Data-based Modelling for the Prediction of Mortality in Acute Kidney Injury Patients

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Abstract

The growth and improved accessibility to electronic health records have promoted the research in medical sciences aided by Computational Intelligence systems. Acute kidney injury (AKI) is a broad disease defined by abrupt changes in renal function. AKI has a high morbidity and mortality rate, with an increase focus on critically ill patients. Feature selection and fuzzy modelling methods are used to build predictors of mortality within patients admitted to the intensive care unit (ICU) that developed AKI. The mortality prediction by stage shows a considerable improvement, in comparison to the models with more patients, and reinforces the importance of a tailored approach to patients in different stages.

Keywords: Acute Kidney Injury, Mortality Prediction, Fuzzy Modelling, Feature Selection

1. Introduction

In the health field, data mining and machine learning techniques are being increasingly used in large databases to create individualized clinical models (i.e. that work for a specific patient, disease or process). These techniques aid in the construction of clinical decision support systems, since they are able to learn rules that might not be explicitly known before [5, 21, 8, 18]. Acute kidney injury (AKI) is a broad disease defined by abrupt changes in renal function. AKI has a high morbidity, with an increase focus on critically ill patients [5]. It is also independently correlated with worse outcomes: AKI patients have a higher mortality rate, a higher requirement of renal replacement therapy (RRT) and a longer hospital stay, than without AKI [1]. With this picture rises a need to identify the patients that have worse possible outcome before the condition progresses. An earlier detection could allow a more careful focus on patients at higher risk, adjusting treatments and improving resource division [23, 1]. Considering the increasing burden of AKI in today's society and the potential aid of intelligent techniques, the aim of this thesis build models to predict the worst outcome – death – on patients that developed AKI. This work will use feature engineering and fuzzy modelling to construct a mortality prediction model. It aims to serve as a first step towards creating a clinical decision support system for patients with AKI. The ultimate goal is to improve patient care by helping clinicians know and better understand the relation (or lack of relation) between common variables and the survival chances of the patients with AKI they see in daily practice [1].

2. Acute Kidney Injury

Acute Kidney Injury (AKI) refers to a wide range of patients: from the ones with small damage changes in the kidney and functional impairment to patients that have real damage to the kidney and need renal replacement therapy (RRT) [1, 3]. AKI was first defined in 2004 by the RIFLE classification system [3] and since then it has suffered some updates that created other systems. The main ones are the AKIN criteria [17] that appeared in 2007 and the 2012 KDIGO criteria [1]. According to those classification systems, AKI has 3 stages, which classifies the development and severity of the disease. The stages separate the mild cases from the more severe ones. The 3 classification systems show very similar results [9]. The classification system used in this work is the AKIN, since it uses less types of measurements then the other two.

2.1. AKIN Classification

The Acute Kidney Injury Network group (AKIN) [17] published the definition and staging criteria for AKI presented in Figure 1. This definitions in known by the name of the group.

The AKI incidence and mortality range depend on the choice of cohort to study, and on the simplifications used. A study conducted just last year

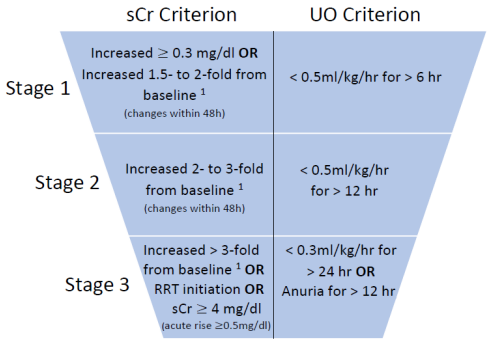

Figure 1: Classification/staging system from AKIN [17] – schema adapted from RIFLE [3].

[1] See Section 2.2.

at this faculty by Vanessa Cunha *et al.* [7] found an AKI incidence of 30.4%. With a higher mortality rate and length of stay (los) for AKI patients comparing to the rest of the subjects.

2.2. Work Specifications

The most common simplification about the sCr criterion application is on the choice of the serum creatinine baseline value. The choice of baseline estimation method can shift the stage in which the patient will be classified [6].

Since the baseline value is not present in the used database, it is necessary to estimate it. There is not one method of estimation that is considered the best. Thus, the following estimation method was chosen: baseline equal to the lowest value of the first three measures of sCr in the ICU. This choice was made considering that the results of this work will be compared to other AKI studies done on the same database [7] and those studies use the mentioned baseline estimation method.

This work focuses on ICU patients since they are at most risk and also because in order to calculate AKI it is necessary to have UO and sCr measurements and outside the ICU they are less and more sparse. It will use data referring to different days because AKI has a very wide temporal range of incidence and mortality.

