Outcome prediction for patients with severe traumatic brain injury using permutation entropy analysis of electronic vital signs data

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Abstract. Permutation entropy is computationally efficient, robust to noise, and effective to measure complexity. We used this technique to quantify the complexity of continuous vital signs recorded from patients with traumatic brain injury (TBI). Using permutation entropy calculated from early vital signs (initial 10~20% of patient hospital stay time), we built classifiers to predict in-hospital mortality, and mobility measured by 3-month Extended Glasgow Outcome Score (GOSE). Sixty patients with severe TBI produced a skewed dataset that we evaluated for accuracy, sensitivity and specificity. With early vital signs data, the overall prediction accuracy achieved 91.67% for mortality, and 76.67% for 3-month GOSE in testing datasets, using the leave-one-out cross validation. We also applied Receiver Operating Characteristic analysis to compare classifiers built from different learning methods. Those results support the applicability of permutation entropy in analyzing the dynamic behavior of biomedical time series for early prediction of mortality and long-term patient outcomes.

1 Introduction

Continuous vital signs (VS), such as heart rate (HR), blood pressure (BP), and oxygen saturation (SpO_2), among others, are sequential assessments of important physiological functions, providing basic evidence of patients' status. Because VS are an early-warning-system of physiologic perturbation, they are usually recorded hourly in the intensive care unit (ICU) setting. However, in most modern ICUs, automated electronic instrumentation is gathering these data continuously, and the massive quantities of high-quality data produced create both a challenge to store, analyze, and interpret and an opportunity to explore novel advanced analytic methods for predicting outcomes. Such predictive algorithms can support advanced instrumentation and decision-assist tools that have the potential to significantly improve clinical outcome for these very ill patients.

A number of approaches have been suggested for utilization of VS data for prediction of adverse outcomes. These analyses attempt to discover the intrinsic patterns that characterize continuous, multivariate, time-series systems. One strategy is to embed the time series into higher dimensional space and then compute various entropies for the elements of the embedded time series. Conventional entropies such as Shannon entropy, Renyi entropy and Tsallis entropy can be calculated given the distribution of elements of the embedded time series. The Renyi entropy of a time series has been used to detect spatially varying multivariate relationships [9] and to study brain injuries [8] and heart rate variability [4,5]. The Tsallis entropy of the elements of a time series has been used to monitor brain injuries after cardiac arrests [2, 24], and to improve the accuracy of gene regulatory networks inference [15].

The initial applications of ordinal pattern and permutation entropy demonstrate this to be very promising in quantifying and analyzing the dynamic behavior of biomedical and other time series. Introduced by Bandt and Pompe [1] in 2002, permutation entropy is a new measure of complexity of time series, and extracts qualitative information from non-linear time series. Examples include identifying temporal gene expression profiles [22], measuring the anesthetic drug effect from electroencephalograms (EEGs) [13, 17], characterizing brainwave data of epileptic patients [14, 18] and sleep EEGs [3, 16], change detection in dynamic systems [5], and financial time series [23].

In this research effort, we have focused on VS classification. Given a number of VS sequences and their corresponding outcomes, we want to train a model to predict the outcome for a new sequence of VS. Permutation-based distribution estimation is used to calculate the Renyi entropy of the multivariate VS series, and to predict the in-hospital mortality and the three-month Extended Glasgow Outcomes Scale (GOSE). The early prediction is achieved by using the continuous automatically collected and stored electronic VS data collected in the first 10~20% of patient hospital stay time. To evaluate the results, we calculated accuracy, sensitivity, and specificity to quantify the performance of classifiers, especially for the imbalanced training/testing data sets. The Areas Under the Curve (AUCs) of the receiver operating characteristic (ROC) are also used to compare classifiers constructed by different learning methods. Using the first 3 days' VS of 5-minute time resolution, overall 91.67% prediction accuracy for mortality (classifier AUC= 0.84, $p < 0.001$), and 76.67% accuracy for 3-month GOSE (classifier AUC=0.71, $p = 0.001$) were achieved with the testing data set.

The remainder of this paper is organized as follows. In section 2, we briefly introduce the permutation entropy and the entropy map that we used for quantifying the characteristics of the dynamic system. In section 3, we describe the dataset and experiment design. We apply the permutation entropy to predict mortality and 3-month GOSE, and present experiment results, evaluated by accuracy and the area under the receiver operator characteristic (ROC) curve. Finally, in section 4, we provide discussions and summary.

2 Method

2.1 Ordinal pattern and permutation entropy

That the physiological status of living things is dynamic but has identifiable and repeated patterns is assumed. Likewise, we assume that these patterns will be different in the healthy, injured, and/or ill individuals and that the patterns will be discernibly different from each other. For example, the VS of healthy individuals fall generally within a range of normal, whereas those of patients suffering from severe traumatic brain injury (TBI) have VS that fall outside of these norms. For instance, if the patient is also losing blood, blood pressure (BP) will fall. Heart rate (HR) increases to compensate for the decreased BP to ensure adequate circulation and oxygenation of the brain, and the increase in HR usually increases the BP, at least temporarily. If blood loss continues, BP falls, and clinicians will usually give fluid, including blood, to raise the BP and insure adequate oxygenation. These changing patterns of HR and BP are accompanied by changes in intracranial pressure (ICP), cerebral perfusion pressure (CPP), and so on.

