Engineering Applications of Artificial Intelligence 49 (2016) 141–148

Contents lists available at ScienceDirect

Engineering Applications of Artificial Intelligence

journal homepage: www.elsevier.com/locate/engappai

Ensemble fuzzy models in personalized medicine: Application to vasopressors administration

Cátia M. Salgado [a,*], Susana M. Vieira [a], Luís F. Mendonça [a,b], Stan Finkelstein [c,d], João M.C. Sousa [a]

[a] LAETA, IDMEC, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal
[b] Escola Superior Náutica Infante D. Henrique Department of Marine Engineering, Paço d'Arcos, Portugal
[c] Massachusetts Institute of Technology, Engineering Systems Division, Cambridge, MA, USA
[d] Massachusetts Institute of Technology, Harvard-MIT Division of Health Sciences & Technology, Cambridge, MA, USA

ARTICLE INFO

Article history:
Received 26 March 2015
Received in revised form
13 October 2015
Accepted 14 October 2015
Available online 3 November 2015

Keywords:
Fuzzy modeling
Fuzzy clustering
Ensemble modeling
Vasopressors administration
Personalized medicine

ABSTRACT

Vasopressors administration in intensive care units is a risky surgical procedure that can be associated with infections, especially if done urgently such as in the case of unexpected systemic shock. The early prediction of a patient's transition to vasopressor dependence could improve overall outcomes associated with the procedure. Personalized medicine in the ICU encompasses the customization of healthcare on the level of individual patients, with diagnostic tests, monitoring interventions and treatments being fitted to the individual rather than the "average" patient. In this scope, this paper proposes an ensemble fuzzy modeling approach to a classification problem based on subgroups of patients identified by individual characteristics. A fuzzy c-means clustering algorithm was implemented to find subgroups of patients and each subgroup was used to develop a fuzzy model. The final classification of the ensemble fuzzy approach is obtained using two output selection criteria: an *a priori* decision criterion based on the distance from the cluster centers to the patients' characteristics, and an a *posteriori* decision criterion based on the uncertainty of the model output. The performance of the proposed approach is investigated using a real world clinical database and nine benchmark datasets. The ensemble fuzzy model approach performs better than the single model for the prediction of vasopressors administration in the ICU, being the *a posteriori* approach the best performer, with an average AUC of 0.85, showing this way the advantage of a personalized approach for patient care in the ICU.

1. Introduction

Vasopressors drugs are used to contract blood vessels so as to increase blood pressure in critically ill patients. The procedure of vasopressors administration is risky, since the catheter insertion involves a surgical procedure that can be associated with infections. These complications are increased when the procedure is done urgently such as in the case of unexpected systemic shock (Herget-Rosenthal et al., 2008). If information is available about which patients are going to need vasopressors beforehand, clinicians will have enough time to safely initiate the central line insertion protocol, prior to the moment of need of vasopressors. Being able to predict within a certain time window a patient's transition to vasopressor dependence will likely improve the outcome of ICU patients, either by reducing the number of times this procedure is implemented or by reducing the risk of infection when the procedure is done.

Previous studies have explored the classification of ICU patients on vasopressors. In Zong et al. (2008), arterial blood pressure and heart rate are taken as inputs to a fuzzy-logic based algorithm that generates a 'vasopressor advisability index'. Following the challenge from PhysioNet and Computers in Cardiology proposed in Moody and Lehman (2009), several algorithms were developed to predict, within a certain time window, which ICU patients would experience an acute hypotensive episode. In Cismondi et al. (2012), a multimodel approach is tested for predicting the risk of death in septic shock patients. Two models were created in parallel, one highlighting sensitivity, and the other highlighting specificity. In Fialho et al. (2011) and Fialho et al. (2013), different approaches combining fuzzy modeling with feature selection were used to classify requirements for vasopressors in septic shock patients, focusing exclusively on two disease-based subsets of patients – pancreatitis and pneumonia. As pointed out by the authors, the fact that different features were selected to classify the different

* Corresponding author.
E-mail address: catiasalgado@live.com (C.M. Salgado).

http://dx.doi.org/10.1016/j.engappai.2015.10.004
0952-1976/

groups is an indicator of the relevance of patient specific models in predictive modeling. In fact, several literature already exists describing predictive modeling across a range of applications in the care of the critically ill, however, much of this modeling has taken the approach of focusing on the general population, i.e., the "average" patient. Two main reasons can be attributed to this tendency: first it is clear that using a heterogeneous group of patients allows the maximization of external validity of the findings and second, there is a lack of data to support the application of model techniques to smaller subsets. However, as the amount of data increases, the tendency for general population modeling decreases, especially because predictive models developed using this approach often perform poorly when applied to specific subsets of patients sharing common characteristics (Strand and Flaatten, 2008). In response to treatment, critically ill patients have substantial individual variation between them, and what works at one time might not work later in the same patient (Kravitz et al., 2004). Personalized medicine encompasses the customization of healthcare on the level of individual patients characteristics, with medical decisions, practices and products being fitted to the individual rather than the "average" patient (FDA Report, 2013). Hence, the near future is likely to see a new era of personalized medicine in the treatment of the critically ill (Celi et al., 2011).

