

Machine Learning for Critical Care: An Overview and a Sepsis Case Study

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Abstract. Biology in general and medicine and healthcare in particular are facing the critical challenge of exponentially increasing data availability. The core of this challenge is putting these data to work through computer-based knowledge extraction methods. In the medical context this could take the form of medical decision support systems for diagnosis, prognosis or general management. Arguably, one of the most data dependent clinical environments is the critical care unit and by extension the whole area of critical care. Fresh approaches to data analysis in critical care are required, and Computational Intelligence and Machine Learning methods have already shown their usefulness in tackling problems in the area. This brief paper aims to be an introduction to the use of such methods in critical care.

Keywords: Machine Learning · Critical care · Intensive care unit

1 Introduction

Biology is experiencing a tectonic shift from being a wet-laboratory-focus science towards becoming a data-centred one, in what could be considered as a pertinent example of the pervasive Big Data paradigm [1]. Medicine as a biological science does not escape from this transformation, which can be understood as the convergence of two factors: the fast evolution of information technology networked systems and the equally fast development of novel and increasingly sophisticated non-invasive data acquisition methods.

A further convergence to consider in this context is that of the increasing dependence of medicine on the omics sciences to fulfill the promises of truly personalized medicine. The omics sciences require large scale concerted efforts

to guarantee the medical community reliable access to large, heterogeneous and ever-growing databases. A central concept to the tasks of managing such complex databases is that of data biocuration [2].

Data is also increasingly a core concern in healthcare and its availability to medical experts is the main building block for the the development of medical decision support systems (MDSS) [3–6]. Decision making in healthcare at clinical environments is often made on the basis of multiple parameters and in the context of patient presentation, which includes the setting and the specific conditions related to the reason for admission and the procedures involved. The data used in clinical decision-making may originate from manifold sources and at multiple scales: devices in and around the patient, laboratory, blood tests, omics analyses, medical images, and ancillary information available both prior to and during the hospitalization.

Arguably, one of the most data dependent clinical environments is the critical care department (CCD) in any of its forms: intensive care unit (ICU), pediatric intensive care unit (PICU), neonatal intensive care unit (NICU) or surgical intensive care units (SICU), and this involves very practical implications for MDSS at the point of care [7]. The ICU environments care for acutely ill patients. Many of their patients, and particularly SICU patients, are technologically dependent on the life-sustaining devices that surround them. Some of these patients are indeed dependent for their very survival on technologies such as infusion pumps, mechanical ventilators, catheters and so on. Beyond treatment, assessment of prognosis in critical care and patient stratification combining different data sources is extremely important in a patient-centric environment.

Of course, the assessment of clinical needs changes depending on the acuity of the patient and conditions present at the point of care. Changes in patient status drive the quantity of data captured within the bedside documentation, either through flow sheets or paper and electronic records. The team supporting the patient, though, ultimately must define what is required and, in order to support clinical decision making, it is also necessary to include other data from the electronic health record and monitoring devices. These include fluid intake and patient output, demographic information, laboratory blood draw assessments, medical images, and so on.

In any case, medical device connectivity in the ICU is essential for providing a complete clinical decision support framework. While electronic medical records in and of themselves offer enormous work flow benefits, the documentation and charting systems are only as good as the data they convey. Due diligence by care providers can be augmented by automated and validated data collection, achieved through a seamless form of medical device connectivity and interoperability that is supported both inside and outside the hospital premises, and that follows the patient throughout the assisting process.

Fresh approaches to data analysis tailored to the needs of the ICU environments are thus required, and some of the most interesting ones are currently stemming from the fields of Computational Intelligence (CI) and Machine Learning (ML), which have already shown its relevance as the basis for MDSS [8] and as tools to improve hospital inpatient care [9].

This short overview paper provides a non-exhaustive state-of-the-art on the use of CI, ML and statistical methods for data analysis in critical care environments. We emphasize the main advantages, limitations and potential challenges of these methods and illustrate all of these by focusing in a single major pathology that is commonplace at the ICU, namely sepsis.

