

Fuzzy Modeling to Predict Administration of Vasopressors in Intensive Care Unit Patients

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Abstract—Vasopressors belong to a powerful class of drugs used in the management of systemic shock in ill patients. The administration of a vasopressor involves the non-trivial process of inserting a central venous catheter. This procedure carries with it inherent risks which are increased when done under urgency such as in the case of unexpected systemic shock. The ability to predict the transition to vasopressor dependence could be expected to improve overall outcomes associated with the procedure. We use three different approaches combining fuzzy modeling with bottom-up (BU), top-down (TD) and ant feature selection (AFS), to classify requirements for vasopressors in shock. We observe that fuzzy models combined with BU feature selection return higher values of sensitivity; fuzzy models with no feature selection and fuzzy models with TD feature selection return higher values of AUC and specificity; features most commonly selected to classify impending use of vasopressors in pancreatitis patients include levels of Sodium and White Blood Cell counts, while for pneumonia patients include levels of Lactid Acid and White Blood Cell Count; and finally, fuzzy models combined with BU and fuzzy models combined with AFS demonstrate the lowest number of selected variables with no significant loss in accuracy.

Keywords: Feature selection, Fuzzy models, Vasopressors, Shock

I. INTRODUCTION

Systemic shock is defined as “an acute clinical syndrome initiated by ineffective blood perfusion, resulting in severe dysfunction of organs vital to survival” [1]. The signs and symptoms of shock include hypotension, tachycardia, cool and clammy extremities, oliguria, dysglycemia, and delirium [1]. Depending on the etiology, mortality figures vary from 23% to 75% [2].

Early recognition and intervention are critical to prevent irreversible organ injury and failure. Unlike other conditions where the clinical diagnosis is made before the treatment is initiated, the treatment of shock often occurs concurrently or ahead of the diagnostic process [3]. This treatment entails three main steps - ventilate, infuse and pump [4] - consisting

respectively of supplying oxygen to the patient until blood gas test results are available, infusion of fluids in order to increase plasma volume and cardiac output, and finally, when fluid administration fails to restore an adequate arterial pressure and organ perfusion, administration of vasopressors [5].

Vasopressors belong to a powerful class of drugs which are extremely useful for managing low blood pressure (hypotension) in patients with systemic shock. In critically ill patients, these drugs are often administered through central venous (CV) lines as they provide a fast and direct access to the central venous circulation [6]. However, inserting this type of line requires significant amounts of time (up to 1 hour, including radiologic imaging to evaluate placement), personnel resources, and can be associated with risks such as bloodstream infection. In the US only, catheter-related bloodstream infections have been reported to occur in 3 to 8% of inserted catheters and are the main cause of nosocomial bloodstream infection in intensive care units, with 80,000 cases annually at a cost of \$300 million to \$2.3 billion [7], [8]. Non-sterile central venous line insertion is more likely in urgent rather than elective scenarios. Simultaneously, there is a growing body of evidence supporting early commencement of vasopressor therapy as the key contributor to improved patient outcomes in certain disease states [9].

Bearing this in mind, being able to predict, within a certain time window, a patient's transition to vasopressor dependence could have great impact in a hospital, and particularly within the ICU environment, where patients are among the sickest in the hospital, for two main reasons: (i) a central line would only be inserted if the patient needs it in fact in the future (reduction in the performance of this procedure) (ii) the central line insertion protocol could be initiated with enough time, prior to the moment of need of vasopressors.

The present work will be a first step towards this major

goal. We will perform a classification task where, for a given set of clinical variables in a specific instant of the patient stay in the ICU, we will try to classify whether the patient was on vasopressors or not, as well as to find which subset of variables allows its better classification. This task will involve the application of soft computing techniques to a de-identified publicly available ICU database - MIMIC II [10]. As with other real-world databases, the dataset dealt with here, contains a relatively large number of non-linear features. Thus, from the engineering point of view, input selection is a crucial step in order to reduce models' complexity and remove inputs that do not improve the classification performance. From the clinical point of view, this feature selection process may bring to light new variables not been previously considered relevant to a given medical condition. In this paper, three different combinations of modeling and feature selection approaches are proposed and compared: fuzzy modeling with bottom-up tree search [11], with top-down tree search [11] and with ant colony feature selection [12].

