2019 IEEE 32nd International Symposium on Computer-Based Medical Systems (CBMS)

# On computer-aided prognosis of septic shock from vital signs

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***Abstract*—Sepsis is a life-threatening condition due to the reaction to an infection. With certain changes in circulatory system, sepsis may progress to septic shock if it is left untreated. Therefore, early prognosis of septic shock may facilitate implementing correct treatment and prevent more serious complications. In this study, we assess the feasibility of applying a computer-aided prognosis system for septic shock. The system is envisaged as a tool to predict septic shock at the time of sepsis onset using only vital signs which are collected routinely in intensive care units (ICUs). To this end, we evaluate the performances of computational methods that take the sequence of vital signs acquired until sepsis onset as input and report the possibility of progressing to a septic shock before any further clinical analysis is performed. Results show that an adaptation of multivariate dynamic time warping can reveal higher accuracy than other known time-series classification methods on a new dataset built from a public ICU database. We argue that the use of computational intelligence methods can promote computer-aided prognosis of septic shock in hospitalized environment to a certain degree.**

***Keywords-sepsis, septic shock, prognosis, time-series classification, vital signs.***

## I. INTRODUCTION

Sepsis is a life-threatening condition which requires special treatment under hospital ICUs. It occurs as a response to an infection in the body and may progress to a stage where the body is unable to provide adequate blood flow to organs. The final stage of the condition is called septic shock, which has a mortality rate of nearly 50 percent [1]. Although improved understanding and recent clinical applications have reduced the risk of dying with sepsis, the number of people who die each year continues to increase due to an overall increase in the number of cases. Therefore, identifying high-risk patients with sepsis is a great challenge. There are many different ways to predict the risk of dying for patients with sepsis. The handiest approach is classifying the patient according to their stage of sepsis, i.e. establishing the prognosis of the disease.

Various methods have been introduced for early identification of sepsis based on computational intelligence techniques such as machine learning or expert systems [2-4]. Existing tools can discriminate sepsis and non-sepsis cases with reasonable accuracy using a set of clinical features obtained from laboratory experiments or physiological measurements.

The number of studies for predicting the stage of sepsis, e.g septic shock, is smaller. Recent studies have employed multivariate logistic regression models for prediction of septic shock [5] [6]. Decision trees were another family of methods used for same problem [7] [8]. Tang et al. [9] employed principal component analysis (PCA) with a non-linear support vector machine (SVM) on time-series physiological waveform datasets. Lukaszewski et al. [10] used molecular tests to obtain expression levels of miRNAs and integrated them with clinical data to develop a model based on a multi-layered perceptron for predicting the risk of septic shock. Some studies have shown that the use of proper feature selection, pre-processing and missing-value imputation techniques could improve septic shock classification performance [11-15]. Finally, Ghosh et al. [16] introduced an adaptive Markov model to predict septic shock from physiological waveform data.

There are two limitations with existing methods. First, they were designed as diagnostic tools such that they are able to classify current condition as a septic shock or not. Here, a negative sample may refer to either a sepsis case without progression to a septic shock or a completely healthy person without any infection but under ICU monitoring. Latter group makes the prediction problem easier because healthy cases usually have physiological measurements within acceptable ranges while the others do not. On the other hand, more challenging expectation is having prognostic tools to get an early warning about the progress of the patient who is already diagnosed as sepsis. Therefore, a prognostic tool here refers classification of patients as septic shock or not where a negative sample is also an infected person. Presence of such tools will guide further clinical treatments and facilitate ICU management activities. Second limitation is the fact that all septic shock prediction methods use lab results obtained from blood, urine and/or molecular sample tests. This requires additional effort and implementation cost with delayed decisions. A common motivation in ICUs is monitoring patients with only routine measurements held by daily nursing activities and getting an early support for clinical decisions [17].

