Proceedings of the
44th IEEE Conference on Decision and Control, and
the European Control Conference 2005
Seville, Spain, December 12-15, 2005

Comparison of Neural Networks, Fuzzy and Stochastic Prediction Models for return of consciousness after general anesthesia

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Abstract— **This paper presents three modeling techniques to predict return of consciousness (ROC) after general anesthesia, considering the effect concentration of the anesthetic drug at awakening. First, several clinical variables were statistically analysed to determine their correlation with the awakening concentration. The anesthetic and the analgesic mean dose during surgery, and the age of the patient, proved to have significantly high correlation coefficients. Variables like the mean bispectral index value during surgery, duration of surgery did not present a statistical relation with ROC. Stochastic regression models were built using the variables with higher correlation. Secondly, fuzzy models were built using an Adaptive Network-Based Fuzzy Inference System (ANFIS) also relating different sets of variables. Thirdly, radial basis function (RBF) neural networks were trained relating different sets of clinical values with the anesthetic drug effect concentration at awakening. Clinical data was used to train and test the models. The stochastic models and the fuzzy models proved to have good prediction properties. The RBF network models were more biased towards the training set. The best balanced performance was achieved with the fuzzy models.**

I. INTRODUCTION

Anesthesia can be defined as the lack of response and recall to noxious stimuli. This complex branch of the medical area is divided into three components: muscle relaxation, unconsciousness (depth of anesthesia) and analgesia. Anesthesia involves the use of three drugs, a muscle relaxant, an anesthetic (hypnotic) and an analgesic. However, the muscle relaxant will not be considered in this research, since it has no influence on the degree of hypnosis, which is the main concern in the operating theatre. The analgesic drug is of more importance since it affects the pharmacodynamics of the anesthetic drug and there is no clear indicator of the degree of pain. The analgesic and anesthetic drugs are interconnected, since they interact with each other so as to achieve an adequate level of depth of anesthesia (DOA) and analgesia [1]. The bispectral index of the EEG (BIS) is used as an indicator of the level of DOA, measuring the degree of depression in the central nervous system [2], [3]. Overall, general anesthesia consists of both loss of consciousness through the action of anesthetic drugs, and the inhibition of noxious stimuli reaching the brain through the acting of the analgesics. The intravenous anesthetic drug propofol is used in combination with different opioids. In this article, only one and new analgesic is considered: remifentanil.

The anesthesiologist is not only concern with obtaining a rapid and safe level of DOA during the induction phase, but also with providing a comfortable and precise return to consciousness (ROC) after surgery [4]. During surgery the drugs are manually controlled to maintain a stable DOA according to the patients' needs and surgical stimulation. The type of surgery and the patients' variability have a major importance in the decision of change in drug dosage during maintenance of anesthesia. However, one question remains the same for all patients: how fast will he/she wake up? Usually the ROC is controlled by trial and error that could lead to critical cases, where the patient awakes too soon with the possibility of trauma. In addition, the reverse situation could occur and lead to a long and hard recovery with the expense of resources. Researchers have tried to control the drugs administration and combination during surgery in order to allow for a fast ROC [5], [6]. From a clinical practical point of view, it would be very helpful if one could predict the time of ROC at the end of surgery. The objective of this research work was to estimate the propofol effect concentration at ROC, using clinical data gathered during induction and maintenance of anesthesia. If the concentration of drug at ROC occurs can be estimated, then time to ROC can be predicted from the drug elimination speed.

In this article, different prediction models were developed in order to predict the patients' ROC. Statistical correlation analysis was performed to determine the clinical variables related with the propofol concentration at ROC. Stochastic regression models were built relating the variables with high correlation and the concentration at ROC. Takagi-Sugeno-Kang (TSK) fuzzy models were developed with the same objective, but using a combination of clinical variables. An Adaptive Network-Fuzzy Inference System (ANFIS) is used to model the parameters of the TSK models. Radial Basis Function (RBF) neural networks were also built relating different sets of clinical values and the concentration at ROC.