Some studies have already explored this issue. In [13], a fuzzy-logic based algorithm was developed, taking arterial blood pressure and heart rate as inputs to generate a 'vasopressor advisability index'. In 2009, following Physionet/Computers in Cardiology Challenge, several algorithms were proposed to predict which patients would experience an acute hypotensive episode beginning within the forecast window. Finally, in [14] the application of some of the knowledge based methods as presented here was used to estimate outcomes in septic shock.

The paper is organized as follows. Section 2 briefly describes the modeling technique and proposed feature selection algorithms. A description of the database, its preprocessing as well as the obtained results are presented in Section 3. Conclusions are drawn in Section 4.

II. METHODS

A. Fuzzy Modeling

Fuzzy modeling is a tool that allows an approximation of nonlinear systems when there is few or no previous knowledge of the system to be modeled [15]. Fuzzy models have several advantages compared to other non-linear modeling techniques. For clinical related classification systems, this approach is particularly appealing as it provides not only a more transparent model, but also a linguistic interpretation in the form of rules. These rules and logical connectives are used to establish relations between the defined features in order to derive a model. A fuzzy classifier contains a rule base consisting of a set of fuzzy if-then rules together with a fuzzy inference mechanism.

There are three general methods to design a fuzzy classifier that can be distinguished [16]: the regression method, the discriminant method and the maximum compatibility method. Given that the classification decision does not change by taking a monotonic transformation of the discriminant function [17], we used in this work the discriminant method. Here, the classification is based on the largest discriminant function,

which is associated with a certain class, regardless of the values or definitions of other discriminant functions. In the discriminant method, a separate discriminant function $d_c(x)$ is associated with each class ω_c , $c = 1, \dots, C$. The discriminant functions can be implemented as fuzzy inference systems. In this work, we use Takagi-Sugeno (TS) fuzzy models [18], which consist of fuzzy rules where each rule describes a local input-output relation. When TS fuzzy systems are used, each discriminant function consists of rules of the type

$$R_i^c : \text{If } x_{i1} \text{ is } A_{i1}^c \text{ and ... and } x_M \text{ is } A_{iM}^c \\ \text{then } d_i^c(x) = f_i^c(x), \quad i = 1, 2, \dots, K \quad (1)$$

where f_i^c is the consequent function for rule R_i^c . In these rules, the index c indicates that the rule is associated with the output class c . Note that the antecedent parts of the rules can be for different discriminants, as well as the consequents. Therefore, the output of each discriminant function $d_c(x)$ can be interpreted as a score (or evidence) for the associated class c given the input feature vector x . The degree of activation of the i th rule for class c is given by: $\beta_i = \prod_{j=1}^M \mu_{A_{ij}^c}(x)$, where $\mu_{A_{ij}^c}(x) : \mathbb{R} \rightarrow [0, 1]$. The discriminant output for each class c , is computed by aggregating the individual rules contribution: $d_c(x) = \frac{\sum_{i=1}^K \beta_i f_i^c(x)}{\sum_{i=1}^K \beta_i}$. The classifier assigns the class label corresponding to the maximum value of the discriminant functions, i.e

$$\max_c d_c(x). \quad (2)$$

The number of rules K , the antecedent fuzzy sets A_{ij} , and the consequent parameters $f_i^c(x)$ are determined using fuzzy clustering in the product space of the input and output variables. The number of fuzzy rules (or clusters) that best suits the data must be determined for classification. The following criterion, as proposed in [19], is used in this paper to determine the optimum number of clusters:

$$S(K) = \sum_{k=1}^N \sum_{i=1}^K (\mu_{ik})^m (\|x_k - v_i\|^2 - \|v_i - \bar{x}\|^2)^2 \quad (3)$$

Values of $S(K)$ were calculated by varying K from 2 to 20. The final number of clusters corresponded to a local minimum where the differences between the values of the criterion are minor. In our case we used a 10% threshold for this difference between two values. A fuzzy clustering and data analysis toolbox was used in this step [20].

B. Feature Selection

Feature selection is generally used to reduce computational complexity, to eliminate features with high mutual correlation [21], and required generalization properties of the model [22]. From the clinical point of view, this process may bring to light new variables that had not been previously considered for a given medical condition.

1) *Bottom-up*: A detailed description of the bottom-up approach used here is reported in [11]. Briefly, the bottom-up approach starts by looking for single features that may influence the process output and works to assemble these single relevant features, to achieve a model with the best performance. This approach deals with feature redundancy in a simple way. Once the features are added one by one, if a feature is redundant it means that it will not improve the model prediction, and for that reason it will not be incorporated in the previously selected subset of features. Considering X the vector containing n features, this feature selection process is described by Algorithm 1. The model evaluation method was generalized by using AUC – Area Under the ROC Curve – as the most suitable performance criteria.