3. Model Construction

The first step taken to build the mortality model was to select the information corresponding to day of interest, followed by the normalization of all the non-binary features and the discretization of the time series using the median, mean and last value for that feature in the day in study, see Section 3.2. After that, the dataset was divided into 10-folds using the MATLAB function *cvpartition* that balances the mortality rate of each fold as much as possible. The training dataset used 9 out of the 10-folds, and the other fold was kept for validation. All of the 10 possible combinations of train/test data were used to create 10 independent models, for the performance to be more independent of the data division. The next step was using the training dataset to select the features, either it uses the feature selection method in Section 3.1 or all the variables entered. The training set with only the features selected, builds the model using the fuzzy modelling algorithms explained in Section 3.3. It is with this model that the threshold is selected. The model is then applied to the testing set using the features selected in the training and it predicts the mortality. The AUC is calculated here, see Section 3.4. The threshold that was computed previously is used to make the output binary, and finally it is calculated the rest of the performance scores presented in Section 3.4.

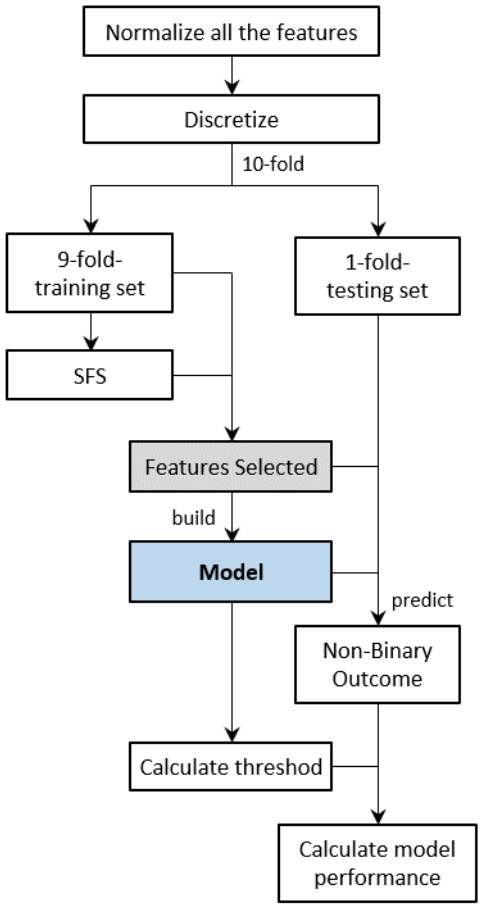

Figure 2: Schema with the steps to create the mortality model.

3.1. Feature Selection

Consider a generic initial set of N features F:

$$F = \{f_1, \cdots, f_k, \cdots, f_N\}.$$

Feature selection consists in selecting the features from set F in order to build a smaller subset F': $F' = \{f_1, \cdots, f_M\}$ with $M < N$ and $F' \subseteq F$

The idea is to discard redundant features and keep the ones that have the highest teaching ability [27]. In this work, the feature selection algorithm used is sequential forward selection (SFS). SFS is a greedy iterative process that progressively evaluates different feature sets combinations. It starts by selecting the feature that individually has the best predictive power, then adds the feature that combined with the previous gives again the best performance, and so on, until there is no improvement in prediction. SFS is a simple method that shows the influence of each feature to the problem study and is highly used in the health area [5, 7, 22]. In this work, the criterion to evaluate the predictive ability during SFS is the AUC (area under curve - see Section 3.4).

3.2. Feature Extraction

Feature extraction methods apply a transformation function to set F in order to obtain a set F'' with new features: $F'' = \{f_1'', \cdots, f_j'', \cdots, f_l''\}$ Feature extraction deals with the fact that some features may be useless by themselves but informative together and that two relevant features may be highly correlated and so they are not both necessary. There are several feature extraction methods, some maintain the dimension of the set of features (e.g. normalization or signal-enhancement methods) others will reduce the number of features (e.g. principal component analysis – PCA) and some methods can even increase the number of features (e.g. discretization) [15, 12].

Having in mind that highly interpretable models are required, it is within the interest of this thesis to keep the meaning of the features intact as much as possible. So only normalization and discretizing methods were used.

There are several techniques to discretize temporal data, the ones used in this model are among the most common ones. It is used the mean value, the median value and the last value for each temporal series.