Bandt and Pompe [1] suggested an approach to time series analysis in which they embedded a continuous timeseries as a symbolic sequence into another space, a process which they called "permutation entropy." One major ingredient of permutation entropy is the ordinal pattern. The ordinal pattern of a sequence of elements $x_1, \ldots, x_n$ is the permutation (re-arrangement) $\pi = (i_1, i_2, \ldots, i_n)$ that sorts the amplitude values in ascending order so that $x_{i_1} \leq x_{i_2} \leq \ldots \leq x_{i_n}$.

The order L permutation entropy of a timeseries $x_{1\ldots N}$ is calculated as follows. Let π_t be the ordinal pattern (i.e. the sorting permutation) for the segment of the timeseries under the sliding window of length L that ends at x_t, i.e. the subsequence $x_{t-L+1}, \ldots, x_t$. Let $S_L = \{\pi_k\}$ be the set of all those unique (alphabet) ordinal patterns π_t. To the timeseries $x_{1\ldots N}$ there corresponds the sequence $\langle \pi_t : t = L, \ldots, N - L + 1 \rangle$ of $N - L + 1$ ordinal patterns from the alphabet S_L. The entropy of this sequence of ordinal patterns is the permutation entropy of the timeseries $x_{1\ldots,N}$. For example, the Shannon permutation entropy is defined in equation (1),

$$H_L = -\sum_{k \in \mathcal{S}_L} P(\pi_k) \log(P(\pi_k)). \tag{1}$$

where $P(\pi_k)$ is the frequency of π_k in the sequence $\langle \pi_t \rangle$. In the work presented here, we use the Renyi entropy with parameter α of the sequence $\langle \pi_t \rangle$ defined as

$$R_L^{(\alpha)} = \frac{1}{1-\alpha} \log(\sum_{k \in \mathcal{S}_T} P(\pi_k)^\alpha). \tag{2}$$

The parameter α in the Renyi entropy acts as a selector of probabilities. It assigns almost equal weight to each possible probability when α is sufficiently close to zero. When α is larger, it puts more weights on higher probabilities. With this property, Renyi entropy can filter out the small probability events, and better capture the essence of the system.

2.2 Multivariate time series

In real applications, a single variable is generally insufficient to sketch the profile of complex dynamic systems, because they respond to multiple factors in a nonlinear manner. For example, many VS are used to monitor TBI patient status – HR, systolic BP (SBP), SpO_2, ICP, CPP, etc. Suppose there are M variables. Given a window size L, vital signs within that window are viewed as one slice of size $M \times L$. Figure 1 demonstrates one example of finding ordinal patterns from

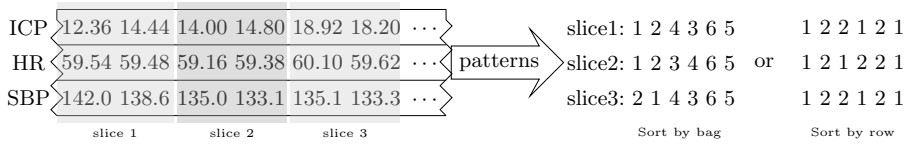


Fig. 1: Illustration of ordinal patterns built by permutation in two ways. The exemplary time series snippet comes from 6 points of 5-min smoothed data from one patient.

a finite sequence of time series. Suppose that there are 3 vital signs ($M = 3$) available for inclusion: ICP, HR, and SBP. Let the window size be $L = 2$. Therefore, one slice constitutes 6 points, which means that we embed VS in a window of size 2 into a higher dimension 6. There are two choices to permute in a slice. The first one considers one slice as one bag. All values in this bag are sorted in an ascending order. For example, in Figure 1, slice 1 can be written linearly as the sequence: (ICP)12.36, 14.44; (HR)59.54, 59.48; (SBP)142.0, 138.6. Labeling each value 1∼6, the values of this sequence can then be sorted into ascending order by applying a permutation $\langle 1\ 2\ 4\ 3\ 6\ 5 \rangle$. Another choice is to sort within each variable, then concatenate them. For the same example, if we sort ICP, HR, SBP in slice 1 separately, and concatenate their local permutation index, we obtain the pattern $\langle 1\ 2\ 2\ 1\ 2\ 1 \rangle$. The second method would help keep each variable isolated even if they may have similar range, and hence maintain the ordinal patterns from each variable.