Ensemble learning is an important branch in the research area of machine learning (Berthold et al., 2010; Dietterich, 1997). Ensemble models have been applied to a wide range of complex real problems (Kittler et al., 1998; Ghosh, 2002; Sharkey and Sharkey, 1997; Dietterich, 2000) and several authors have demonstrated the advantages of using this type of approach, in weather forecasts (Xiong et al., 2001; Weigel et al., 2008), credit risk (Twala, 2010; Finlay, 2011), fault diagnosis (Mendonça et al., 2009) and clinical care (Cismondi et al., 2012; Krawczyk and Schaefer, 2012). The rationale behind ensemble classification is the creation of many classifiers such that the combination or selection of their output improves the performance of the single classifier (Polikar, 2006). In literature, distinct types of architectures topology and decision criteria strategies have been proposed and discussed. Serial architectures use a primary classifier to evaluate a given instance, and when that classifier is not able to classify some new pattern, another one is trained in order to be accurate on the errors of the previous. A third and fourth classifier can be added, and so on. Parallel architectures use the combination of the output of several models trained in parallel to obtain the final decision. Various methods have been proposed for combining classifiers, where relevant triggering or aggregating mechanisms are defined to activate or define a suitable interaction between them (Polikar, 2006; Woods et al., 1997; Ho et al., 1994). These include majority voting (Kittler et al., 1998), Bayesian voting (Dietterich, 2000), bagging (Breiman, 1996), boosting (Freund, 1990; Schapire, 1990) and classifier selection (Kuncheva, 2000; Didaci et al., 2005).

In this paper, we propose an ensemble model approach for personalized medicine based on fuzzy clustering and fuzzy modeling. Unsupervised fuzzy clustering is used to identify similar patients and generate different data divisions. Each division is used to train individual models, resulting in a specific model for each group of similar patients. Thus, in contrast to previous approaches by Cismondi et al. (2012), Fialho et al. (2011), Fialho et al. (2013), submodels are developed for specific groups of patients identified by fuzzy clustering. Two selection decision criteria are proposed to obtain the final classification: an *a priori* decision based on data properties, i.e., distance from the cluster centers to the patient characteristics; and an *a posteriori* decision approach based on the uncertainty of the model output. The goal is to see if larger predictive performance can be achieved using an ensemble model, as compared to a single model approach. This hypothesis is tested on a real problem for the prediction of vasopressors dependency in ICU patients and in nine benchmark datasets from the UCI benchmark repository (Blake and Merz, 1998).

The outline of the paper is as follows: in Section 2, the basis for the clustering methodology is introduced, followed by the description of fuzzy modeling and model performance measures. In Section 3, the two proposed ensemble approaches are described. Section 4 presents a description of the benchmark and vasopressors datasets that are used to evaluate the performance of the models, followed by a discussion of results in Section 5. Conclusions and future work are drawn in Section 6.

2. Methods

2.1. Clustering

Clustering is an unsupervised learning task that aims at decomposing a given set of samples into subgroups based on data similarity (Kruse et al., 2007). In this work, fuzzy clustering is used to divide ICU patients in subgroups.

Fuzzy clustering allows each sample to belong to more than one cluster with different membership degrees. Fuzzy c-means (FCM) is the most popular objective function based fuzzy clustering algorithm. It was first developed by Dunn (1973) and improved by Bezdek (1981). In FCM, the clustering of a dataset X containing N samples, into C clusters is defined to be optimal when it minimizes the c-means functional formulated as

$$J_f(X, U_f, V) = \sum_{i=1}^{C} \sum_{j=1}^{N} \mu_{ij}^m d_{ij}^2(x_j, v_i), \tag{1}$$

where $U_f = [\mu_{ij}]$ is a $C \times N$ matrix, called a fuzzy partition matrix, $V = [v_1, v_2, \ldots, v_C], v_i \in R^n$ is a vector of cluster prototypes (centers), $m \in [1, \infty[$ is the weighting exponent which determines the clustering degree of fuzziness, d_{ij} is the distance between data point x_j and cluster center v_i, and is a squared inner-product distance given by (2), where A is a norm-inducing matrix:

$$d_{ij}^2(x_j, v_i) = (x_j - v_i)^T A (x_j - v_i) \tag{2}$$

Since the FCM algorithm requires the definition of C, (Bezdek, 1981), a validity measure called separation index, S, was used to find the most adequate number of clusters in the data (Xie and Beni, 1991). This measure uses a minimum-distance separation for partition validity, and is defined as

$$S = \frac{\sum_{i=1}^{C} \sum_{j=1}^{N} (\mu_{ij})^2 \| x_j - v_i \|^2}{N_{min\ i,k} \| v_k - v_i \|^2} \tag{3}$$

Other measures, such as partition index (Bensaid et al., 1996), partition entropy (Pal and Bezdek, 1995) and partition coefficient (Pal and Bezdek, 1995) were also used for comparison purposes. However, for the sake of simplicity and as no significant differences were found, only the results for the separation index validation measure are shown. For the clustering step, Matlab Fuzzy Clustering and Matlab Data Analysis toolboxes were used (Balasko et al., 2005).

2.2. Fuzzy modeling

Fuzzy modeling is a tool that allows approximation of nonlinear systems when there is little or no previous knowledge of the problem to be modeled (Sugeno and Yasukawa, 1993). This approach provides a transparent, non-crisp model, and allows linguistic interpretations in the form of rules and logical connectives, which are particularly useful in clinical scenarios. These rules are used to establish relations between the defined features in order to derive a model. A fuzzy classifier contains a rule base