2372-9198/19/$31.00 ©2019 IEEE
DOI 10.1109/CBMS.2019.00028

In this study, we address these two challenges and offer a framework for computer-aided prognosis of septic shock with minimal data. The framework is envisaged as a tool to predict septic shock at the time of sepsis onset using only vital signs which are collected routinely in ICUs. The present article evaluates the feasibility of applying such tool in terms of the accuracy of septic shock prediction. To this end, we built a dataset of sepsis patients comprising the sequences of several vital signs measured before sepsis onset time and their labels for septic shock. Then, we adapted existing algorithms for time-series classification for the problem and presented their performance results on new dataset. We finally discuss current limitations and future challenges in deployment of such tool.

## II. METHODS

### A. Data collection and preprocessing

The dataset was collected from v1.4 release of the Medical Information Mart in Intensive Care (MIMIC)-III database [18]. The MIMIC database contains anonymous data from more than 40,000 patients admitted to Beth Israel Deaconess Medical Center (Boston, MA) between 2001 and 2012. Recently, a sepsis cohort was built from this database based on the latest clinically agreed definition of sepsis, called Sepsis-3 [19]. They analyzed 23,620 ICU admissions from MIMIC-III database. After applying a set of exclusion criteria, a final cohort of 11,791 patients was released. A clinical criterion, called Sequential Organ Failure Assessment (SOFA) score was calculated for each patient at time of last antibiotics administration and a culture sample draw. Then, a sepsis onset time is predicted based on the significant change in SOFA score. Taking the initial time of the earliest culture draw or antibiotics administration as the suspicion of infection, a window up to 48 hours before this time and 24 hours after this point was analyzed. If the increase of SOFA score between the beginning and end of this window is larger than twice, then the first such hour was predicted as sepsis onset time.

We collected the measurements of six different vital signs for each of 12 hours prior to predicted sepsis onset time. These include heart rate, blood pressure, respiratory rate, oxygen saturation, Glasgow Coma Scale (GCS - eye opening) and temperature. If there is more than one measurement for any one-hour bin, the values were averaged. To build our own dataset for septic shock, we applied two further inclusion criteria: (1) a sepsis onset time can be predicted, and (2) at least one measurement is available for each of the vital signs 12 hour prior to predicted onset time. Each patient was labelled by his/her ICD9 code to determine positive (ICD9 of 785.52) and negative samples. This was resulted in a dataset of 3,270 ICU stays comprising six physiological measurements on 12 time points, predicted onset times, SOFA scores and binary class labels (210 positives) for septic shock.

The imputation of missing data is performed by a carry-forward scheme, where latest measurement is carried forward to fill subsequent empty time points. The time points that precede the collection of any measurements are back-filled with the first subsequent hour with recorded value.

### B. Problem formulation

Given a sequence of vital signs collected until sepsis onset, the task is to predict whether the current patient will progress to a septic shock condition or not. More formally, the problem can be considered as a time-series binary classification task where the input is a short multi-variate signal of physiological measurements and the output is a binary value representing the occurrence of septic shock. Here, we consider two different families of computational methods for time-series classification to adapt for septic shock prediction: (1) model-based and (2) instance-based methods.

### C. Model-based methods

A model-based time-series classification method takes a number input samples with relevant class labels and builds a model that can distinguish optimally between predefined classes. A key problem in this context is how to feed this model with time-series signals of varying lengths, different scales and potential time-shifts. One of the common solutions is to extract a fixed-number of numerical features and use this vectorized transformation of time-series signal as input samples. Being inspired from some recent applications [20-22], we extract the following features from time-series vital signs in our case: mean, median, variance, entropy, root mean square, interquartile range, mean absolute deviation, and quantiles for five evenly spaced cumulative probabilities.

