Electromyogram prediction during anesthesia by using a hybrid intelligent model

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Abstract In the search for new and more efficient ways to administer drugs, clinicians are turning to engineering tools. The availability of these models to predict physiological variables are a significant factor. A model is set out in this research to predict the EMG (Electromyogram) signal during surgery, in patients under general anaesthesia. This prediction hinges on the Bispectral Index™(BIS) and the infusion rate of the drug Propofol. The results of the research are very satisfactory, with error values of less than 0.67 (for a Normalized Mean Squared Error). A hybrid intelligent model is used which combines both clustering and regression algorithms. The resulting model is validated and trained using real data.

Keywords EMG, BIS™, Clustering, MLP, SVM

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1 Introduction

Interest in the application of advanced computing engineering techniques has intensified considerably in recent years (Lemaître et al. 2015). A number of different approaches stand out. For instance, the enormous rise in the digitalization of information in this field has brought about the use of big data tools for extracting information and generating inferences as to its relevance. Artificial intelligence (AI) techniques have given rise to tools for the planning and optimization of resources in healthcare systems. At the same time, the role of AI techniques is becoming widely extended in different clinical procedures and applications. One example is the use of automatic devices for delivering drugs during general anaesthesia, which is of great interest in anaesthesiology. Numerous advanced commercial devices for the infusion of drugs are based predicting the patient's reactions during anaesthesia to establish the correct dosage of the drugs. Thus, the availability of reliable predictions for the evolution of the patient's variables is essential to establish the correct dosage.

It is necessary to regulate three main variables during surgery under general anaesthesia: hypnosis, analgesia, and neuromuscular blockade. A different drug is used for each of these variables. In Totally IntraVenous Anesthesia (TIVA) Propofol is the drug of choice (for hypnosis), Remifentanil (for analgesia) and Rocuronium (for muscular relaxation). For more information on the control of hypnosis (Hemmerling et al. 2013; Méndez et al. 2016; Reboso et al. 2012; Jove et al. 2018b; Casteleiro-Roca et al. 2015b, 2018; Jove et al. 2018c). The crucial point of these aspects in the control of hypnosis lies in the fact that there are different robust indices available for measuring the profundity of the hypnosis. BIS™is one of the most widely accepted indices of them all as set out in (Sigl and Chamoun 1994). This index is obtained through the frequency processing of the ElectroEncephaloGram (EEG) signal. BIS™is dimensionless and varies from between 100 (awake) and 0 (no electrical activity in the brain), and a BIS™target of 50 is usually considered appropriate for general anaesthesia.

The control of analgesia is still at a less advanced stage of development, as finding a reliable pain assessment index is difficult. On the other hand, EMG is a reliable and safe way of measuring the neuromuscular blockade in a patient. An improper regulation of this variable gives rise to undesirable consequences in the surgery process (patient movements, invalid measurements of the signal, etc.). Consequently, it is essential to develop a monitoring system that can predict the EMG response of the patient both reliably and accurately.

This work proposes the application of intelligent techniques for predicting the degree of muscular relaxation (EMG) from information gathered during surgery. In some previous work, like (Cui et al. 2018), the authors try to improve the prediction accuracy in medical field like epileptic seizure using the EEG signal. Standard regression methods are usually based on Multiple Regression Analysis (MRA) techniques, which are widespread in applications in different fields (Calvo-Rolle et al. 2014, 2015; Ghanghermeh et al. 2013; Vega Vega et al. 2018; Manuel Vilar-Martinez et al. 2014; Casteleiro-Roca et al. 2019a). However, there are limitations to these methods which impede their level of performance (Calvo-Rolle et al. 2015; Jove et al. 2018a,d; Quintián et al. 2016; Casteleiro-Roca et al. 2019b; Aláiz-Moretón et al. 2019; González Gutiérrez et al. 2018). Numerous new proposals, both hybrid or straightforward, based on Soft Computing techniques have been developed to progress this situation. As is shown in (Calvo-Rolle et al. 2013, 2011; Casteleiro-Roca et al. 2015a; de Cos et al. 2008; de Cos Juez et al. 2010; Ferreiro García et al. 2014, 2013; García Nieto et al. 2012; Ghanghermeh et al. 2013; Machon-Gonzalez et al. 2010; Quintián et al. 2014; Quintián-Pardo et al. 2012; Bursa et al. 2015) these techniques have made great strides in the aforementioned areas. Moreover, intelligent techniques are used previously in different works like (Vrbaški et al. 2019) and (Jiang et al. 2018) to increase the model accuracy used in clinical diagnosis (Artificial Neural Networks) and composition of marine water (Support Vector Regression).