II. CLINICAL DATA

Data collected during 20 surgical interventions were used to model a typical patient's ROC, using the effect concentration of propofol. The level of DOA was manually controlled by the anesthesiologist using as reference the patient's vital signs and BIS monitor. The following clinical signs were recorded during the surgery every 5 seconds: BIS, infusion

This work was supported by the Portuguese Foundation for Science and Technology, Lisboa, Portugal

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rate of propofol and remifentanil. The infusion rates were used to calculate the plasma and effect concentration of both drugs, as described in the following sections. The 20 patients studied were ASA (physical state score of the American Society of Anesthesiologists) 1/2, 45±17 years, 66±10 kg, 162±8 cm, 13 female. The data from 16 patients was used to develop the prediction models and the remaining 4 patients were used for testing.

A. Pharmacokinetic model

The pharmacokinetic models of the two drugs were constructed using a 3-compartment model. The pharmacokinetic parameters were gathered from the literature, these parameters reflect the age, gender, weight and height of the patients. For propofol, the parameters from Schnider [7] were used, whereas for remifentanil, the parameters from Minto [8] were used.

B. Effect compartment

The effect compartment is a hypothetical compartment describing the delay between the plasma concentration and the effect concentration.The pharmacodynamic parameters k_{e0} used for propofol and remifentanil, were described by Schnider [9] and Minto [10].

III. Methods

Three different structures of models for predicting the propofol effect concentration at ROC, were tested in this article.

A. Stochastic models

Correlation analysis was used to determine the most useful and informative clinical variables related with the propofol effect concentration at ROC. However, one usually wants to be more explicit about the form of the relationship between two variables. Regression analysis is a statistical technique for modelling and investigating the relationship between two or more variables [11]. The objective is to determine the relationship between a single regression variable *x* and a response variable *y*.

B. Fuzzy models

A fuzzy inference system was used to model the propofol effect concentration at ROC into a fuzzy Takagi-Sugeno-Kang (TSK) model [12]. The TSK fuzzy system is constructed from the following rules:

$$\begin{array}{c} If\ x_1\ is\ C_1^l\ and\ ...\ and\ x_n\ is\ C_n^l\ then \\ y^l = c_0^l + c_1^l x_1 + \ldots + c_n^l x_n \end{array} \quad (1)$$

where C_i^l are fuzzy sets, c_i^l are constants, and $l = 1, ..m$. That is, the antecedent parts of the rules is the same as in the ordinary fuzzy IF-THEN rules, but the consequent parts are linear combinations of the input variables. Given an input x= $(x_1, \ldots, x_n) \in U \subset R^n$, the output $f(x) \in V \subset R$ of the TSK fuzzy model is computed as the weighted average of the y^l's, (2).

$$f(x) = \frac{\sum_{l=1}^{m} y^l w^l}{\sum_{l=1}^{m} w^l} \quad (2)$$

$$w^l = \prod_{i=1}^{n} \mu_{C_i^l}(x_i) \quad (3)$$

where $\mu_{C_i^l}(x_i)$ is the membership function of x_i in the fuzzy set C_i^l.
The ANFIS identifies a set of parameters through a hybrid learning rule combining the back-propagation gradient-descent and the least squares method. This was used to determine the parameters for the fuzzy TSK model [13]. The ANFIS system was built through the fuzzy toolbox available for MATLAB. The following properties were used for the models:a grid partition or subtractive clustering on the training data to generate the initial fuzzy inference system (FIS) structure; Gaussian input membership functions; hybrid optimisation method.

C. Radial basis neural networks

A radial basis function network (RBF) is a feedfoward network with a single hidden layer and radially symmetric activation functions, in this work Gaussian activation functions were used, as in (4):

$$R(x, s) = e^{-\frac{1}{2} x^T s^{-1} x} \quad (4)$$

where *s* is a positive definite matrix of parameters. The hidden layer consist of neurons described by (5):

$$z_j = R(u - m_j, s_j) \quad (5)$$

where m_j, s_j denote vectors of parameters of j-th neuron, and *u* is the input vector. Finally, the input-output function represented by the network is:

$$y = \sum_{j=1}^{Q} a_j R(u - m_j, s_j) \quad (6)$$

where a_j are weights of the output neuron (*Q*=16 in this study). RBF networks are universal approximators [14]. The RBF network was built through the neural networks toolbox available for MATLAB. The RBF uses as inputs a set of clinical parameters and as output the propofol effect concentration at ROC.