Due to their common use in computer-aided diagnosis systems, we consider four different machine learning models to develop septic shock classifiers: (1) Linear Regression, (2) Support Vector Machine (SVM), (3) LogitBoost, and (4) Random Forest. Linear Regression builds simply a linear model that relates input variables to the response variable. SVM is a model generated by a two-step procedure: first, the high dimensional input space of the SVM is non-linearly mapped into a higher dimensional feature space, and then, a linear hyperplane is constructed in this feature space with the largest possible margin separating the classes of the data. In our experiments, we applied a random feature expansion scheme to approximate a Gaussian kernel implementation [23]. LogitBoost is the ensemble-aggregation algorithm based on boosting of several weak learners [24]. Here, we use a set of decision trees with the cost function of logistic regression to implement logitboost as a binary classifier. Random Forest builds a number of multiple decision trees to train a model, where a decision tree is a flowchart-like structure in which each internal node represents a test on a feature representing the corresponding sample [25]. After training the forest, it enables to pass each test row through it, in order to output a prediction. A query is classified by voting over built decision trees.

### D. Instance-based methods

In time-series classification, a powerful alternative to model-based methods is to employ pairwise similarity

between input instances to infer class variables. Given a query to be classified, an instance-based method scans through each training sample to compute a pairwise similarity score between the query and that sample, by taking account for temporal behavior of the data. The majority label owned by nearest samples is reported as predicted class. An important concern in this implementation is how to infer pairwise similarity between two multivariate signals with different scales and potential time lags. In our study, we consider two elastic time-series measures, dynamic time warping (DTW) and alignment of textures (ALoT), to score similarity between the sequences of vital signs, $X=(x_1,x_2,...,x_m)$ and $Y=(y_1,y_2,...,y_m)$. DTW computes a distance score $D(X, Y)$, instead of a similarity score, by aligning observed values of the input time-series signals to minimize the total absolute difference between individual observations at each time point (Algorithm 1).

**Algorithm 1. DTW($X$, $Y$)**

1: Let $H$ be an $m \times m$ matrix initialized to $\infty$
2: $H(0,0) \leftarrow 0$
3: for $i \leftarrow 1$ to $m$ do
4: for $j \leftarrow 1$ to $m$ do
5: $H(i, j)= dist\ (x_{i-1}, y_{j-1}) + min(H(i\text{-}1, j\text{-}1), H(i\text{-}1, j), H(i, j\text{-}1))$
6: return $(D(X, Y) \leftarrow H(m, m))$

In a typical implementation of DTW on one-dimensional signals, the *dist* function in step 5 refers to the simple arithmetic difference of the inputs. Since we have several physiological measurements at the same time, we use a multi-channel version of DTW and implement *dist* function as Euclidean distance between multivariate measurements at any time point.

The ALoT algorithm [26] is considered as an alternative to DTW for calculating the similarity $S(X, Y)$ based on the alignment of inputs (Algorithm 2). The function *toTexture* (steps 2 and 3) is used to transform the input signal into a sequence of textures extracted from the observed time-series data [27]. ALoT computes the Hamming distance between the bit sequences that represent the observed local texture (*distHamming* in step 6).

**Algorithm 2. ALoT($X$, $Y$)**

1: Let $H$ be an $m$+1 × $m$+1 matrix initialized to zero
2: $A \leftarrow toTexture(X)$
3: $B \leftarrow toTexture(Y)$
4: for $i \leftarrow 2$ to $m+1$ do
5: for $j \leftarrow 2$ to $m+1$ do
6: $H(i, j)=max(H(i\text{-}1, j\text{-}1) - distHamming(a_{i-1}, b_{j-1}), H(i\text{-}1, j) - \sigma, H(i, j\text{-}1) - \sigma)$
7: return $(S(X, Y) \leftarrow H(m+1, m+1))$

## III. RESULTS

We applied model-based and instanced-based methods in our dataset for binary classification of septic shock. Model-based methods were first fed directly by the sequence of physiological measurements as features. Since same number of measurements were taken for each patient (or imputed missing data accordingly), the models did not suffer from the problem of varying length inputs here. Then, the inputs were replaced by extracted features from time-series. Table 1 lists the prediction accuracy for each method in terms of Area under Receiver Operating Characteristics curve (AUROC) with leave-one-out cross validation tests. The ensemble methods built over decision trees (RF and Logitboost) are more successful than the geometric methods (LR and SVM) in separating between classes. RF performs better than all other model-based methods. Using extracted features instead of direct feed of the vital sign measurements can provide a slight improvement in the accuracy of RF, although this is not consistent with the results of other learning methods.