According to [23], a Receiver–Operator Characteristics (ROC) curve can be used to study the behaviour of two–class classifiers. This is a function of the true positive ratio versus the false positive ratio. Consequently, in order to compare the performance of various classifiers, the AUC can be used. It corresponds to the total performance of a two-class classifier integrated over all thresholds:

$$AUC = 1 - \int_0^1 FP(FN)dFN \quad (4)$$

where FP and FN represent, respectively, the false positive rate the false negative rate. The true positive rate and true negative rate are respectively named as Sensitivity and Specificity and, in this particular scenario, correspond to the cases where the patient was correctly classified as being on vasopressors and the cases where the patient was correctly classified as not being on vasopressors.

Algorithm 1 Bottom-Up Feature Selection

For each feature in the feature vector X that does not belong to the features of the model:

repeat

Build model using previous features of the model combined with each feature in the feature vector X that does not belong to the features of the model

Compute AUC;

Select the combination of features with the highest value of AUC as the new features of the model;

until AUC does not increase or the end of the feature vector is reached.

Select the final features;

2) *Top-Down*: A different approach based on a top-down tree search method was also used to select the most relevant features. This approach begins with all the available features, and removes those with the worst performance. The proposed top-down approach is described in Algorithm 2.

This algorithm differs from the bottom-up approach, as it begins with all the features and starts discarding features from stage to stage. Advantages include the reduction of the number of iterations per stage and, in some cases, of the number of stages, which, in lower dimension problems,

Algorithm 2 Top-Down Feature Selection

$i = 0$, where i is the stage number;

repeat

if $Stage = 0$ **then**

Build a model using all the available features;

$m = n$; where n is the number of initial features

else

$i = i + 2$

Build a model using the features not discarded at the previous stage;

end if

Compute AUC_i ;

for $j = 1$ **to** m **do**

Build model using all the features except feature j ;

Compute $AUC_{i+1,j}$

if $AUC_{i+1,j} < AUC$ **then**

Discard the feature j not used in modeling;

end if

end for

$m = m - p$, where p is the number of discarded features;

until (no feature is discarded) OR (model has only one feature) OR ($AUC_i > AUC_{i-2}$)

ultimately leads to the overall reduction of the computational time. However, when the number of features is large, given that this approach will use more inputs to build each model from the beginning, the identification of each model can be computationally intensive.

3) *Ant Colony*: Ant Colony Optimization (ACO) a method suited to find minimum cost paths in optimization problems described by graphs [24]. This paper uses the ant feature selection algorithm (AFS) proposed in [12], where the best number of features is determined automatically by considering two objectives: minimizing the number of features (*feature cardinality* - N_f) and maximizing the prediction performance. Two cooperative ant colonies formed by g ants, optimize each objective. The first colony determines the number (cardinality) of features and the second selects the features based on the cardinality given by the first colony. Thus, two pheromone matrices and two different heuristics are used.

The objective function of this optimization algorithm aggregates both criteria, the maximization of the model performance and the minimization of the feature cardinality:

$$J^k = w_1(1 - AUC^k) + w_2 \frac{N_f^k}{n} \quad (5)$$

where $k = 1, \dots, g$, AUC is the performance criterion previously defined in [23] and n is the total number of features. The weights w_1 and w_2 are selected based on experiments.

The heuristic value used for each feature (ants visibility) for the second colony, is computed as $\eta_{f_j} = AUC_j$ for $j = 1, \dots, n$, where AUC_j quantifies the relevance of each feature in the prediction model.

For the feature cardinality (first colony), the heuristic value is computed using the Fisher discriminant criterion for feature

selection [25]. Considering a classification problem with two possible classes, class 1 and class 2, the Fisher discriminant criterion is described as

$$F(i) = \frac{|\mu_1(i) - \mu_2(i)|^2}{\sigma_1^2 + \sigma_2^2} \quad (6)$$

where $\mu_1(i)$ and $\mu_2(i)$ are the mean values of feature i for the samples in class 1 and class 2, and σ_1^2 and σ_2^2 are the variances of feature i for the samples in class 1 and 2. The score aims to maximize the between-class difference, minimize the within a given class spread and thus to limit the number of features chosen by the AFS algorithm, which can be particularly useful when the number of available features is large. Other currently proposed rank-based criteria generally come from similar considerations and show similar performance [25].