IV. Results

The results are presented in four steps. First, the correlation analysis in search for informative variables with respect to the propofol concentration at ROC. Second, the structure and results of the stochastic models. Thirdly, the structure and results of the fuzzy TSK models. Finally, the structure and results of the RBF neural networks. The data was divided into training and testing data sets. These sets are constituted by the data of 16 and 4 patients, respectively.

TABLE I

CORRELATION COEFFICIENTS BETWEEN SEVERAL CLINICAL VARIABLES DURING SURGERY AND THE PROPOFOL EFFECT CONCENTRATION AT ROC.

Variable	Correlation coefficient	Statistical *p-value*
BIS minimum at induction	0.073	0.788
Time to BIS minimum at induction (min)	0.282	0.29
Mean BIS during surgery	0.012	0.963
Mean propofol dose during surgery (mg/kg/min)	0.504	0.046
Mean remifentanil dose during surgery (μg/kg/min)	0.688	0.003
Duration of surgery (min)	0.262	0.326
Age	0.691	0.003
Lean body mass (LBM)	0.192	0.486

A. Correlation analysis

A set of clinical variables were analysed for correlation with the propofol effect concentration at ROC. Table 1 shows the correlation coefficients for: minimum BIS value at induction, time to reach minimum BIS value at induction, mean BIS value during surgery, propofol mean dose during surgery, remifentanil mean dose during surgery, duration of surgery, patient age and patient lean body mass (LBM). These clinical variables were chosen for several reasons. The BIS minimum value at induction represents the maximum initial central nervous system depression (considering that all patients received the same initial target concentration of 5 $\mu g/ml$). The time to reach the minimum BIS value at induction represents the speed of the initial response. These two clinical variables are related to the patient's initial response and were investigated because of the possible relation between the initial response of the patient (loss of consciousness) with his/her recovery characteristics (ROC). The propofol and remifentanil mean dose during surgery represents the dose requirements of each patient (inter variability) to maintain a stable DOA. The duration of surgery was used to evaluate if the elimination of propofol was influenced by the duration of infusion. The patient's age and LBM also represent the patient's individual parameters and may have influence on the drugs clearance and distribution. All analysed variables are available to the anaesthetist before the recovery phase and, therefore, can be used to predict.

Analysing Table I, one can see that only the mean propofol dose and the mean remifentanil dose during surgery, and the age of the patient had high correlation coefficients with statistical significance ($p<0.05$).

B. Stochastic models

Regression models were obtained for the three variables with significant correlation with the propofol concentration at ROC using the data from 16 patients (training data set). Equation Eq. (7) presents the stochastic model for the propofol concentration at ROC (y) using the propofol mean dose during surgery (x), this model shall be referred to as Stochastic Model 1.

$$y = 9.9556x + 0.1451 \tag{7}$$

Eq. (8) presents the stochastic model for the propofol concentration at ROC (y) using the remifentanil mean dose during surgery (x), this model shall be referred to as Stochastic Model 2.

$$y = 7.6479x + 0.4164 \tag{8}$$

Eq. (9) presents the stochastic model for the propofol concentration at ROC (y) using the age of the patient (x), this model shall be referred to as Stochastic Model 3.

$$y = -0.0204x + 2.2999 \tag{9}$$

A statistical *t-test* was used to determine the level of confidence in the slope of each regression model. The slope of Stochastic Model 1 was proved to be significantly positive ($p<0.025$). The slope of Stochastic Model 2 was proved to be significantly positive ($p<0.01$). The slope of Stochastic Model 3 was proved to be significantly negative ($p<0.01$).