The main objective of this study is to set up a hybrid model for predicting the EMG signal from the BIS™signal and the infusion rate of the propofol. The K-means clustering algorithm is used to develop this model by creating groups of data with a similar behaviour. After that, several regression methods are verified for each group to select the most optimal method based on the lowest Mean Squared Error (MSE) achieved.

This paper is structured as follows. After this section, the BIS™case study is set out, followed by the approach of the model and the algorithms considered. The best configuration established by the hybrid model is detailed in the results section. Finally, our conclusions and future work are presented.

2 Case of study

When a patient is undergoing surgery with general anesthesia, a clinical protocol should be followed to achieve satisfactory performance. Concerning the protocol, a standard monitoring routine was used, including pulse, oximetry, ECG and non-invasive blood pressure. A venous catheter with an antireflux valve was placed in one arm. An initial bolus of rocuronium is administered at the beginning of surgery to achieve muscular blockade. New rocuronium bolus doses are applied in case of signs of muscular activity is observed in the patient. The administration of propofol was done in closed-loop to maintain a BIS™target of 50 (Pérez et al. 2011; Sánchez et al. 2009). The protocol for the administration of remifentanil consists of an infusion of 0.25 mcg/kg/min just before induction and modified in accordance with the requirements of the analgesia. The clinicians are instructed to maintain this dosage unless the hemodynamic situation of the patient gives rise to an adjustment in the remifentanil. Thus, the prevention of unexpected painful stimuli or an insufficient level of analgesia which might affect the stability of BIS™is achieved. The infusion of propofol and remifentanil ceases at the end of the surgery, and the patient recovers.

The arrangement of the equipment in the operating room is detailed in figure 1. As can be seen, the main elements are, the BIS™monitor, infusion pumps, and a laptop PC on which the main monitoring program runs. Communications with the devices is carried out using RS-232 interfaces.

As already stated, this work focuses on the modelling of EMG in patients under general anaesthesia. Depending on the protocol followed, the EMG signal is predicted in accordance with both the dose of Propofol and the BIS™signal. The scheme of the input/output is detailed in figure 2.

Only ASA I and II patients undergoing general anaesthesia are considered in thus study. The American Society of Anaesthesiologists define the ASA score to

Fig. 1 Case of study. The operating theater

Fig. 2 Case of study. The administration of the propofol is considered the input, together with the signal obtained by the BIS™monitor; the EMG signal will be the predicted output of the model

classify the physical status of the patients. A normal healthy patient corresponds to ASA I, while ASA II patients are those with a mild systemic disease. ASA $\geq$ III are patients with a psychiatric or neurological disorder, or a patient with a pacemaker. Demographic data such as age, gender, build, etc. are taken into account in the data gathered from the patients.

3 Model approach

The scheme defined for the model approach is detailed in Figure 3. Taking the behaviour of the system and the tests carried out into account, it is possible to segment the dataset into several ranges. As a result, several clusters are created and a regression model is implemented for the single output for each one. As shown in figure 3, the overall model has two inputs (the *Propofol* - drug and the Bispectral index *BIS*™) and one output (Electromyogram signal EMG). The cluster selector block connects the selected models with the output. Only the best model is implemented in each figure cluster block. The cluster for a specific input is selected based on the Euclidean distance between the input and the centroids in each cluster.

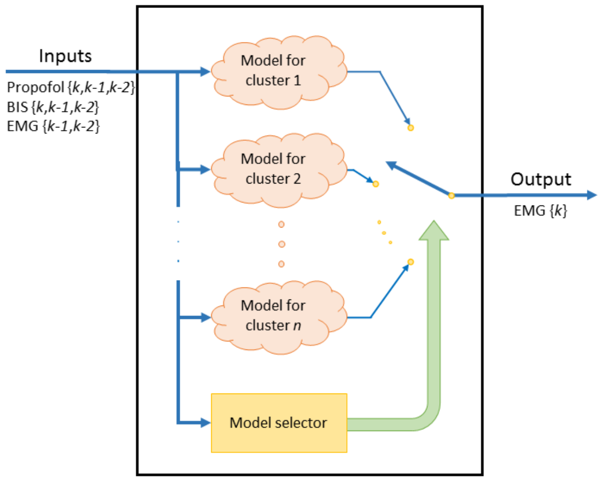

Fig. 3 Model approach

The modelling process is shown in Figure 4. Despite the figure only detailing the data division for training and testing, the dataset has been processed using cross-validation (*k-fold*) to ensure the best results for the chosen model. The *k-fold* model validation (shown in figure 5) provides a more real performance and a better generalization (Bishop 2006).