2 Machine Learning and Computational Intelligence in Critical Care

ML, CI and, more in general, other advanced strategies for data analysis under the umbrella concept of Artificial Intelligence (AI) have of late demonstrated not just their promise, but their actual value in different fields of biology and health. They include, amongst others and not exhaustively, bioinformatics [10, 11], genetics and genomics [12, 13], clinical applications [14], medical decision support and clinical diagnosis [15, 16], oncology [17, 18], psychiatry and neurological disorders [19, 20], or cytopathology [21].

Critical care might seem too narrow a field as to provide a particular perspective on the use of ML and CI. The situation is actually the opposite: this type of methods is being applied to critical care problems with a variety of approaches of astonishing depth and breadth.

In fact, a full review of such applications is well beyond the scope of this brief overview paper. A very recent discussion and review paper of this type can be found in [22]. It provides a very interesting point of view according to which researchers in the field should consider the need to focus as much in data-related challenges as in the development and application of appropriate data modelling techniques. That is, from a Data Mining perspective, we are advised to shift part of our focus from the data modelling stage to the data understanding and pre-processing stages. Authors in [22] consider three main challenges, namely *compartmentalization*, *corruption* and *complexity*. Compartmentalization would include problems related to data privacy and anonymization, data integration from potentially heterogeneous databases, and data harmonization in terms of consistent definition of concepts throughout databases. Corruption would involve different types of data errors, issues of data missingness and data imprecision (usually due to a lack of matching goals in the data acquisition and the data modelling processes). Finally, complexity, including issues of prediction, state estimation and data multi-modality. This latter challenge bridges the stages of data pre-processing and modelling.

Reviews in this field are not necessarily this recent and can be traced back to the early century in work by Hanson and Marshall [23], who already stated that the ICU environment is particularly suited to the deployment of AI-based analytical strategies due to the wealth of available data and the promise they hold of increased efficiency in inpatient care due to their specific characteristics.

Specific sub-fields of critical care, such as *alarm algorithms* in critical care monitoring have also been reviewed in some detail [24]. More recent work in this sub-field [25] proposed the use of Artificial Neural Networks (ANN) and Decision

Trees (DT) for the design of patient-specific alarm algorithms in real time. DTs [26] and Random Forests (RF) [27], an extension of DTs, have recently been proposed for the reduction of false cardiac arrhythmia alarms and also for the assessment of prognosis in Sepsis [28].

All these reviews reflect the broad palette of methods available to practitioners in critical care. They include, not exhaustively, ANN [29–31] and Support Vector Machines (SVM) [32] for mortality prediction, or Deep Reinforcement Learning [33] for medicine dosing. Other applications of Deep Learning (the current *reincarnation* of ANNs) include that for the unsupervised learning of phenotypical features in longitudinal sequences of serum uric acid measurements, in [34].

Other less standard methods include Bayesian Networks (BN), used in [35] for medicine dosing and in [36] for event detection in patient monitoring. Gaussian Processes (GP) have also been used in patient vital signals monitoring after surgery [37], amongst other applications. Unsupervised hierarchical clustering was used in [38] for the identification of physiologic patient states at the ICU.

One of the medical problems in critical care to which more attention has been paid from the point of view of ML and related techniques is that of the management of the sepsis pathology, mostly from the point of view of diagnosis and prognosis, which will be discussed in more detail in the following sections.

Fuzzy systems and rule extraction, mostly as strategies for increasing the interpretability and usability of the results have been proposed: A Fuzzy DSS for the management of post-surgical cardiac intensive care unit (CICU) patients was described in [39]. The problem of rule generation was addressed in [40, 41], the latter together with an ANN.