The mean absolute error was determined for the results of the models on the training and testing data set, i.e. the 16 patients used to develop the models and the remaining 4 patients, respectively (Table II).

TABLE II

MEAN ABSOLUTE ERROR OF THE STOCHASTIC MODELS FOR THE PROPOFOL EFFECT CONCENTRATION AT ROC ON THE TRAINING AND TESTING DATA SETS.

Model	Training data set	Testing data set
Stochastic Model 1	0.35	0.25
Stochastic Model 2	0.28	0.27
Stochastic Model 3	0.29	0.32

The testing errors of the three stochastic models proved to be statistically different (ANOVA $p<0.001$). Fig. 1 shows the testing error variability for the three stochastic models. The testing errors of Stochastic Model 1 and Stochastic Model 2 have statistically equal means (*t-test* p=0.507). The mean of the testing error for Stochastic Model 3 is statistically different from zero (*t-test* $p<0.025$). The Stochastic Model 1 has the smallest testing error and the highest training error. However, Stochastic Model 2 has a balanced performance in both sets of data. Fig. 2 shows the results of the training and testing data set for Stochastic Model 2.

C. Fuzzy models

Six different sets of the clinical variables evaluated for statistical correlation were used as inputs to TSK fuzzy models to estimate the propofol effect concentration at ROC. Not only the variables with significant correlation coefficients were used, since the TSK models trained by ANFIS are more powerful for data fitting and may use extra information in a productive way. In addition, variables may have a nonlinear

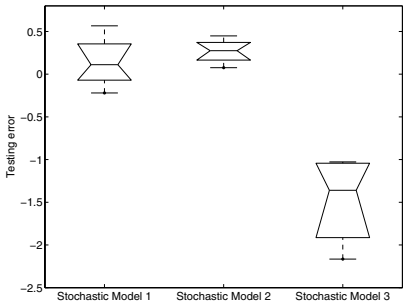

Fig. 1. Testing error variability for the three Stochastic Models.

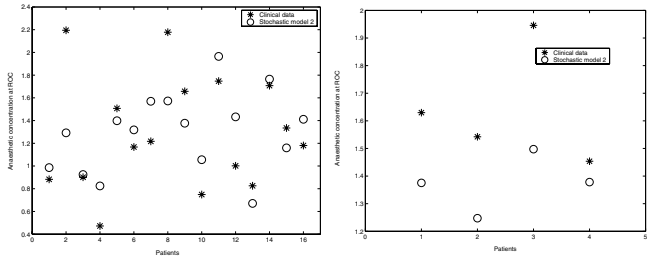

Fig. 2. Results of the Stochastic Model 2 on the training and testing data sets.

correlation. The TSK models were named according to the input set used: Fuzzy Model 1 uses as inputs the minimum BIS at induction and the time to reach that value; Fuzzy Model 2 uses as inputs the propofol and the remifentanil mean dose during surgery; Fuzzy Model 3 uses as inputs the propofol and the remifentanil mean dose, and the mean BIS value during surgery; Fuzzy Model 4 uses as inputs the propofol and the remifentanil mean dose during surgery, and patient's age; Fuzzy Model 5 uses as inputs the mean propofol dose and the duration of surgery; and Fuzzy Model 6 uses as inputs the propofol and the remifentanil mean dose, the mean BIS value during surgery, and the duration of surgery.

The initial FIS used by ANFIS is generated using grid partition according to the specified number of membership functions. All the membership functions are Gaussian. A number of 3 and 5 membership functions for each input were tested. In addition, subtractive clustering was used to determine the input membership functions. The ANFIS was able to optimise the parameters of all the fuzzy TSK models. Table III shows the mean absolute errors for Fuzzy Model 1 to Fuzzy Model 6, considering the training and testing data sets. The best performance was achieved for Fuzzy Model 2 with 25 rules (grid partition), Fuzzy Model 4 with 10 rules (subtractive clustering), Fuzzy Model 5 with 8 rules (subtractive clustering) and Fuzzy Model 6 with 16 rules (subtractive clustering). The testing error variability for these models is presented in Fig. 3, and the testing errors of these models are not statistically different (ANOVA p=0.905). The means of the testing errors of Fuzzy Model 2 (25 rules), Fuzzy Model 4 (10 rules), Fuzzy Model 5 (8 rules) and Fuzzy Model 6 (16 rules) are not statistically different from zero (*t-test* p=0.740, p=0.529, p=0.824, and p=0.189, respectively).