The data used comes from different features that represent measurements that are not comparable, and have vary different ranges of values. Due to the use of a distance function in fuzzy c-means (see Section 3.3), the data was normalized for the interval [0,1] before the implementation of clustering and modeling techniques [11]. The Min-Max normalization was applied to each feature i:

$$\bar{x}_i = \frac{x_i - \min(x_i)}{\max(x_i) - \min(x_i)} \tag{1}$$

In this work the input data has binary features and non-binary features, the output data is binary. Only non binary features need to be normalized.

3.3. Fuzzy Modelling

The non-linear modelling tool used in this work is Takagi-Sugeno (TS). The TS fuzzy model is a combination of a logical and mathematical model, where the fuzzy antecedents are formed by logical rules, and where the consequent part is a mathematical function. The antecedents divide the input space into a number of fuzzy regions per input and the consequent functions describe the behaviour of the systems within a given region. The rules are written as: [7, 24, 25]

R_i : If x_1 is A_{i1}, $\cdots$ and x_N is A_{iN}
then $y_i = a_i^T x + b_i,\ i = 1, 2, \cdots, C$

where R_i corresponds to rule number i out of C. The input vector is $x = (x_1, \cdots, x_N)$, N is the number of features, A_{iN} is the fuzzy set for the pair R_i rule and N feature. The output variable is y_i, for the i^{th} rule, with a_i as a parameter vector and b_i as an offset.

The final model output y is computed from the weighted average of each output rule:

$$y = \frac{\sum_{i=1}^{K} \beta_i\ y_i}{\sum_{i=1}^{K} \beta_i} \tag{2}$$

being β_i the degree of fulfillment of rule i: $\beta_i = \prod_{n=1}^{N} \mu_{A_{in}}(x)$ and $\mu_{A_{in}}$ the membership function of the antecedent A_{in} : $\mu_{A_{in}}(x) : \mathbb{R} \to [0, 1]$.

In this work, the number of fuzzy rules and the antecedent fuzzy sets are determined by fuzzy c-means.

To obtain the fuzzy model it is going to be applied the fuzzy c-means (FCM) clustering algorithm. Clustering is an unsupervised algorithm that partitions data into several groups. These groups are not know *a priori*, they are built in a way that the data inside the same group is more related with each other than with data from other groups [13, 24]. Being fuzzy allows the data to belong in some degree to several groups, so the groups can overlap. The purpose is to minimize an objective function. The FCM objective function was formulated as: [4, 2]

$$\mathbf{J}(\mathbf{X}; \mathbf{U}, \mathbf{V}) = \sum_{i=1}^{C} \sum_{k=1}^{N} \mu_{ik}^m D_{ik}^2 \tag{3}$$

where $\mathbf{X}$ is the regression matrix and y the output vector. The dataset is divided in C clusters: $2 \leq C \leq N$. $\mathbf{U}$ is the partition matrix $\mathbf{U}= [\mu_{ik}]$ that satisfies $\mu_{ik} \in [0, 1]$. $\mathbf{V}$ is the vector of clusters centers $\mathbf{V} = (v_1, v_2, \cdots, v_C)$ and D_{ik}^2 is the Euclidean distance between the data and the i-th cluster: $D_{ik}^2 = d^2(x_k, v_i) = (x_k - v_i)^T \cdot (x_k - v_i)$. m is a weighting exponent that determines the fuzziness, or degree of overlap, of the resulting clusters $m \in [1, \infty[$.

To choose the parameters: number of clusters - C and fuzziness - m, several simulations were made varying C, and m, to check how the model performed. The number of clusters is a key parameter since it determines the number of rules in the fuzzy model. As a result, adjusting this parameter had a greater impact in the accuracy and precision of the fuzzy model than the modifications applied to m. For this reason, the fuzziness was fixed to 2 and just the number of clusters were tailored for each model.

3.4. Model Assessment

The main performance score used in this work is the AUC (area under the receiver-operating characteristic (ROC) curve) gives a good assessment of the balance between sensitivity and specificity, two important scores when dealing with highly imbalanced datasets. It is a performance rate that is easy understandable by caretakers and is frequently used in the medical literature [5, 23, 7], making it possible to compare methods and models easily.

The real output data (the target data) is binary since the subject either died (1) or not (0) so the predicted outputs will have to be binary too. However, the prediction values that are given by the model vary between 0 and 1 and so they have to be transformed, using a threshold, that separates the outputs in to one of the two classes. For the choice of the aforementioned threshold t, values that are $< t$ will be considered as 0 (the patient survived) and for values be considered as 1 (the patient did not survived). The choice of the threshold will influence all the performance evaluation, except AUC. Several thresholds possible, between 0 and 1, were tested iteratively with a step length of 0.01. The selected t was the one that had the smallest difference between sensitivity and specificity. This choice was to have the best trade-off between true positives and false positives [26, 22].