III. RESULTS

A. MIMIC II Database

This paper used a de-identified publicly available ICU database named MIMIC II (Multiparameter Intelligent Monitoring in Intensive Care), containing data from 26,655 admitted patients. Data was collected over a six-year period, from Boston's Beth Israel Deaconess Medical Center, commencing in 2001. This database has two distinctive groups of data: the clinical database consisting of data integrated from different information systems in the hospital (patient demographics, medications, laboratory tests, etc), and a second group containing high resolution waveforms recorded from the bedside monitors in the intensive care units [10].

In this work we focused exclusively on the clinical data for two specific subsets of patients – pancreatitis and pneumonia. Given that these patients are usually treated differently – surgically and medically – we hypothesized that the circumstances related to the initiation of vasopressors are also distinct. In order to select these subsets, ICD9 (International Classification of Diseases) codes were used. These data included a total of 154 pancreatitis and 820 pneumonia patients, and 32 input variables, including vital signs, laboratory tests and urine output, sampled from one to every twelve hours, during the length of stay of the patient in the ICU. The output was formed as a binary classification with value one if, the patient was on vasopressors, and zero if not. The list of vasopressors for which the classification was performed included: phenylephrine, norepinephrine and dopamine. Their use represented 75% of all vasopressor administration events in the database. Other data inclusion criteria included: only data regarding the first stay of a patient in the ICU was considered; a period of at least six hours had to exist between the admission of the patient to the ICU (and commencement of the acquisition of data) and the administration of vasopressors; and only patients that were on vasopressors for more than two hours were included.

B. Data Preprocessing

Modern intensive care units are undergoing a significant evolution that is being driven by rapid improvements in

technology as well as changes in healthcare policy. The growth of computer networking and information storage technologies has been accompanied by an increase in the complexity and number of biosensors used in the ICU, thus generating large amounts of data [26]. However, this has also contributed to issues of what to do when data are collected in different frequencies or when it is partially lost or absent. In this way, data preprocessing represents a crucial step since it defines the reliability of the information that will be used in later stages of the knowledge discovery process.

In the present work, in order to manage differences in frequency of collection, Heart Rate samples were used as a template to align the remaining variables. This choice is based on being the most frequently measured variable. A detailed description of this alignment process is presented in [27].

In general, ICU data can be missing either because they are perceived to be irrelevant for the current clinical problems (thus, not recorded), or because exogenous interventions or endogenous activities have rendered the data useless [26]. When it is possible to prove that a variable was not measured during a certain period of time because of an intentional reason (e.g. ventilator parameters when a patient is extubated), this missing segment is considered as non-recoverable. In this work, these non-recoverable missing segments were deleted. On the other hand, if the variable was suppose to exist, but for some unintentional reason (e.g. cable disconnection) it is missing, this absent segment is considered recoverable and thus, proper imputation techniques can be applied [27], [28]. In this work, a cubic interpolation was used to impute values to the recoverable missing segments.

C. Simulation and Results

The general goal of this work entailed classifying, for a specific time point of a patient stay in the ICU, whether vasopressors were being administered or not, as well as to find which subset of variables allows its better classification. Classification methods were used combining fuzzy modeling with three feature selection techniques: bottom-up (BU), top-down (TD) and ant feature selection (AFS). For purposes of comparison, a fourth method using fuzzy modeling without feature selection (No FS) was also used. In order to evaluate the performance of these models, three different criteria were used: AUC, specificity and sensitivity. The entire algorithm was run in two separate sections: feature selection and 10-fold cross-validation. Ten iterations were used during the feature selection step, thus obtaining ten different combinations of features. The combination returning the best value of AUC was selected and used on a 10-fold cross-validation step to assess how the built fuzzy model would perform. Final results are presented as an average of all these 10 folds.