TABLE III

MEAN ABSOLUTE ERROR OF THE FUZZY MODELS FOR THE PROPOFOL EFFECT CONCENTRATION AT ROC ON THE TRAINING AND TESTING DATA SETS. * - USING GRID PARTITION; + - USING SUBTRACTIVE CLUSTERING

Model	Structure	Training data set	Testing data set
Fuzzy Model 1	9 rules*	0.001	9.72
	25 rules*	$2e^{-005}$	5.41
	6 rules+	0.09	11.31
Fuzzy Model 2	9 rules*	0.03	0.69
	25 rules*	$3e^{-004}$	0.41
	4 rules+	0.15	0.41
Fuzzy Model 3	27 rules*	$8.5e^{-008}$	0.56
	125 rules*	$3e^{-004}$	0.76
	10 rules+	$3.2e^{-004}$	1.2
Fuzzy Model 4	27 rules*	$1.2e^{-007}$	0.47
	125 rules*	$1.9e^{-007}$	0.61
	10 rules+	$3.2e^{-005}$	0.47
Fuzzy Model 5	9 rules*	0.02	4.25
	25 rules*	$1.1e^{-005}$	41.63
	8 rules+	$7.5e^{-004}$	0.43
Fuzzy Model 6	81 rules*	$3.3e^{-006}$	1.51
	16 rules+	$1.9e^{-005}$	0.3

Fig. 4 shows the results of the Fuzzy Model 2 with 25 rules (grid partition) and Fuzzy Model 2 with 4 rules (subtractive clustering) on the training and testing data sets. The testing errors of Fuzzy Model 2 with 25 rules and Fuzzy Model 2 with 4 rules are not statistically different (*t-test* p=0.715), however, there is a clear difference between training errors. Fig. 5 shows the results of the Fuzzy Model 5 with 8 rules (subtractive clustering) and Fuzzy Model 6 with 16 rules (subtractive clustering) on the training and testing data sets.

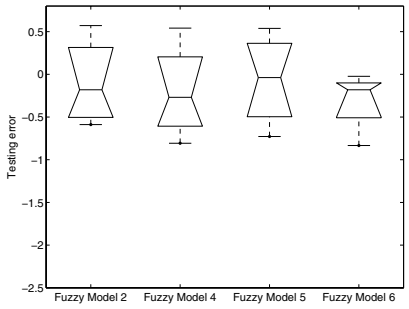

Fig. 3. Testing error variability for the Fuzzy Models with smallest mean absolute testing error: Fuzzy Model 2 (25 rules - grid partition), Fuzzy Model 4 (10 rules - subtractive clustering), Fuzzy Model 5 (8 rules - subtractive clustering) and Fuzzy Model 6 (16 rules - subtractive clustering).

D. RBF neural networks

The RBF networks models were named in a similar manner to the fuzzy TSK models, according to the data sets used as inputs. All sets of inputs were tested. Table IV shows the mean absolute errors for RBF Model 1 to RBF Model 6, considering the training and testing data sets. Fig. 6 shows the testing error variability for the RBF models with the smallest mean absolute testing error. The testing errors for RBF Model 2, RBF Model 5 and RBF Model 6 are not statistically different (ANOVA p=0.975). The means of the