Beyond [41], other studies have deployed ANNs for the study of Sepsis. Amongst them, [42] presented a clinical study examining Systemic Inflammatory Response Syndrome (SIRS) and Multiple organ dysfunction syndrome (MODS) in the ICU after cardiac and thoracic surgery. The initiatives related to the application of ANNs to the study of Sepsis have also resulted in expert systems such as the one called SES, described in [43], which was designed for the diagnosis of pathogens and prescription of antibiotics. Ross and co-workers [44] derived a system of ordinary differential equations together with an ANN model of inflammation and Septic Shock.

SVM models have also been used for the prediction of Sepsis. Kim and co-workers [45] applied them to study Sepsis in post-operative patients. Wang *et al.* [46] built a DSS for the diagnosis of Sepsis. Tang and colleagues [47] presented a SVM-based system for Sepsis and SIRS prediction from non-invasive cardiovascular spectrum analysis.

ML methods have also been used with varying success for the more specific problem of the prediction of mortality caused by Sepsis. A diagnostic system for Septic Shock based on ANNs (Radial Basis Functions -RBF- and supervised Growing Neural Gas) was presented in [48]. Also in this area, Brause and colleagues [49] applied an evolutionary algorithm to an RBF network (the MEDAN Project) to obtain, over a retrospective dataset, a set of predictive attributes for

assessing mortality for Abdominal Sepsis. BN models were used in [50,51], kernel methods were used in [52] and Relevance Vector Machines (RVM), SVM variants with embedded feature selection, were used in [53].

The following section focuses exclusively and in some detail in some of the authors' work on the application of ML and related methods to the analysis of different problems in the management of sepsis.

3 Machine Learning for the Analysis of Sepsis as a Paradigmatic Critical Care Pathology

3.1 Sepsis: Some Basic Background

The official consensus definition of the sepsis pathology has evolved over the decades. The last consensus meeting held in 2016 provided new definitions for Sepsis and its complications [54]. With the objective of increasing the specificity in diagnosing Sepsis in clinical practice, the new definitions include organ dysfunction for the diagnosis. As a consequence, the term Severe Sepsis is no longer used and the use of the SIRS [55] for diagnosing Sepsis is also not recommended. Instead, the role of the Sequential Organ Failure (SOFA) [56] score becomes even more prominent in the diagnosis and management of Sepsis.

However, the calculation of the SOFA score can be time consuming since it requires to perform blood tests to assess coagulation, liver and renal function. Therefore, to make executive decisions and admit patients into the ICU, the quick SOFA (qSOFA) score has been defined, which assesses mental status, systolic blood pressure (SBP) and respiratory rate [54].

In this context, *Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection* and *Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection*. Septic Shock is defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [54].

Even though the current definitions are yet to be widely adopted in critical care processes, they also set the basis to validate the common ground to study the pathophysiology of Sepsis and its prognosis at multiple levels of analysis. They include the study of the inflammatory response during sepsis and its association with organ dysfunction both from already available clinical data and also at a transcriptomics, proteomics and metabolomics level for better understanding the underlying mechanisms of the process.

3.2 Review of the Definitions of Sepsis Through Causal Probabilistic Networks

This section describes a study for the identification of key prognostic factors in patients that suffered a septic shock during their stay in the ICU. The analyses presented here are based on the publicly available MEDAN database [57], which

recorded data from 71 voluntary cooperating German ICUs between 1998 and 2002.

The data from the MEDAN database was processed with causal probabilistic networks (CPN). CPNs are recognized in bioinformatics and computational biology as relevant representations capable of modeling causal relationships more precisely than standard clustering or regression models. CPNs also have sound statistical foundations for inferential modeling [58] and for handling noise and missing data.

The implementation of the CPNs was based on the *Causal Explorer* public library [59] with the three-phase dependency analysis algorithm (TPDA). This algorithm consists of three phases: drafting, thickening and thinning. In the drafting phase, TPDA produces an initial set of edges based on a simpler test (basically just having sufficient pairwise mutual information). This first draft is a graph without loops. In the second phase, TPDA adds edges to the current graph when the pairs of nodes cannot be separated using a set of conditional independence tests. The graph produced by this phase will contain all the edges of the underlying dependency model. In the thinning phase each edge is examined and it will be removed if the two nodes of the edge are found to be conditionally independent. The threshold value for our TDPA implementation is 0.05.

