regression. The used optimization algorithm was Levenberg–Marquardt; gradient descent was used to finish the training phase, and the performance function was set to mean squared error.

The LS-SVR was trained with the self auto-tuning implemented in the toolbox for MATLAB developed by KULeuven-ESAT-SCD. The kernel of the model was set to radial basis function, and the type was ‘Function Estimation’ to perform regression. The optimization function is ‘simplex’ and the cost-criterion is ‘leaveoneoutlssvm’ with ‘mse’ as a performance function.

Table 1 shows the best mean absolute error (MAE) in each cluster. It was decided to show the MAE because, as the ANI signal has a range from 0 to 100, this value is a real percentage of error.

The regression techniques for each cluster are shown in Table 2, where the best hybrid configuration is marked in bold. This choice was made according to the less hybrid MSE, shown in Table 3, that was obtained taking into account the number of samples in each cluster.

Once the best configuration is selected, another model is trained with all the data from the 13 patients (without K-fold cross-validation). Given the small size of the dataset and the difficulty of obtaining more data from patients during surgery, the model was validated with the data from 2 patients undergoing a complete surgery. The chart of the real (blue continuous line) and predicted (red dashed line) ANI signals for the first patient are shown in Fig. 7. In this figure, the black dotted lines are included to represent the times with failures in ANI signal.

The charts figures are divided in different subfigures, and it is possible to appreciate that the part where the predicted signal has more errors occurs when the real ANI signal has failures (black dotted line). In Fig. 8, the charts for the second testing patient are shown, and it is possible to confirm that the model achieved good results with no dependence of the patient.

Table 4 shows different performance measures calculated with the validation data (not used in the modeling phase). These measures are the MSE, the MAE, and also the normalized MSE (NMSE) and the mean absolute percentage error (MAPE).

5 Conclusions

Very good results are achieved with the model described in this research. The main aim of the study was to predict the ANI signal. The validation tests using data from two patients during a complete surgery showed that the output of the model fits the real signal with very small error.

This model was obtained from a real dataset of 13 patients using a 10 K-fold cross-validation method. The approach is based on intelligent techniques, selecting the best algorithm configuration to train the final model. The tests performed on the hybrid intelligent model showed that the regression technique whose model leads to lowest MSE is a combination of LS-SVR and ANN with 5 and 6 neurons in the hidden layer. This model achieves an error of at

Table 1 Best MAE for each cluster

No. of Clusters	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Global model	8.2671	–	–	–	–
2	8.6724	7.8817	–	–	–
3	**10.3670**	**7.8255**	**7.9929**	–	–
4	12.3109	7.3376	7.7564	8.2283	–
5	8.4106	12.3932	7.3711	7.7617	8.1807
6	8.5501	13.0157	7.6364	6.8030	8.6106
7	7.0869	8.7982	12.9908	6.8433	7.5856
8	6.8502	8.4535	13.0756	7.5731	6.4382
9	8.3157	6.8406	8.8573	13.0720	7.5834
10	11.2199	11.0361	6.7533	8.4414	12.9735

No. of Clusters	Cluster 6	Cluster 7	Cluster 8	Cluster 9	Cluster 10
Global model	–	–	–	–	–
2	–	–	–	–	–
3	–	–	–	–	–
4	–	–	–	–	–
5	–	–	–	–	–
6	7.8270	–	–	–	–
7	8.6617	7.8577	–	–	–
8	8.6511	8.1463	8.0148	–	–
9	6.5073	8.6156	8.1677	7.9807	–
10	7.2847	6.4954	8.6857	8.0276	7.8395

Table 2 Best algorithm for each cluster

No. of Clusters	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Global model	ANN8	–	–	–	–
2	ANN7	ANN8	–	–	–
3	**LS-SVR**	**ANN5**	**ANN6**	–	–
4	LS-SVR	ANN7	ANN7	ANN7	–
5	ANN4	LS-SVR	ANN5	ANN7	ANN5
6	LS-SVR	LS-SVR	LS-SVR	LS-SVR	ANN5
7	LS-SVR	ANN2	LS-SVR	LS-SVR	LS-SVR
8	LS-SVR	LS-SVR	LS-SVR	LS-SVR	LS-SVR
9	ANN2	LS-SVR	LS-SVR	LS-SVR	LS-SVR
10	LS-SVR	ANN1	LS-SVR	ANN1	LS-SVR