Before analysing the obtained results, it is important to note some of the issues found during simulation. In determining the optimum number of fuzzy rules (clusters), in most cases, the number of clusters returned by the criterion described in equation 3 was between five and eight. However, in a few cases, the number of clusters was higher then eight, which also

TABLE I

MEAN AUC, SENSITIVITY, SPECIFICITY USING FUZZY MODELING COMBINED WITH BOTTOM-UP (BU), TOP-DOWN (TD), ANT FEATURE SELECTION (AFS), NO FEATURE SELECTION (NO FS) AND FEATURES MANUALLY SELECTED IN [13] (MANUAL FS) TO CLASSIFY THE USE OF ALL THREE VASOPRESSORS

Method	[13]			Pancreatitis			Pneumonia		
	AUC	Specificity	Sensitivity	AUC	Specificity	Sensitivity	AUC	Specificity	Sensitivity
BU	-	-	-	0.87 ± 0.02	0.83 ± 0.05	0.90 ± 0.03	0.80 ± 0.02	0.78 ± 0.02	0.81 ± 0.03
TD	-	-	-	0.87 ± 0.02	0.89 ± 0.03	0.85 ± 0.05	0.80 ± 0.01	0.81 ± 0.03	0.80 ± 0.03
AFS	-	-	-	0.83 ± 0.02	0.84 ± 0.06	0.82 ± 0.04	0.76 ± 0.01	0.81 ± 0.04	0.71 ± 0.05
No FS	-	-	-	0.90 ± 0.02	0.92 ± 0.02	0.87 ± 0.05	0.80 ± 0.02	0.82 ± 0.02	0.79 ± 0.03
Manual FS	(0.77)	0.84	0.70	0.63 ± 0.01	0.55 ± 0.02	0.72 ± 0.02	0.63 ± 0.01	0.62 ± 0.02	0.64 ± 0.02

TABLE II

NUMBER OF SELECTED FEATURES (NO. SEL. FEATURES) AND LIST OF MOST COMMONLY SELECTED FEATURES (MOST SELECTED) WHEN USING FUZZY MODELING COMBINED WITH BOTTOM-UP (BU), TOP-DOWN (TD), ANT FEATURE SELECTION (AFS) AND THE FEATURES MANUALLY SELECTED IN [13] TO CLASSIFY THE USE OF ALL THREE VASOPRESSORS

Method	[13]		Pancreatitis		Pneumonia	
	No. Sel. Features	Most Selected	No. Sel. Features	Most Selected	No. Sel. Features	Most Selected
BU	-	-	2-3	14, 10, 12	3-5	28, 12, 18, 22
TD	-	-	26-29	All except 16, 5, 32, 7, 4	29-31	All except 6, 13
AFS	-	-	4-5	14, 30, 29, 12	8	7, 12, 16, 28, 8, 2, 31
Manual FS	2	1, 3	2	1, 3	2	1, 3

meant significantly higher computational times. Comparing the three feature selection methods regarding their execution times, fuzzy modeling combined with BU was the fastest (20 minutes in average for ten iterations), followed by fuzzy modeling combined with AFS and, finally, taking almost twice as the first, fuzzy modeling combined with TD.

In the first part of this work, we focused on comparing our results with other studies [13], where the classification of whether vasopressors were being administered or not, was made without distinguishing between them. In the second part of the work, we do distinguish and explore each of the vasopressors individually, i.e. a specific output was defined for each of the three vasopressors (phenylephrine, norepinephrine and dopamine).

1) *Classification of general use of vasopressors:* In [13], a fuzzy-logic based algorithm was developed to predict the need for vasopressor therapy, using the same MIMIC II database but with different criteria for patient selection. These models were built using as inputs two manually selected features - arterial blood pressure and heart rate. As shown in Table I, their algorithm achieved a specificity of 0.84 and a sensitivity of 0.69. The 0.77 value for AUC was estimated by us based on the respective values of specificity (0.84) and sensitivity (0.70). As mentioned, a comparison between the performance of our models with [13] was carried. However, it is important to note that it was not possible to identify which specific vasopressor(s) were included in their work, neither the criteria used to select patients. Furthermore, the conditions in which the values of specificity and sensitivity were obtained were not clear. Accordingly, some caution is needed when analysing and comparing the two approaches.

Main results follow: using the same two variables as in [13], the proposed fuzzy models returned lower values of AUC, specificity and sensitivity; however, when applying them to all variables or when combining them with any of the proposed automated feature selection processes, both AUC, specificity

and sensitivity were shown to be significantly higher than in [13]. This indicates that for the specific models and data subsets chosen in this work, the two features used in [13], do not contain information that allows the correct classification of the outcome (the use of vasopressors). This is confirmed by Table II, where it is possible to observe that the features most commonly selected to classify impending use of vasopressors in pancreatitis patients include levels of Sodium (feature no. 14) and White Blood Cell counts (feature no. 12), while for pneumonia patients include levels of Lactid Acid (feature no. 28) and White Blood Cell Count (feature no. 12). These sets of features differ completely from the ones chosen in [13]. Despite the limitations, these results suggest that for the purpose of classifying whether vasopressors were being administered or not, both the proposed fuzzy model approach without feature selection and the fuzzy model approach combined with any of the automated feature selection processes, significantly outperformed previous approaches [13].