For ICU admission, the graph presented in Fig. 1 was obtained. In this graph, the dependence relations show the link between between SIRS and the ICU outcome variable and point toward a strong relationship between the SIRS diagnosis and patient outcome in the ICU.

It is also important to analyse how would SIRS relate to organ dysfunction measured through the SOFA score (Fig. 2). The resulting TPDA graph also shows a strong relation between SIRS and SOFA and the statistical dependence of SIRS with the SOFA score is therefore clear. In this graph, it is also important to note the strong relation between the SOFA score and severity measured by the APACHE II [60] and SAPS II [61].

The results of applying Causal Explorer to the analysis of the MEDAN data set provide evidence to support the very recent official modifications in the clinical definition of sepsis [54], in the sense that SIRS relates to organ dysfunction and it is therefore convenient to give more prominence to the latter for its diagnosis. However, it is also important to note the role of the inflammatory response in patient outcomes and also in the physiopathology of Sepsis.

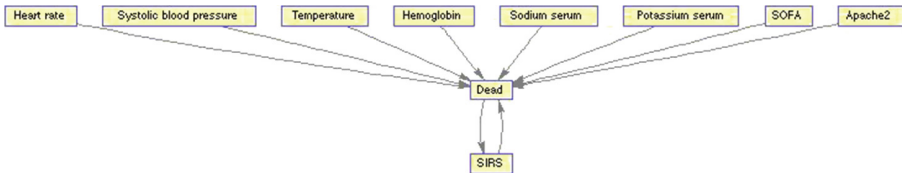


Fig. 1. Conditional independence map for data at ICU admission.

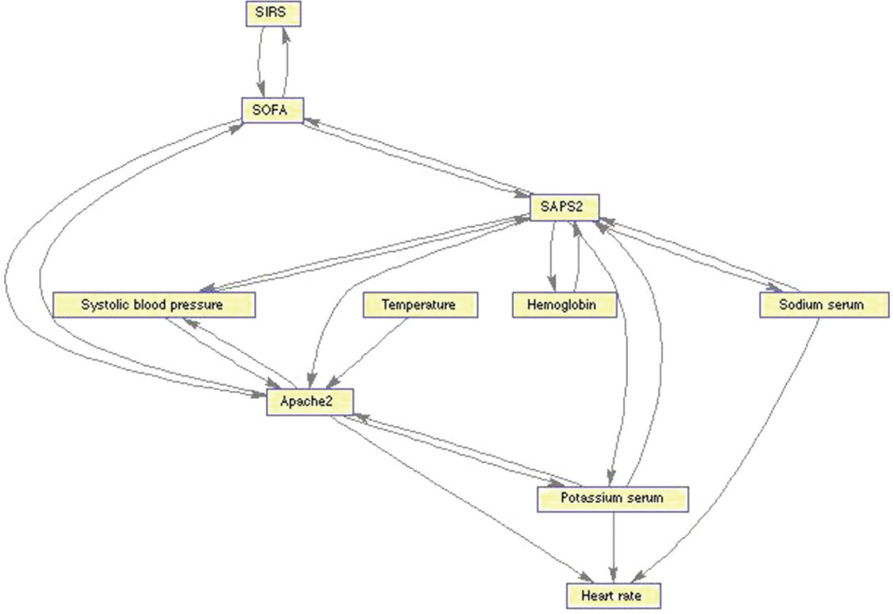


Fig. 2. Conditional independence map for organ dysfunction at ICU admission.

3.3 Finding Prognostic Factors Through Machine Learning

Here, we provide an overview of the use of a latent model-based feature extraction approach, namely Factor Analysis (FA), to obtain new sets of descriptors, or prognostic factors, for the prediction of mortality due to Sepsis. Within this framework, the reported experimental results are readily interpretable.