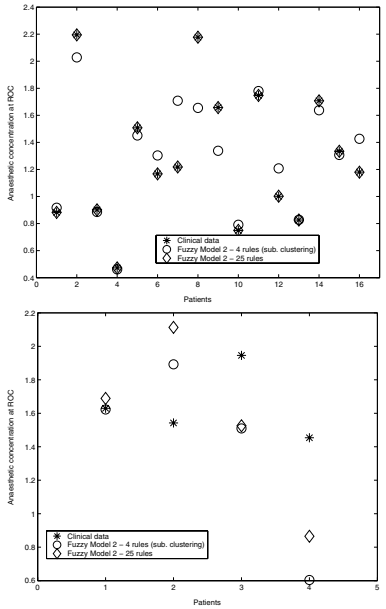

Fig. 4. Results of the Fuzzy Model 2 with 25 rules (grid partition) and Fuzzy Model 2 with 4 rules (subtractive clustering) on the training and testing data sets.

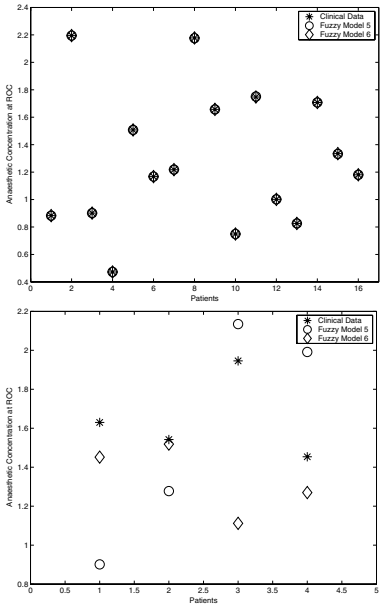

Fig. 5. Results of the Fuzzy Model 5 with 8 rules (subtractive clustering) and Fuzzy Model 6 with 16 rules (subtractive clustering) on the training and testing data sets.

TABLE IV

MEAN ABSOLUTE ERROR OF THE RBF MODELS FOR THE PROPOFOL EFFECT CONCENTRATION AT ROC ON THE TRAINING AND TESTING DATA SETS.

Model	Training data set	Testing data set
RBF Model 1	$2.5e^{-015}$	2.57
RBF Model 2	0.09	0.65
RBF Model 3	$2.6e^{-006}$	32.9
RBF Model 4	$5.7e^{-006}$	1.16
RBF Model 5	$5.9e^{-012}$	0.31
RBF Model 6	$1.8e^{-012}$	0.31

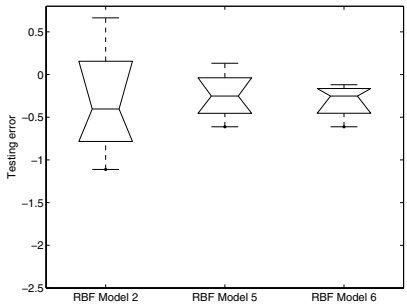

Fig. 6. Testing error variability for the RBF Models with smallest testing error: RBF Model 2, RBF Model 5 and RBF Model 6.

testing errors of these three RBF models are not statistically different from zero (*t-test* p=0.455, p=0.206, and p=0.064, respectively). Fig. 7 shows the results on the training and testing data sets of the RBF Model 6. Note that the predicted anaesthetic concentration at ROC on the testing data set is constant, not capturing the data.

V. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

The correlation analysis showed that duration of surgery, patient's LBM, and initial patient's response (as reflected on BIS) are not statistically related with the propofol effect concentration at ROC. This suggests that the clearance of propofol in the body is not related with duration of infusion (i.e. does not accumulate) and with the LBM of the patient. The initial patient response as evaluated by the minimum BIS value, does not present statistical correlation. However, this may be because of the rapid induction technique of a propofol concentration target of 5 μg/ml. Such a fast decay in BIS and abrupt pharmacokinetic/pharmacodynamic changes may obscure some patient's important individual characteristics. This would be an interesting topic to analyse in future research with different induction techniques. The drugs' mean dose during surgery, proved to be important variables in the prediction process. In addition, patient's age had a high correlation coefficient with the propofol effect concentration at ROC.