3.1 The Obtaining and Description of the Dataset

The dataset has been obtained from several patients undergoing general anaesthesia using Propofol during surgery. The three variables used in this research (BIS™, EMG and the Propofol infusion rate) have been monitored during the surgery. A preconditioning stage was considered for the BIS™and EMG. The dataset is made up of the data from a total of 15 patients. As the signals vary slowly during the acquisition phase, a low pass filter was implemented to avoid measurement

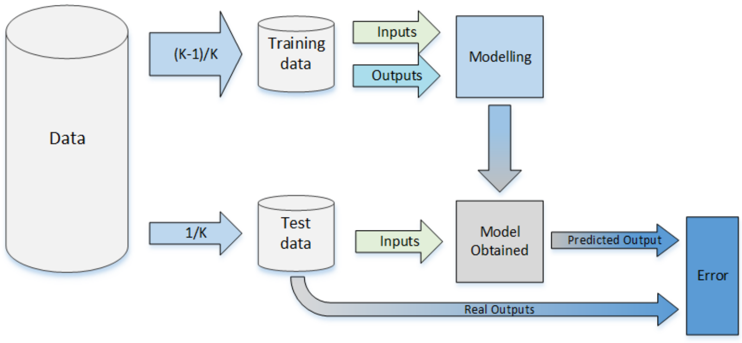

Fig. 4 Modeling process

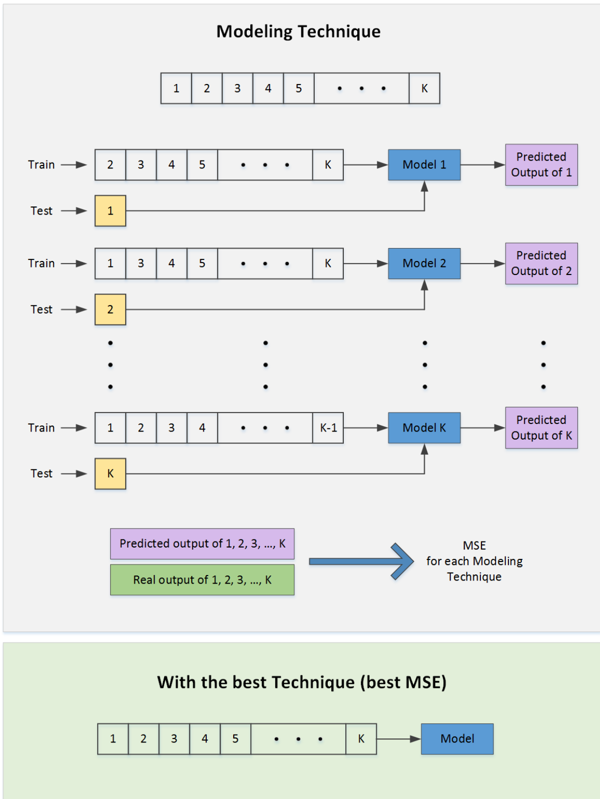

Fig. 5 K-fold Model validation

noise. Neither the induction phase nor the recovery phase were considered in this study. Consequently, the results are only valid for predicting the EMG during the surgery itself. Under the aforementioned conditions, the dataset used contains 16668 samples.

Furthermore, all of the data from two patients were isolated from the training process, in order to carry out the validation of the hybrid. This data was then used with the different hybrid configurations to select the one which provided the best results.

3.2 Used Techniques

Two different types of technique were used in this research. Firstly, from the point of view of the creation of the model, a clustering technique was used to segment the data. In this case the K-means algorithm is selected, and is detailed in the Clustering Techniques section. After the clustering, three different regression algorithms were used; the Polynomial regression, Artificial Neural Networks and Support Vector Regression. All of the clustering algorithms are explained in the Regression Techniques section. The techniques tested in this study to establish the best model are described below.

3.2.1 Data Clustering. The K-means algorithm Clustering Technique

Clustering is an unsupervised technique for grouping data together in which their similarity is measured (Qin and Suganthan 2005; Ye and Xiong 2007). The objective of clustering algorithms is to organize unlabeled feature vectors into clusters or groups, so that the samples within a cluster are similar to each other (Kaski et al. 2005). The K-means algorithm is a partitional clustering algorithm usually used with the square-error criterion, which minimizes the error function shown in equation 1.