Additional comments can be made regarding the results obtained in Table I. First, higher values of AUC, specificity and sensitivity were in general obtained for the pancreatitis subset than for the pneumonia one. This might be related to the size of these subsets. As mentioned, the first contained 154 patients while the second contained 820. Most likely, the smaller subset contained a more homogeneous group of patients whose clinical condition was similar during the periods when vasopressors were being administered or not. Secondly, it is also possible to observe that fuzzy modeling with No FS and fuzzy modeling combined with TD feature selection returned the highest values of AUC and specificity. However, these models did not return the best values of sensitivity. In other words, they performed the best in classifying when patients were not on vasopressors, but the worst in correctly classifying which patients were on vasopressors. The best values of sensitivity were given by fuzzy modeling combined with BU feature selection.

From the analysis of Table II, it can be pointed out that:

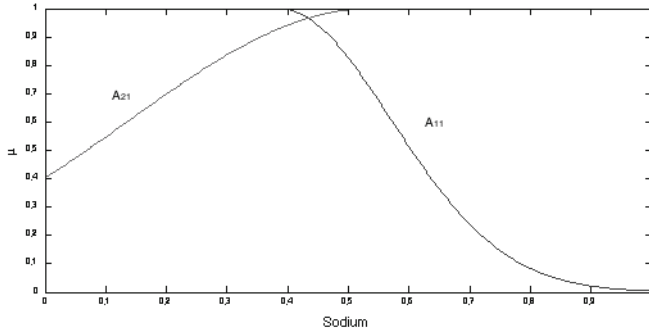


Fig. 1. Sodium's membership functions for cluster 1 (A_{11}) and 2 (A_{21})

BU and AFS techniques selected fewer features than the TD approach; in general, less features were selected for the pancreatitis subset than for the pneumonia subset; and finally, a certain consistency seems to exist between the variables most commonly selected by BU and AFS within each subset, but little or no agreement exists between the variables selected in the two subsets. In other words, this means that different variables were selected as being able to correctly classify the same outcome, between the pancreatitis and pneumonia subset of patients, thus pointing that the use of patient-specific models should be considered in future studies. In future works, it would be interesting to include a penalty for models with large numbers of features. This will reduce the number of features in the final model.

Finally, as an example, the rules built for the specific case of classifying the impending use of vasopressors in pancreatitis patients when using fuzzy modeling combined with BU, are presented:

1. **If** Sodium is A_{11} & White Blood Cell is A_{12} & BUN is A_{13} & Chloride is A_{14} **Then** $y(k) = 1.9 \cdot \text{Sodium} - 1.4 \cdot \text{WhiteBloodCell} - 3.2 \cdot \text{BUN} + 0.36 \cdot \text{Chloride} + 2.2$

2. **If** Sodium is A_{21} & White Blood Cell is A_{22} & BUN is A_{23} & Chloride is A_{24} **Then** $y(k) = -0.52 \cdot \text{Sodium} + 0.23 \cdot \text{WhiteBloodCell} + 0.073 \text{BUN} + 0.55 \cdot \text{Chloride} - 0.094$

Given that two clusters were defined, two rules were obtained. The variables used to build the rules (Sodium, White Blood Cell, BUN and Chloride) were pre-selected by the BU feature selection process. A_{kj} corresponds to the membership function of cluster k for variable j . For example, in Figure 1, A_{11} and A_{21} correspond respectively to Sodium's membership functions for cluster 1 and 2. $y(k)$ corresponds the output of the model for cluster k . After the defuzzification step, all clusters outputs are combined into a single output, by averaging them. This final output takes a real value between 0 and 1 which, by using a pre-determined threshold (in this work defined as 0.12), is set to 1 if it is over this threshold, and 0 if it is below.