4. Data Pre-Processing

This work used data from the MIMIC-III database, *Medical Information Mart for Intensive Care*. This is a large database of ICU patients with data collected from 2001 to 2012. One of the advantages of using MIMIC-III is that it is publicly accessible, under the condition of passing an on-line ethics course and signing of a data use agreement in [14]. Another is that the database includes a lot of information such as demographics, vital sign measurements made at the bedside, laboratory test results, procedures, medications, caregiver notes, imaging reports, and mortality (both in and out of hospital) spread across 26 tables [5, 14].

The database has information about whether a patient was diagnosed with AKI at the time of admission or not (in their ICD-9 codes), but there is no information regarding AKI development during the patient ICU stay. So it is necessary to check each patient physiologic information and to calculate if a patient ever developed AKI, when and if so in what stage he was.

The following exclusion criteria was applied:

- MIMIC-III does not contain paediatric information, only neonates - bellow 1 year old - and adults - over 15 years old. The two groups are very distinct, and this study of mortality will focus only in adults, so it is necessary to exclude the neonates patients.
- The AKIN staging criteria requires the values of serum creatinine (sCr) and urine output (UO) of each patient. Only patients with an ICU stay longer than 24 hours, at least three measures of sCr and one measure of UO at every six hours will be considered. Otherwise, these patients are excluded because there is not enough data to diagnose AKI and determine a stage [5, 16].
- Some patients were admitted more than once in the ICU, the recurrent patients represent around 13% of the ICU cohort. Therefore, an extra rule had to be created to establish only one ICU stay per patient. Thus, only patients who developed AKI for the first time or when the first AKI event was triggered, were included. This way, the models are trained with data pertaining to the very first onset of AKI, when it is harder to predict the risk of mortality. Additionally, this rule helps to avoid biased assessments.

The MIMIC-III has 44,476 patients, with the exclusion criteria the databased was reduced to 10,135 subjects.

4.1. Repeated Data

In MIMIC-III, each measurement or concept have a specific and unique code called *Item ID* (e.g. Item ID = 211, describes measurements of heart rate (HR)). Nonetheless, there are duplicated codes for each concept (e.g. HR has two codes assigned: Item ID = 211 and Item ID = 220045). This is due to the fact that the information comes from two distinct critical care information systems and also because of the free text nature of data entry in the older system. In consequence a semi-manual identification of repeated data had to be performed to capture as much values as possible. The first step was doing a text search to look for other codes with similar names, the second was looking for information in [20] to see if the select codes were measuring the same thing (e.g. sodium levels can be taken from urine samples or blood samples, they both appear

as sodium but they are not comparable) an the last step was performing box plots by code to see if the range of values was similar and if they were comparable. This repeated data identification was also useful to find values measured in different units (i.e. weight in lb or kg) and to convert them all to the same.

4.2. Time Series

The variables with the most relevant information for each patients care, such as the electronic chart for routine vital signs, laboratory values, ventilator settings, etc, are considered a time series, since it is possible to see the measurements over time. For the final cohort of patients it was performed a frequency analysis to assess the codes with the most information. From the almost 3,000 codes, only 50 of them had over 90%, after the 50 codes mark the amount of variables per value rapidly decreases, and less than 500 codes had more than 10% of the patients. Those 50 most measured variables were extracted. The non-numeric variables were excluded and it was done the repeated analyse mentioned above, some codes were repeated variables and were merged in one feature and some more codes were added because they represented the same variable. After this, the extracted time series had 32 variables.

From those 32 variables, 2 were Weight and Height. These two variables have a lot of records with the same value, because they have codes for previous values, which means that just one measurement of weight can be extended to the entire patient length of stay. For this reason the two variables were dicretized to their median value and were studied like the other discrete data.

4.3. Discrete data

Various studies [23, 28, 10] correlate AKI incidence and prognosis with demographic characteristics of the patient, particularly age, gender and race/ethnicity. Race and gender are not numerical values, so it was divided the patient into binary classes, male patients were assigned with value 1 in gender and female with 0, and black patients were assigned with value 1 for race and other races with 0. The in ICU mortality was assessed and those who did not survived were assigned with value 1, and those who did with 0. The AKI stage was determined for each day, and used as a discrete value. AKI stage, age, weight and height are numeric values so they were normalized used the Min-Max normalization; gender, race and in ICU mortality are binary so they maintained their regular value.

4.4. Other Considerations

The temporal series were separated by days since admission, and it was used data from the last day. Then it was necessary to remove the outliers, performing a visual analysis. Then The temporal series were discretized using the mean, median or last value.