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

The final clustering will depend on both the initial cluster centroids and the value of K (the number of clusters). Selecting the K value is the most critical choice as it requires specific prior knowledge of the number of clusters found in the data, which is not an easy task. The K-means partitional clustering algorithm is computationally very effective and works especially well if the data are close to its cluster, and the cluster is hyperspherical in shape and well-separated in the hyperspace.

3.2.2 Regression Techniques

Polynomial Regression A polynomial regression model may generally also be defined as a linear summation of basis functions (Bishop 2006; Casteleiro-Roca et al. 2014; Heiberger and Neuwirth 2009; Wu 2007; Zhang and Chan 2011). The number of basis functions depends on the number of inputs in the model, together with the degree of the polynomial used.

With a degree 1, the linear summation could be defined as that detailed in equation 2 (for two inputs). The model becomes more complex as the degree increases. Equation 3 details a second polynomial degree.

$$F(x) = a_0 + a_1x_1 + a_2x_2 \tag{2}$$

$$F(x) = a_0 + a_1x_1 + a_2x_2 + a_3x_1x_2 + a_4x_1^2 + a_5x_2^2 \tag{3}$$

Artificial Neural Networks (ANN): MultiLayer Perceptron (MLP) A multilayer perceptron is a feedforward artificial neural network (Wasserman 1993; Zeng and Wang 2010). It is one of the most commom ANNs because of its robustness and relatively simple structure. However, the architecture of the ANN must be chosen well in order to obtain good results. The MLP is made up of one input layer, one or more hidden layers and one output layer.

Each layer is made up of neurons, with a specific activation function. In the most common configuration, all of the neurons from a layer have the same activation function. This function might be: Step, Linear, Log-sigmoid or Tan-sigmoid. Equation 4 details the Tan-sigmoid function. All of the layers in the MLP have weighted connections between the neurons of each layer.

$$F(t) = \frac{e^t - e^{-t}}{e^t + e^{-t}} \tag{4}$$

It is possible to define the output of an MLP as shown in equation 5 (Rynkiewicz 2012).

$$f_\theta(x) = \beta + \sum_{i=1}^{k} a_i \phi(w_i^T x + b_i) \tag{5}$$

where:
$x = (x(1), ..., x(d))^T \in \Re^d$ is the vector of inputs
k is the number of hidden layers
ϕ is a bounded transfer function
$\theta = (\beta, a_1, ..., a_k, b_1, ..., b_k, w_{11}, ..., w_{kd})$ is the parameter vector of the model
$w_i = (w_{i1}, ..., w_{id})^T \in \Re^d$ is the parameter vector for the hidden unit i

Support Vector Regression (SVR), Least Square Support Vector Regression (LS-SVR) Support Vector Regression is a modification of the algorithm of the Support Vector Machines (SVM) for classification. The basic idea of SVR is to map the data into a high-dimensional feature space F via a non-linear mapping and then apply linear regression in the space (Cristianini and Shawe-Taylor 2000; Steinwart and Christmann 2008; Vapnik 1995).

The Least Square formulation of the SVM is called the LS-SVM. An approximation of the solution is obtained by solving a series of linear equations. It is comparable to the SVM as regards its generalization performance (Suykens and Vandewalle 1999; Wang et al. 2012). The application of the LS-SVM to regression is known as LS-SVR (Guo et al. 2012; Wang and Wu 2012). In the LS-SVR, the insensitive loss function is replaced by a standard squared loss function, which constructs the Lagrangian by solving a linear KarushKuhn-Tucker (Equation 6).

$$\begin{bmatrix} 0 & I_n^T \\ I_n & K + \gamma_{-1} I \end{bmatrix} \begin{bmatrix} b_0 \\ b \end{bmatrix} = \begin{bmatrix} 0 \\ y \end{bmatrix} \tag{6}$$

where:
I_n is a vector of n ones
T means transpose of a matrix or vector
γ a weight vector
b regression vector
b_0 is the model offset

Only two parameters (γ, σ) are necessary in the LS-SVR, in which σ is the width of the kernel used (Wang and Wu 2012).

4 Results

The current value of the BIS™signal together with the Propofol infusion rate (the flow rate of the drug) were used to obtain the model. Two previous values of the inputs were involved in training the models to include the dynamic of the modelled system. The prior values of the desired output (the EMG signal) were also added.