In the reported experiments [62], the obtained prognostic factors were used to predict mortality through standard Logistic Regression (LR), a method commonly used in medical applications [63, 64] and widely trusted by clinicians. The prediction accuracy results herein reported improve on those obtained with current standard data descriptors and therefore provide support for the use of these new factors as risk-of-death predictors in ICU environments.

In this work, we resorted to a prospective observational cohort study of adult patients with severe sepsis. The study was conducted at the Critical Care Department of the Vall d’Hebron University Hospital (Barcelona, Spain), and it was approved by the Research Ethics Committee of the Hospital. The database consists of data from patients with severe sepsis and septic shock, collected at the ICU by the Research Group in Shock, Organic Dysfunction and Resuscitation (SODIR), between June, 2007 and December, 2010. During this period, 354 patients with severe sepsis (medical and surgical patients) were admitted in the ICU. The collected data show the worst values for all variables during the first 24h of evolution for Severe Sepsis. Organ dysfunction was evaluated through the SOFA score system. Severity was evaluated through the APACHE II score.

A set of 34 features was used for the mortality prediction analyses. The full list can be found in [62].

Factor Interpretation from a Clinical Viewpoint. The application of FA resulted in a consistent 14-factor model of the original data set. The cumulative proportion of total (standardized) sample variance explained by this model was found to be 83.27%.

Taking into consideration the highest factor loadings (in absolute value) for every given variable, these factors were mapped into different easily interpretable clinical descriptors, explained as follows:

- Factor 1: Related to cardiovascular function and, more specifically, to the cardiovascular SOFA score and use of vasoactive drugs.
- Factor 2: Corresponds to haematologic function (as presented in the haematologic SOFA score and the total platelet count).
- Factor 3: Corresponds to respiratory function, Respiratory SOFA score and PaO_2/FiO_2 ratio.
- Factor 4: Corresponds to the use of mechanical ventilation and PPlateau.
- Factor 5: Corresponds to the 24 h SSC bundles and glycaemic indices.
- Factor 6: Related to the micro-organism producing the Sepsis and whether this sepsis polymicrobial or not.
- Factor 7: Corresponds to renal function measured by the SOFA score and total SOFA score.
- Factor 8: Corresponds to the administration of antibiotics and haemocultures taken during the first 6 h of ICU stay.
- Factor 9: Relates to the number of organs in dysfunction for a moderate SOFA and the total number of organs in dysfunction.
- Factor 10: Related to the hepatic function measured by the SOFA score.
- Factor 11: Corresponds to the CNS function measured by the SOFA score and the number of organs in dysfunction.
- Factor 12: Related to the loci of Sepsis and whether the infection is polymicrobial or not.
- Factor 13: Corresponds to the APACHE II score and worst lactate levels.
- Factor 14: Relates the total number of organs in dysfunction.

The factors obtained with this method are coherent with the SOFA score as a description and measure of organ failure and dysfunction [56], combined with the management guidelines defined by the Surviving Sepsis Campaign [65]. Therefore, it can be safely concluded that they are related to SOFA and the actions taken to mitigate this organ deterioration. This is a result of particular interest. One of the main challenges in mortality prediction is that of producing flexible models that can robustly fit the observed data without the need for unnecessary contextual assumptions, and in the presence of subtle interactions between covariates.

Mortality Prediction Using Logistic Regression over 14 Factors. Mortality prediction was then performed using the obtained 14-factor FA solution as starting point. The performance of the model was evaluated by 10-fold cross validation. Table 1 shows the coefficient estimates β , Z-Scores and maximum and minimum values resulting from fitting a LR model to the 14 factors (inputs) and the outcome in the ICU (output) and removing those factors yielding Z-Scores smaller than 1.96. The Z-Scores measure the effect of removing one factor from the model [66,67]. A Z-score greater than 1.96 in absolute value is significant at the 5% level and provides a measure of the relevance for the prediction of a given factor.