2) *Classification of the specific use of phenylephrine, norepinephrine or dopamine:* In the second part of this work, as previously mentioned, we tried to explore the individual use of each of the three vasopressors. First, in accordance to what

TABLE VII
LIST OF FEATURES

Feature Name	Feature Number
Heart Rate	1
Temperature C	2
Arterial BP (Systolic)	3
Respiratory Rate	4
SpO2	5
Hematocrit	6
Potassium	7
Glucose	8
Creatinine	9
BUN	10
Platelets	11
White Blood Cell	12
Red Blood Cell	13
Sodium	14
Chloride	15
Arterial CO2	16
Magnesium	17
NBP	18
NBP Mean	19
PTT	20
INR	21
Arterial PaCO2	22
Arterial PaO2	23
Arterial pH	24
Arterial Base Excess	25
Ionized Calcium	26
Phosphorous	27
Lactic Acid	28
Calcium	29
CVP	30
Urine Out Foley	31
Arterial BP (Dyastolic)	32

was found in Table I, by comparing Table III and IV it is possible to observe that better results were obtained for the pancreatitis than for the pneumonia subset of patients. Second, developed models seem to perform the best in classifying when dopamine is administered, followed by phenylephrine and lastly in classifying the use of norepinephrine. Finally, fuzzy modeling with No FS and fuzzy modeling combined with TD returned again the best values of AUC and specificity, while fuzzy modeling combined with BU returned the best values of sensitivity.

From Tables V and VI several comments can be made regarding the set of selected features. First, contrarily to what was expected, having more features selected did not mean that models would perform better. For example, in classifying if dopamine was being administered to a pneumonia patient, after ten iterations of fuzzy modeling combined with BU, an average of two to four variables were selected. However, the model with the best values of AUC was the one where only two variables allowed to classify this outcome. Another interesting finding is that there is a certain agreement between the variables most commonly selected by BU and AFS. Most obvious examples include levels of Sodium (Table VII - Feature no. 14) and BUN (Table VII - Feature no. 10) in explaining the use of phenylephrine in pancreatitis patients, and levels of INR (Table VII - Feature no. 21) in explaining the use of dopamine in pneumonia patients. However, there are still a few cases (e.g. norepinephrine in pneumonia patients) where

TABLE III

PANCREATITIS SUBSET: MEAN AUC, SENSITIVITY, SPECIFICITY USING FUZZY MODELING COMBINED WITH BOTTOM-UP (BU), TOP-DOWN (TD), ANT FEATURE SELECTION (AFS) AND NO FEATURE SELECTION (NO FS) TO CLASSIFY THE USE OF EACH OF THE THREE VASOPRESSORS

Method	Phenylephrine			Norepinephrine			Dopamine		
	AUC	Specificity	Sensitivity	AUC	Specificity	Sensitivity	AUC	Specificity	Sensitivity
BU	0.92 ± 0.02	0.89 ± 0.03	0.94 ± 0.04	0.86 ± 0.01	0.84 ± 0.04	0.89 ± 0.05	0.99 ± 0.01	0.99 ± 0.02	1 ± 0.00
TD	0.94 ± 0.03	0.95 ± 0.03	0.93 ± 0.04	0.87 ± 0.02	0.92 ± 0.03	0.83 ± 0.05	0.99 ± 0.01	0.99 ± 0.01	1 ± 0.00
AFS	0.87 ± 0.03	0.85 ± 0.05	0.88 ± 0.04	0.81 ± 0.02	0.87 ± 0.04	0.77 ± 0.04	0.97 ± 0.02	0.97 ± 0.02	0.98 ± 0.05
No FS	0.94 ± 0.03	0.95 ± 0.03	0.94 ± 0.05	0.90 ± 0.02	0.94 ± 0.03	0.85 ± 0.00	0.98 ± 0.05	0.99 ± 0.01	0.96 ± 0.08

TABLE IV

PNEUMONIA SUBSET: MEAN AUC, SENSITIVITY, SPECIFICITY USING FUZZY MODELING COMBINED WITH BOTTOM-UP (BU), TOP-DOWN (TD), ANT FEATURE SELECTION (AFS) AND NO FEATURE SELECTION (NO FS) TO CLASSIFY THE USE OF EACH OF THE THREE VASOPRESSORS