The clustering results are set out in Table 1 It details the number of samples in each cluster that would be used in the subsequent training phase (regression). As the K-means performance is dependent on the initial state, the clustering process was repeated 20 times using a random initialization. Finally, the best result was saved. The configuration ranged from 2 to 10 clusters with the objective of creating different topologies (the overall model was also taken into account). Those clusters made up of less than 15 samples were not taken into account because it is not possible to generalize the results obtained. Because of this restriction, only the last 3 clusters have been used. If the Dataset had been divided into more clusters, one of them would have had less than fifteen samples.

	Cl-1	Cl-2	Cl-3	Cl-4	Cl-5	Cl-6	Cl-7	Cl-8	Cl-9	Cl-10
Global	16,668									
Hybrid 2	1,953	14,715								
Hybrid 3	1,777	7,363	7,528							
Hybrid 4	113	1,707	7,283	7,565						
Hybrid 5	104	193	1,499	7,361	7,511					
Hybrid 6	104	193	1,450	3,743	4,677	6,501				
Hybrid 7	104	126	193	1,433	3,629	5,176	6,007			
Hybrid 8	72	94	192	1,396	1,857	2,657	5,151	5,249		
Hybrid 9	72	94	117	192	1,368	1,576	3,195	4,707	5,347	
Hybrid 10	34	64	77	192	501	1,184	1,522	3,330	4,875	4,889

Table 1 Number of samples in each group

The MLP-ANN regression algorithm was trained for different configurations. Each one always had one hidden layer, however the number of neurons in the hidden layer varied from 1 to 15. The activation function of these neurons was tan-sigmoid for all tests. The output layer neuron had a linear activation function. The Levenberg-Marquardt training algorithm used with gradient descent as a learning algorithm. The performance function was set to mean squared error.

The LS-SVR was trained with self-tuning implemented with the toolbox for MatLab developed by KULeuven-ESAT-SCD. The kernel of the model was set to the Radial Basis Function (RBF), and 'Function Estimation' was the type to carry out the regression. The optimization function is 'simplex' and the cost-criterion is 'leaveoneoutlssvm' with 'mse' as a performance function.

For Polynomial regression, the order of the polynomial trained varies from 1^{st} to 3^{th} order.

In each cluster, the models were trained using 10 *k-fold* cross-validation to calculate the MSE. The tables 2 and 3 show the results of the regression phase. It is essential to clarify that these are the results of the regression for each clusters, not the results for the overall hybrid model.

	Cl-1	Cl-2	Cl-3	Cl-4	Cl-5	Cl-6	Cl-7	Cl-8	Cl-9	Cl-10
Global	ANN-11									
Hybrid 2	ANN-12	ANN-11								
Hybrid 3	ANN-13	ANN-15	ANN-11							
Hybrid 4	ANN-14	ANN-11	ANN-12	ANN-12						
Hybrid 5	ANN-15	ANN-13	ANN-14	ANN-11	ANN-11					
Hybrid 6	ANN-15	ANN-13	ANN-15	ANN-11	ANN-11	ANN-15				
Hybrid 7	ANN-15	ANN-15	ANN-12	ANN-12	ANN-11	ANN-11	ANN-11			
Hybrid 8	ANN-12	ANN-15	ANN-12	ANN-14	ANN-12	ANN-11	ANN-14	ANN-12		
Hybrid 9	ANN-15	ANN-15	ANN-11	ANN-14	ANN-11	ANN-12	ANN-11	ANN-14	ANN-12	
Hybrid 10	ANN-14	ANN-11	ANN-14	ANN-13	ANN-12	ANN-15	ANN-14	ANN-11	ANN-12	ANN-13

Table 2 Best regression algorithm for each cluster

	Cl-1	Cl-2	Cl-3	Cl-4	Cl-5	Cl-6	Cl-7	Cl-8	Cl-9	Cl-10
Global	17.0269									
Hybrid 2	85.8454	73.3045								
Hybrid 3	161.7695	916.4728	17.2438							
Hybrid 4	115,620.8594	127.242	404.5852	34.2655						
Hybrid 5	31,453.9693	139.0142	2,771.3183	76.4582	9.3726					
Hybrid 6	31,084.3591	346.5657	2,328.3394	88.6406	6.9587	240.0986				
Hybrid 7	188,504.7883	25,694.4674	323.9173	1,755.4830	19.4460	62.8884	93.1562			
Hybrid 8	30.7835	89,278.5938	175.0898	2,598.5439	1,059.9914	18.8639	42.8423	16.4565		
Hybrid 9	104.3152	31,522.9476	7,844.2444	179.8004	1,042.5252	13.4443	5.0633	11.049	50.1531	
Hybrid 10	91.9125	23,616.8478	42.0771	357.5190	3,061.8144	1,800.4709	111.1007	4.7231	16.6663	86.4915