As shown in Table 1, factor 3, related to *Mechanical Ventilation* and *Pplateau*, shows the strongest effect together with factor 13, which is related to the APACHE II score. Factor 8 (Hepatic Function measured with the SOFA Score) and factor 10 (related to the number of Dysfunctional Organs) are also found to be relevant. It is worth noting at this stage that, with LR, the factors related to the *Surviving Sepsis Campaign* show no strong effect on mortality prediction. This result may be due to the low compliance with the *Surviving Sepsis Campaign Bundles* for the first 6 and 24 h of evolution (26.18% and 44.06% respectively for the ICU under study). However, it is interesting to note that factor 9 (antibiotic administration and haemocultures) presents a higher impact than that of factor 6 (24 h bundles with glycaemic indexes). For the ICU under analysis, 80.22% of patients received antibiotics during the first 6 h of evolution and 77.14% had haemocultures during the same period of time. In fact, timely administration of antibiotics and performance of haemocultures are considered critical to improving the prognosis of septic patients.

Regression on the 14 factors together with 10-Fold cross validation resulted in an Area Under the ROC Curve (AUC) of 0.78. A decision threshold of $\gamma = 0.68$ was automatically selected (for the maximization of the discrimination probability) to decide whether the patient survives. This 10-fold cross-validation experiment yielded an AUC of 0.78, an error rate of 0.24, a sensitivity of 0.65 and a specificity of 0.80. The results of LR over latent factors is presented in Table 1. This table also shows that the two most representative factors are F10 and F13, which correspond to organ dysfunction measured through the SOFA score and illness severity measured through the APACHE II score combined with the worst lactate levels.

Table 1. Results for LR over latent factors with 10-fold cross validation

	β coeff	MAX	MIN	Z-score
Intercept	1.22	1.53	.87	7.11
F4	-0.54	-0.23	-0.86	-3.38
F10	-0.69	-0.38	-1.05	-4.26
F9	-0.51	-0.21	-0.81	-3.36
F13	-0.49	-0.24	-0.74	-3.80

Comparison with Logistic Regression over a Selection of the Original Variables. Further experiments aimed to compare the predictive ability of the FA 14-factor solution with that of the original data variables were carried out. For that, the most significant clinical attributes were selected in a backward feature selection process (in our case, the backward feature selection removes those variables resulting in non-significant Z-scores). The selected attributes were: the total number of dysfunctional organs; the APACHE II score; and the worst lactate levels. The corresponding coefficients, maximum and minimum values and Z-scores for these three variables are presented in Table 2.

Table 2. Results for LR with 10-fold cross validation

	β coeff	MAX	MIN	Z-score
Intercept	4.20	3.11	5.29	7.56
APACHE II	-0.08	-0.13	-0.04	-3.77
Worst lact.	-0.25	-0.38	-0.11	-3.63

Regression on the most significant attributes together with 10-fold cross validation yielded an AUC of 0.75, a lower result than the one obtained with the FA solution. Following the procedure outlined in the previous subsection, a decision threshold of $\gamma = 0.68$ was automatically selected. This resulted in a prediction error over the test data of 0.3 (higher than the FA solution), a specificity of 0.72, and a sensitivity of 0.64.

Comparison with the APACHE II Mortality Score. The Risk-of-Death (ROD) formula based on the APACHE II score can be expressed as [60]:

$$\ln \left(\frac{ROD}{1 - ROD} \right) = -3.517 + 0.146 \cdot A + \epsilon \quad (1)$$

Where A is the APACHE II score and ϵ is a correction factor depending on clinical traits at admission in the ICU. For instance, if the patient has undergone post-emergency surgery, ϵ is set to 0.613. The application of this formula with a threshold of $\gamma = -0.25$ to the population under study yielded an error rate of 0.28 (higher than the FA solution), a sensitivity of 0.82 and a specificity of 0.55. The AUC was 0.70.

3.4 Sepsis Mortality Prediction from Observed Data

The previously reviewed studies analyzed dependence relations between the different variables and clinical traits and exploited their marginalization to study Sepsis and its prognosis through CIM, FA, LR and the APACHE II score. Here, we review the use of kernel methods to analyse the available data.