TABLE I. COMPARISON OF METHODS FOR SEPTIC SHOCK PREDICTION

| Approach | Sequence Representation | Method | AUROC |
|---|---|---|---|
| Model-based | Direct | LR | 0.571 |
| | | SVM | 0.573 |
| | | Logitboost | 0.716 |
| | | RF | 0.717 |
| | Extracted Features | LR | 0.514 |
| | | SVM | 0.521 |
| | | Logitboost | 0.640 |
| | | RF | 0.721 |
| Instance-based | Direct | Ensemble DTW | 0.490 |
| | | Ensemble ALoT | 0.571 |
| | | Multichannel DTW | **0.730** |

TABLE II. PREDICTION PERFORMANCE WITH VARYING COMBINATIONS OF VITAL SIGNS.

| Vital signs used in alignment | | | | | | AUROC |
|---|---|---|---|---|---|---|
| heart rate | blood pressure | respiratory rate | oxygen saturation | GCS | temperature | |
| + | - | - | - | - | - | 0.589 |
| - | + | - | - | - | - | 0.568 |
| - | - | + | - | - | - | 0.656 |
| - | - | - | + | - | - | 0.573 |
| - | - | - | - | + | - | 0.577 |
| - | - | - | - | - | + | 0.532 |
| + | + | + | + | + | + | 0.703 |
| + | + | + | + | + | - | 0.730 |
| + | + | + | + | - | + | 0.702 |
| + | + | + | - | + | + | 0.690 |
| + | + | - | + | + | + | 0.671 |
| + | - | + | + | + | + | 0.638 |
| - | + | + | + | + | + | 0.686 |

Instance-based methods were applied in two different ways: ensemble of single channel alignments and simultaneous multichannel alignment. In the former case, each vital sign contributes the similarity score independently and adds up to the final score by simple averaging of individual similarity scores for all vital sign sequences. Later case aligns all sequences concurrently to evaluate their integrative effects. In ensemble single channel application, ALoT performs slightly better than DTW although its accuracy is not yet practical. Multichannel DTW achieves AUROC of 0.73 and outperforms all others including model-based methods.

Since multichannel DTW achieved highest accuracy in predicting septic shock, further experiments were conducted with this method. Contribution of vital signs in prediction ability was evaluated by two ways: (1) running the algorithm with each of single vital sign alone and (2) leaving out one of the vital signs at each time and running the algorithm with remaining measurements (Table 2). The results determine that none of the individual signs is representative enough to model the prognosis of septic shock when used alone; however, respiratory rate is the most descriptive measurement. This empirical result aligns with the fact that most severe symptoms which appear in progressing to septic shock are related to respiratory system. In our setup, temperature is the least effective vital sign in explaining the progress to a septic shock. Use of temperature in predictive model even lowers the accuracy. The best prediction performance can be achieved when other five vital signs are used in combination.

Figure 1 evaluates the effect of $k$ (number of neighbors used for majority voting in instance-based classification) on prediction performance. The highest accuracy was achieved when $k$ is 21. There is an absolute decrease in the performance when $k$ becomes lower. No further improvement is observed for higher values of $k$.