No. of Clusters	Cluster 6	Cluster 7	Cluster 8	Cluster 9	Cluster 10
Global model	–	–	–	–	–
2	–	–	–	–	–
3	–	–	–	–	–
4	–	–	–	–	–
5	–	–	–	–	–
6	ANN6	–	–	–	–
7	ANN4	ANN5	–	–	–
8	ANN6	ANN3	ANN6	–	–
9	ANN2	ANN4	ANN5	ANN5	–
10	LS-SVR	LS-SVR	ANN2	ANN2	ANN4

Table 3 Hybrid MSE for each combination

No. of clusters	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Hybrid MSE	113.0991	112.4629	**111.6747**	111.8557	112.8173

No. of clusters	Cluster 6	Cluster 7	Cluster 8	Cluster 9	Cluster 10
Hybrid MSE	112.2949	112.9054	113.1251	113.2711	111.8772

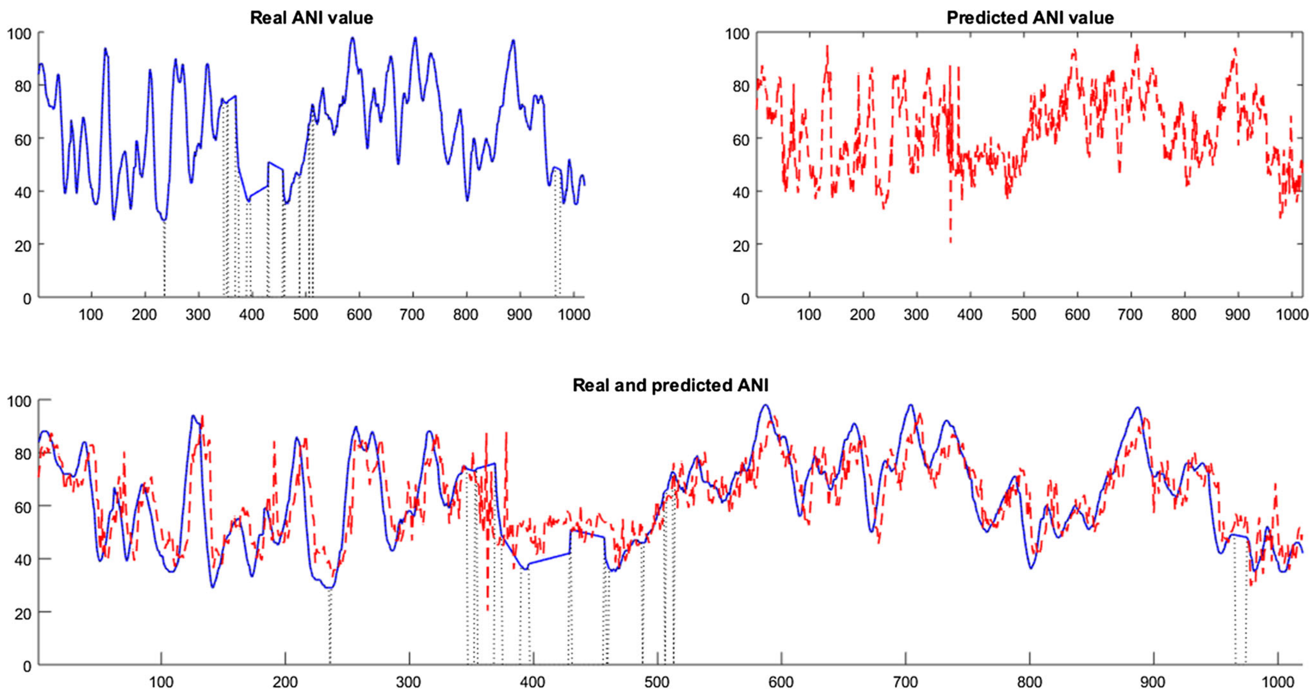


Fig. 7 All the surgery ANI signal for the first testing patient. Real (blue continuous) and predicted (red dashed) ANI signals (color figure online)

most a 10% in the prediction, which is very good performance, taking into consideration that the ANI signal range goes from 0 to 100 and the model predicts the signal with 40 s in advance.

From a clinical point of view, the proposal of this hybrid intelligence model involves different enhancements. Minto proposed a pharmacokinetic model trying to correlate the Remifentanil infusion rate to the effect site concentration in patients [35]. Pharmacodynamics models have been also proposed to relate the effect site concentration to clinical signs [36]. However, this is the first study that establishes a preliminary correlation between the Remifentanil dose and novel measure proposed as a measurement of analgesia. As a result, the Analgesia Nociception Index may be related to the supply of Remifentanil and the presence of painful stimuli considering the EMG information.

The model proposed could be applied to several systems related to different fields with the aim of improving specifications or predicting signals. It is important to emphasize that quite satisfactory results have been obtained with the approach proposed in this research.