Method	Phenylephrine			Norepinephrine			Dopamine		
	AUC	Specificity	Sensitivity	AUC	Specificity	Sensitivity	AUC	Specificity	Sensitivity
BU	0.80 ± 0.02	0.76 ± 0.03	0.83 ± 0.03	0.80 ± 0.01	0.80 ± 0.03	0.81 ± 0.03	0.90 ± 0.01	0.95 ± 0.03	0.85 ± 0.04
TD	0.83 ± 0.01	0.85 ± 0.01	0.81 ± 0.03	0.79 ± 0.01	0.80 ± 0.01	0.77 ± 0.03	0.91 ± 0.02	0.98 ± 0.01	0.84 ± 0.05
AFS	0.80 ± 0.02	0.81 ± 0.05	0.80 ± 0.04	0.77 ± 0.01	0.78 ± 0.04	0.76 ± 0.04	0.85 ± 0.03	0.93 ± 0.04	0.78 ± 0.05
No FS	0.85 ± 0.03	0.88 ± 0.04	0.81 ± 0.03	0.82 ± 0.02	0.83 ± 0.02	0.80 ± 0.03	0.91 ± 0.03	0.97 ± 0.02	0.85 ± 0.05

TABLE V

PANCREATITIS SUBSET: NUMBER OF SELECTED FEATURES (NO. SEL. FEATURES) AND LIST OF MOST COMMONLY SELECTED FEATURES (MOST SELECTED) WHEN USING FUZZY MODELING COMBINED WITH BOTTOM-UP (BU), TOP-DOWN (TD), ANT FEATURE SELECTION (AFS) AND NO FEATURE SELECTION (NO FS) TO CLASSIFY THE USE OF EACH OF THE THREE VASOPRESSORS

Method	Phenylephrine		Norepinephrine		Dopamine	
	No. Sel. Features	Most Selected	No. Sel. Features	Most Selected	No. Sel. Features	Most Selected
BU	3-4	14, 10, 15	4-5	12, 9, 20, 15	2-3	28, 6
TD	30-32	All except 32	31-32	All except 25	31-32	All except 25
AFS	4-5	14, 10, 29, 15	4-5	11, 2, 12, 24	3-5	20, 2, 4, 8, 18

TABLE VI

PNEUMONIA SUBSET: NUMBER OF SELECTED FEATURES (NO. SEL. FEATURES) AND LIST OF MOST COMMONLY SELECTED FEATURES (MOST SELECTED) WHEN USING FUZZY MODELING COMBINED WITH BOTTOM-UP (BU), TOP-DOWN (TD), ANT FEATURE SELECTION (AFS) AND NO FEATURE SELECTION (NO FS) TO CLASSIFY THE USE OF EACH OF THE THREE VASOPRESSORS

Method	Phenylephrine		Norepinephrine		Dopamine	
	No. Sel. Features	Most Selected	No. Sel. Features	Most Selected	No. Sel. Features	Most Selected
BU	9-13	18, 19	9-12	15, 28, 12, 9	2-4	21, 6
TD	29-31	All except 2,32	30-32	All except 32	29-31	All except 32
AFS	10-12	19, 15, 17, 22, 32, 2	10-13	19, 32, 10, 16, 24, 12	2-4	21, 12

a total disagreement exists between the two sets of selected features. This may be an indicator that for this specific problem of classifying the use of vasopressors, different and specific rules should be determined in order to explain the use of each of the three vasopressors. This highlights the importance and applicability of combining feature selection techniques with predictive models.

IV. CONCLUSIONS

Evidence based medicine firstly requires medicine based evidence. Modern intensive care units fill databases with large amounts of data which go some way to addressing this. However, these databases commonly contain large amounts of data acquired from different sources, and require reliable tools to process the information and integrate results in a human-understandable way. Given the particularly appealing feature for clinicians of providing transparent models and a linguistic interpretation in the form of rules, fuzzy models were used in the present work. In order to reduce the number of rules and bring to light new variables not previously thought relevant, a feature selection process was added to the models.

A classification task was performed to determine which set of clinical variables best predicted the likely administration of vasopressors. It was demonstrated that all the proposed approaches outperform previous works. Fuzzy models combined with BU feature selection returned higher values of sensitivity (i.e. perform better in classifying when a vasopressor was being administered), while fuzzy models with No FS and fuzzy models with TD feature selection returned higher values of AUC and specificity (i.e. performed better in classifying when a vasopressor was not being administered). The fact that different features were selected to classify the same vasopressor in two different subsets of patients (pancreatitis and pneumonia), points to the future exploration of patient-specific models. Finally, fuzzy models combined with BU and fuzzy models combined with AFS utilize less variables with no significant loss in accuracy. Given the advantage of model ease of interpretation while maintaining high levels of accuracy, we believe that fuzzy modeling combined with these last two feature selection techniques provide opportunities for further studies in this area.

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