The stochastic regression models and *t-test* showed that the higher the drugs' dose during surgery, the higher the propofol concentration at ROC. In contrast, the older the patient the smaller the propofol effect concentration at ROC. Leading to the conclusion that age has influence on the patient's sensitivity to the drug. The Stochastic Model 3 using the patient's age had the worst performance among the stochastic models, with a large testing error variability and an average statistically different from zero. Stochastic Model 2 had the best balanced performance among the stochastic models, however its testing error was not significantly different for the that of Stochastic Model 1.

The best model structure for the training data set did not have the best performance on the testing data set. This leads to the conclusion that it may have been overfitted/overtrained

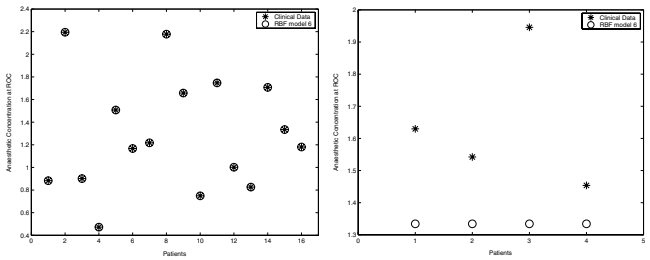

Fig. 7. Results of the RBF Model 6 on the training and testing data sets.

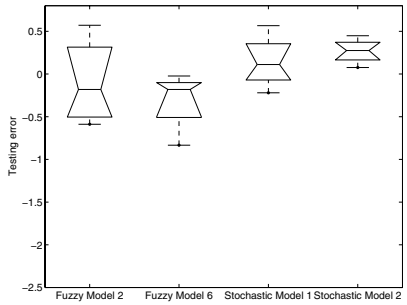

Fig. 8. Testing error variability for the Fuzzy Model 2 (25 rules - grid partition), Fuzzy Model 6 (16 rules - subtractive clustering), Stochastic Model 1 and Stochastic Model 2.

to the training data (i.e. it is a biased model), this was the case of RBF Model 6. The models performed well on the training data set, reaching almost perfection. The results on the testing data set reflect the effectiveness of the models when generalizing. The clinical variables mean propofol dose, mean remifentanil dose during surgery, and patient's age were the most relevant when analysing the propofol effect concentration at ROC using the models, in accordance with the correlation analysis. For the TSK models the best balanced performance was achieved with Fuzzy Model 6 with 16 rules using subtractive clustering, however, it looses in computation efficiency due to the large number of inputs. In fact, the model with 5 input membership functions (625 rules) was already too costly to compute. The use of subtractive clustering improved the results in some cases, since it tries to capture the data unique distribution and relation. Comparing the results of all prediction models, Fuzzy Model 6 had the smallest testing error and Fuzzy Model 2 (25 rules - grid partition) also presented a good balance between training and testing data sets. These fuzzy models had good prediction properties and were able to capture efficiently the information in the data, this may be a more adequate technique for such size of data sets. For the RBF models the best performance in training and testing data sets, was achieved with RBF Model 6, however, Fig. 6 showed that the model did not capture the data. In fact, the RBF model 6 gave the same output for all 4 patients. In addition, RBF Model 5 also gave constant testing results except for one patient.

Overall, the testing errors of Fuzzy Model 2 (25 rules), Fuzzy Model 6 (16 rules), Stochastic Model 1 and Stochastic Model 2 were not statistically different (ANOVA p=0.175, Fig. 8). Stochastic Model 2 had the smallest testing error variability, however Fuzzy Model 2 had a more significant testing error average of zero (*t-test*, p=0.740) and the best balance between training and testing data sets.

B. Future Works

The possibility of prediction for the propofol effect concentration at ROC, will facilitate the anaesthetist work during recovery, accelerate the patient's ROC improving the patient's conditions. Furthermore, it will save time and resources, and allow for a better patient's recovery quality. Overall, it would help to reduce the critical cases of early recovery. This model can also help the anaesthetist to gradually adjust the drugs' dose to allow a faster or slower return of consciousness. These results also lead to further research to study the patient's sensitivity to the drugs, which could help in a better dosage control to maintain an adequate level of DOA.

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