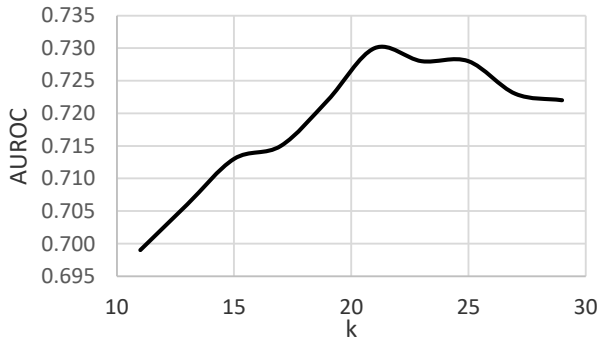


Figure 1. Effect of $k$ in prediction performance

We questioned the necessity of sequential measurement data for all time points during 12 hours prior to sepsis onset. To evaluate this, we replicated the experiments for several cases given in Table 3. When we use instant measurements on predicted onset time, the model achieves AUROC of 0.697. The performance is lower when instant values

measured 12 hours before the onset are used. Having six sequential measurements increases the accuracy in any case, whilst the best prediction performance is achieved when all 12 time points are used in the alignment. The measurements that are closer to sepsis onset time are more descriptive than earlier records.

TABLE III. EFFECT OF USING SEQUENTIAL DATA ON PREDICTION PERFORMANCE.

| Measurements used | AUROC |
|---|---|
| Single measurement, 12h prior to onset | 0.681 |
| Single measurement, 0h prior to onset | 0.691 |
| Last 6 measurements, 6h prior to onset | 0.697 |
| Last 6 measurements, 0h prior to onset | 0.709 |
| Last 12 measurements, 0h prior to onset | 0.730 |

## IV. DISCUSSION AND CONCLUSION

The present study aims at assessing the feasibility of a computational system that monitors the sequence of easily accessible vital signs to predict septic shock early on sepsis onset time. The novelty is twofold. First, the system is considered as a prognostic tool where the positive case refers to an unfavorably progressed stage of current disease while the negative case is still a diseased sample. Second, the tool is supposed to employ only non-invasive measurements which are routinely collected in ICU setting for decision support.

The study assesses the prediction accuracy of existing algorithms for time-series classification when adapted for septic shock prediction from vital signs. The results determine that an adaptation of multichannel dynamic time warping can achieve the highest accuracy compared with all other instanced-based and model-based methods. This can be attributed to the fact that DTW can model sub-temporal changes associated with the progress of septic shock whereas statistical features extracted from short time-series of vital sign sequences are not enough to represent these behaviors. On the other hand, ALoT did not perform with competitive accuracy because these relationships are more related with the exact values of physiological measurements rather than their texture.

The results argue that the respiratory rate is most descriptive in explaining the progress to septic shock while using other four vital signs, i.e. heart rate, blood pressure, oxygen saturation and Glasgow Coma Scale is also helpful in increasing prediction accuracy. The changes in temperature prior to sepsis onset are not relevant to possibility of septic shock in later stages. Most effective time period for reliable predictions is last 12 hours to onset time. Using all measurements through this period can result with higher accuracy compared with using fewer measurements.

Practical limitations of such tool arise from classical problems in the field of computer aided decision support in health domain [28]; these are unavailability of enough data, class imbalance in training data and missing/incorrect measurements. Although MIMIC database can offer the community a plenty amount of data in this respect, the number of labeled septic shock cases is not sufficient when time-series data are considered. The class imbalance problem was handled in this study at the assessment level by using AUROC instead of computing direct precision and recall values as performance criteria, although resampling could have been another solution. Recent studies have shown that advanced missing data imputation techniques can improve the prediction accuracy [14, 29]. Therefore, a practical solution for septic shock prognosis should consider implementing convenient techniques for handling with small and imbalanced data and imputing missing values.

## ACKNOWLEDGMENT

This study is partially funded by ERANet-LAC Program with reference ELAC2015/T09-0819 (SPIDEP Project – Design and implementation of a low cost smart system for pre-diagnosis and telecare of infectious diseases in elderly people). Funding bodies have not taken an active role in the implementation of the study.

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