Table 3 Mean Squared Error in the regression phase for each cluster

Once the best regression technique is selected, all of the the training data from each cluster is used to train a local model another time with the best algorithm using all of the cluster data without using *k-fold* cross validation. Then, the validation data that was isolated from the training data at the beginning of the modelling phase is then used to select the best configuration of the hybrid model. The validation data was used as the input for the different hybrid models. Since the hybrid configuration has still not been selected, the inputs are the same for the 10 models (the overall and the 9 hybrid ones), using the Euclidean distance to choose the local model for each input, and the specific regression model for each cluster.

The Table 4 shows the values of the Normalized Mean Squared Error for the different configurations of the entire model. The minimum is achieved using a hybrid configuration with two local models. The Table 5 details the different error measurements for the best configuration. The selected values are the Mean Absolute Error - MAE, Mean Absolute Percentage Error - MAPE, Mean Squared Error - MSE, and Normalize Mean Squared Error - NMSE. As the lowest errors are came about from two local models, the final hybrid configuration divides the data into two clusters.

	NMSE
Global	0.8974
Hybrid 2	**0.6676**
Hybrid 3	1.0142
Hybrid 4	0.736
Hybrid 5	0.9711
Hybrid 6	0.9999
Hybrid 7	0.9801
Hybrid 8	0.9847
Hybrid 9	0.9552
Hybrid 10	1.0027

Table 4 Normalized Mean Squared Error (NMSE) for the different configurations

	MAE	MAPE	MSE	NMSE
Hybrid 2	1.6954	11.6119	97.5768	0.6676

Table 5 Mean Absolute Error - MAE, Mean Absolute Percentage Error - MAPE, Mean Squared Error - MSE, and Normalize Mean Squared Error - NMSE

The validation test (Figure 6) shows a representation of the validation data on a time scale. It is possible to appreciate the accuracy of the model to the predicted data (the green dots in the Figure 6 are very close to the real data (blue dots).

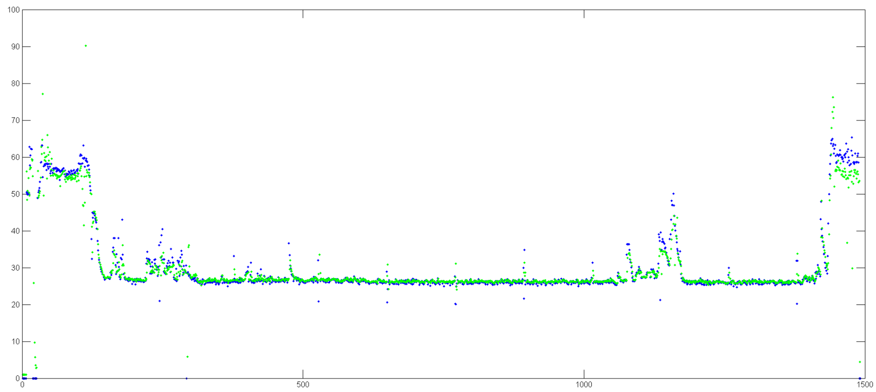

Fig. 6 Test with the validation data

5 Conclusions and future works

This study provides a precise way of modelling the EMG. The established model predicts the EMG from the BIS™signal and the quantity of the drug Propofol given to the patient.

This model was obtained from a real dataset. The approach is based on a hybrid intelligent system, by combining different regression techniques in local models. After numerous tests, an analysis of the results shows that the best model configuration has 2 clusters. The regression techniques used in the clusters were Artificial Neural Networks with one hidden layer and 11 and 12 neurons in it. The best average MAE obtained using this configuration was 1.6954.

This analysis could be applied to several different systems with the objective of improving other specifications such as: efficiency, performance and features of the material obtained. It is important to emphasize that the results obtained using the approach proposed in this research are entirely satisfactory.

As future works, the authors will study another indices used in surgery and they aim to predict the signals at an earlier stage (some instants later). This capability would allow more time for the anaesthetist is attend the patient, to react when a change in the signals is predicted by the model.

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