Table 3. Summary of prognosis indicators and their corresponding accuracies

Method	AUC	Error rate	Sens.	Spec.
LR-FA	0.78	0.24	0.65	0.80
LR	0.75	0.30	0.64	0.72
APACHE II	0.70	0.28	0.82	0.55
RVM	0.86	0.18	0.67	0.87
SVM-Quotient	0.89	0.18	0.70	0.86
SVM-Fisher	0.76	0.18	0.68	0.86
SVM-EXP	0.75	0.21	0.70	0.82
SVM-INV	0.62	0.22	0.70	0.82
SVM-CENT	0.75	0.21	0.70	0.82
SVM-GAUSS	0.83	0.24	0.65	0.81
SVM-LIN	0.62	0.26	0.62	0.78
SVM-POLY	0.69	0.28	0.71	0.76

In our approach [52], we first embedded the data in a suitable feature space, and then used algorithms based on linear algebra, geometry and statistics for inference. With this informal definition, it becomes apparent that all the methods used so far could be kernelized as long as we used the appropriate mappings, spaces, measures and topologies. Given the simplicity of the models used here (we only have multinomial and multivariate Gaussian distributions, which can be efficiently modelled algebraically by means of the Regular Exponential Family), we proposed to use a generative approach and exploit the inner data structure in order to build a set of efficient closed-form kernels best suited for these two distributions. In particular, we assessed the performance of the Quotient Basis Kernel (QBK) [52], the simplified Fisher kernel against other state-of-the-art methods such as, support vector machines with a Gaussian, Polynomial and linear kernels, generative kernels based on the Jensen-Shannon metric (Centred, Inverse and Exponential kernels) [68] and RVM [53] as sepsis mortality predictors.

All model performances were evaluated over a random test population consisting of 15% of the available data. The models were trained with 10-fold cross-validation and with 70% of data reserved for training and 15% of the data reserved for validation. Table 3 shows the results for all the experiments.

4 Conclusions

In this short overview paper, we have described the increasingly complex challenge posed by the current data availability surplus in medicine in general and critical care in particular. ML and related advanced data analysis methods have provided evidence of their value in extracting usable knowledge from these data. The many different approaches to the use of these methods in the CCD have been surveyed and the main challenges they face have been outlined.

We have exemplified the potential of ML by focusing on the Sepsis pathology. Attention has been paid to the new definitions of Sepsis and the relevance of using SIRS in its diagnosis. To address this problem, we have used conditional independence models, which have shown a dependence of SIRS in both organ dysfunction measured through the SOFA score and ICU outcome. In the light of these results, it is our opinion that the SIRS should still be considered in the study of the pathophysiology of Sepsis.

One of the main limitations of the quantitative methods for the assessment of ROD currently in use at the ICU is their lack of specificity (i.e. the high number of false positive cases they incur), which not only puts an extra risk on an already severely affected patient population, but also results in an unnecessary burden for National Health Systems. In this regard, ML and related techniques can play an important role as they improve the overall performance by combining the indicators already in place with other clinical variables, which are routinely measured.

Attending to the nature of clinical data available in the ICU, it is possible to better assess prognosis through a proper embedding of the data. The techniques proposed in the case study of this overview are related to regular exponential families in general and to the multinomial and Gaussian exponential families that resulted in the generative kernels outlined in previous sections. The accuracy of routinely used methods for assessing prognosis of septic patients in the ICU (LR and the APACHE II) yield acceptable accuracy but their performance in terms of specificity is limited. The RVM and LR over latent factors have been shown to yielded an acceptable performance. However, the kernel methods presented the best balance in all these performance parameters. It is also important to note that the QBK and the simplified Fisher kernel yielded the best results, as shown in Table 3. It is also important to note that both QBK and simplified Fisher kernel can be represented through graphical models, increasing their interpretability.

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