Although the measurements chosen were the most common in the dataset, there was still a lot of missing data. The choice between eliminating patients and variables, was done in a way that maximized the amount of data. The total of variables for the final cohort was 26, being one of them the AKI stage calculated and has 7,323 subjects.

5. Results

The final cohort was divided in 5 different ways to create the dataset the model: one with all the patients in the cohort and an other with just patients that developed AKI, both with the AKI stage as a feature, the other 3 were built for patients in each stage and the stage was not used as a feature.

As it was mentioned in the previous chapters, the data was normalized using Min-Max for each dataset, afterwards the missing data was removed and the cohort reduced to 7,323 patients. The remaining data was discretized using first the median value, and then the last value and the mean value (see Section 4.3). Transforming one dataset into three child datasets. The different child datasets were used to build fuzzy models. As it was explained in Section 3, a 10-fold cross-validation was performed to each child dataset. And of those child datasets were modelled twice: with or without sequential forward selection (SFS).

5.1. Solution of SFS

The global solution of SFS is set as the relative frequency of selection, i.e. the percentage of times each variables, separated by the method of discretization. The variables select more often is the mean value of potassium (ID 20), the mean and median value of urine output (ID 29), the median value of white blood cells count (ID 30), the median and last value of blood urea nitrogen (ID 5), the last value of chloride (ID 7) and the class of race (ID 33) when used with last and mean values.

5.2. Comparison of the Approaches

The best global AUC scores found in each child dataset for each of the 3 different approaches to discretize the variables are presented: without SFS in Table 1, and with SFS in Table 2. The maximum values were all above 0.9. It shows that overall SFS had very little impact on the final results. However, the method of discretization as a considerable effect on performance scores, the mean value provide better results than the median or the last values.

6. Conclusions

AKI is been increasingly studied to build prediction models, and the advantages of analysing more specific patients are well known [5, 19]. However, this

Table 1: Highest average AUC values – without SFS – best score for each of the child datasets highlighted.

	Median	Last Value	Mean
All Patients	0.81 ± 0.03	0.82 ± 0.02	0.86 ± 0.02
AKI Patients	0.83 ± 0.03	0.84 ± 0.02	0.87 ± 0.03
Stage 1	0.83 ± 0.03	0.84 ± 0.05	0.88 ± 0.03
Stage 2	0.76 ± 0.08	0.74 ± 0.10	0.82 ± 0.07
Stage 3	0.91 ± 0.05	0.89 ± 0.07	0.92 ± 0.05

Table 2: Highest average AUC values – with SFS – best score for each of the child datasets highlighted.

	Median	Last Value	Mean
All Patients	0.81 ± 0.02	0.81 ± 0.02	0.86 ± 0.03
AKI Patients	0.83 ± 0.03	0.84 ± 0.02	0.88 ± 0.03
Stage 1	0.83 ± 0.04	0.84 ± 0.03	0.88 ± 0.03
Stage 2	0.75 ± 0.09	0.74 ± 0.09	0.81 ± 0.06
Stage 3	0.90 ± 0.05	0.89± 0.06	0.92 ± 0.02

work is one of the firsts to build models by dividing the subjects in study per stage of AKI. This work used sequential forward selection and fuzzy modelling to construct a mortality prediction model using data from a large ICU database, with a focus on a patient last day. The results show a very promising path.

The first separation between all the patients in the ICU and the ones who developed AKI during their length of stay shows improvement in the ability to predict mortality. The average AUC increased form 0.86 ± 0.02 to 0.88 ± 0.03.

The separation by stage has different results. The models for patients with stage 2 AKI had the worst performance, but they still reached an average AUC of 0.82 ± 0.07. Stage 1 models have better results than models for all patients but have almost the same scores as the models for AKI patients (with all stages). Stage 3 models not only have the highest average scores with 0.92 ± 0.05 for AUC, 0.83 ± 0.07 for accuracy, 0.82 ± 0.08 for sensitivity and0.84 ± 0.08 for specificity, but also has some models that reached an AUC of 1.00.

This work demonstrates that one day before the outcome the patients already have strong indications of what the outcome will be, and shows the importance and the positive results that may arrive from continuing to work in this problem.

One of this works limitations comes from the fact that this is a retrospective analysis and, besides other typical limitations [6], the hardest is to transpose these results into real time, since in real time it is not possible to now beforehand when the last day is going to be.

A suggestion for future work is to create a daily prediction model, by stages of AKI, that would be performed in a closed loop: the model would be fed with the data corresponding to the day in question and with the outcome prediction of the model from the last day. Another suggestion is applying other techniques of feature extraction and feature selection.

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