6 Future works

The present work opens new future research lines. The most important work for accomplishing could be to increase the prediction time, with the aim to give more reaction time to the medical staff. Then, some advantages are achieving like the fitness drug delivery, problems detection in advance, deviations detection due to other clinical reasons, and so on.

From the automatic control perspective, the availability of a model makes it possible to test new control strategies for the closed-loop of analgesia. Different studies have concluded that closed-loop systems for hypnotic drug supply shows better performance than manual administration [37]. Specifically, the application of predictive control

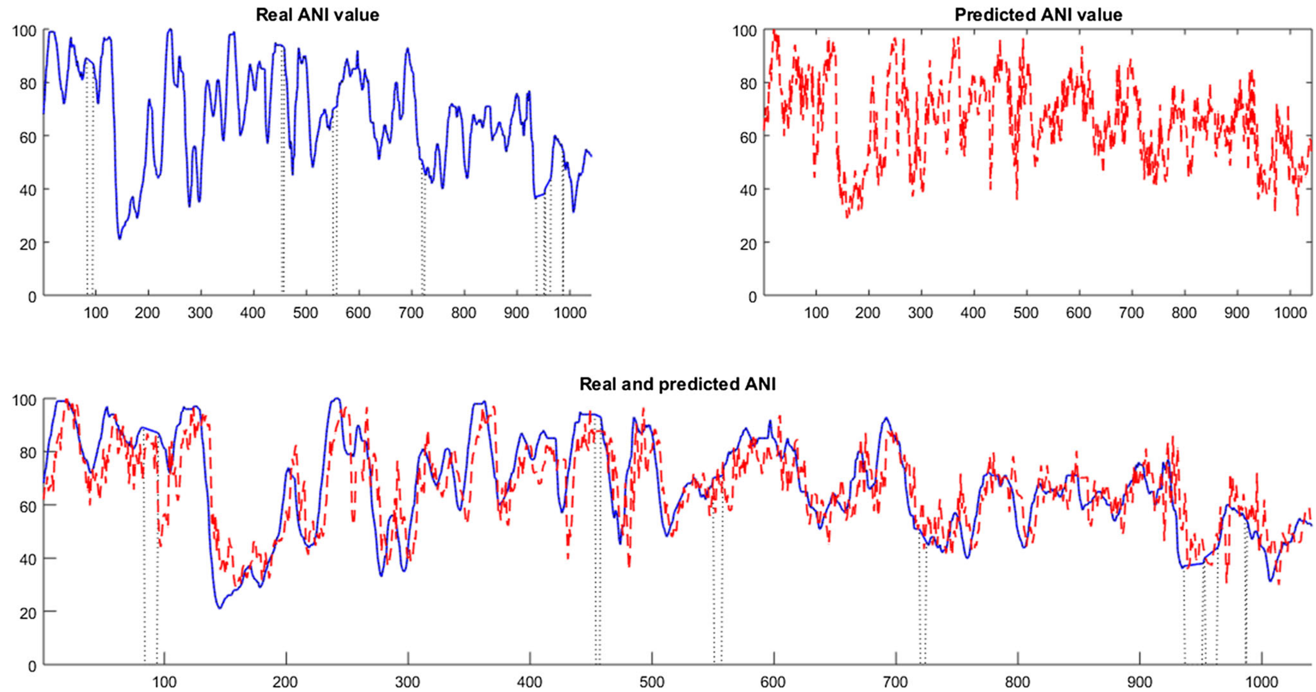


Fig. 8 All the surgery ANI signal for the second testing patient. Real (blue continuous) and predicted (red dashed) ANI signals (color figure online)

Table 4 Validation performance measures

Validation patient	MSE	MAE	NMSE	MAPE (%)
First patient	116.6117	8.2676	0.5672	14.9489
Second patient	131.7943	8.8820	0.5570	14.6742

strategies has been applied to the anesthetic scenario due to the results obtained [2, 38]. The model proposed in this study is able to predict the ANI response for a wide time interval. As a result, model-based predictive controllers could be also applied.

It could be developed an ANI sensor fault detection based on the deviation of the real signal with the prediction. With the same principle, it could be possible to detect patient problems when there are the above deviations and the sensor is not the problem reason.

Another possible research line is to include more monitored variables during the surgery, with the aim to increase the accurate, and to explore possible interactions between the different administrated drugs. As future works, the possibility of obtaining a wider dataset could enable the authors to validate the final model using nested cross-validation.

Under a more general point of view, the proposed method can be extended to other indicators for health monitoring so that quality of patient monitoring will be increased.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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