With the permutation entropy, we can construct a feature for each patient, and apply the supervised learning methods, such as decision tree, support vector machines, and discriminant analysis to build models from known outcomes. Furthermore, instead of using a single feature, we can create a family of features using different parameters in the entropy calculation. This strategy is more practical, for the following reasons. First, a family of features will leave the learning methods to select the most appropriate features with the data provided. This is always desired since we have limited knowledge to determine optimal window size and the parameter values for entropy calculation. Besides, using a different set of parameters may help us find more patterns that exist in other different spaces.

2.3 Evaluations

To evaluate results, not only the accuracy, but also the sensitivity, specificity and ROC analysis are utilized to compare performance of different classifiers. The ROC is a tool to depict the tradeoff between sensitivity and specificity. One major reason we adopt the ROC AUC for classifier comparison is that the dataset is skewed, and the ROC AUC is insensitive to the skewness of data sets [7]. Such property of ROC curves provides us a way to evaluate the classifiers without worrying about the datasets from which they were trained. Instead of using one single point, we can use the instance statistics to produce a full ROC curve by calculating the class label scores [7]. Provost *et al.* [20] described a method of calculating the ROC by assigning a score to each instance that reaches the leaf of the decision tree. That score is equal to the ration of positive class labels assigned to that leaf during training. Platt [19] suggested a way of estimating posterior probability from the output of a support vector machine by fitting a sigmoid function.

3 Experiments and Results

3.1 Data and setup

After removal of patient identifiers, continuous, automated electronic VS data collected over the course of hospitalization from patients with severe TBI were analyzed using permutation entropy to predict in-hospital mortality and 3-month GOSE outcomes. These patient data were part of a larger study of prediction factors after severe TBI that is ongoing at the R Adams Cowley Shock Trauma Center, Baltimore, Maryland. Our dataset was collected during 2008 and 2009 from 60 sequentially admitted individuals, 9 female and 51 male, 8 of whom died while in hospital. The average duration of stay in hospital was 16 days (range, 1.5 to 53 days); 52 patients remained in the hospital longer than 1 week; and 27 patients stayed longer than 2 weeks. Among the 52 patients discharged from the hospital alive, follow-up interviews were carried out at 3 months post-discharge to assess functional outcomes of patients after treatment in terms of an 8-category scale [10]: dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, and upper good recovery. Categories 1 to 4 are defined as "unfavorable" (value 1) and categories 5 to 8 as "favorable" outcomes (value 0). For 3-month GOSE in our dataset, 25 individuals had "favorable" outcome and 35 had "unfavorable" outcome, which, for our purposes, give a relatively balanced data set.

The raw, every-6-seconds data were preprocessed to deal with noise due to unstable attachment of sensors, patients' movement and missing values. To reduce the negative effect of noise, VS data were smoothed in a 5-minute tumbling window, as previously described [11]. In addition, gaps often occur at the start of the vital sign sensor placement or because patients were moved between hospital units (ICU, Operating Room, etc.). Table 1 shows the percentage of missing points of six selected VS. To utilize all information, we perform some impute

techniques, by using the k-nearest neighbors' average as the surrogate values. Another approach is to use the average values of the VS as the fill-in value.

Determining the optimal selection of VS with which to set up the experiment parameters can be difficult, that is, which values are optimal for the window size and the α range of the Renyi entropy. Therefore, our parameters were selected based on the following considerations. First, a group of VS that are frequently used in clinical diagnosis were chosen, such as ICP, CPP, SBP, SpO_2, etc. Those VS with the lowest percentage of missing points and missing data were selected to increase the chances of preserving more patterns, therefore more accurately characterizing the changing physiologic dynamics. A dataset was also tested for change of accuracy with and without removing a given vital sign. Correlated or dependent variables may be included in the dataset for ordinal pattern finding. However, it will not be redundant to include those variables when the relationship among those correlated variables are not order preserving. Hence, for simplicity, the rule of thumb is followed to select VS.

Using the above criteria and tests, a group of five VS were selected (see Table 1) and tested iteratively. Then the range of window size was selected for a block of vital signs among 3, 6, 12, equivalent to VS collection durations 15, of 30 and 60 minutes. In addition, the range for the Renyi entropy parameter α was selected as 0.1 to 2.0 with step size 0.01.

Table 1: Percentage of available values for selected vital signs

Vital signs	Percentage of available points			
	First 1 day	First 2 days	First 3 days	All
HR	90.07%	93.05%	94.53%	87.60%
SpO_2	87.04%	90.79%	92.38%	85.20%
SBP	88.71%	91.80%	93.23%	81.65%
SI=HR/SBP	88.71%	91.80%	93.23%	81.65%
ICP	68.63%	78.14%	79.81%	37.72%
CPP *	65.69%	74.51%	76.48%	36.45%

*not included due to its limited contribution to accuracy.

3.2 Prediction for mortality and 3-month GOSE

With the above setting, experiments were conducted to predict in-hospital mortality and 3-month GOSE. Since the sample size of 60 instances does not form a very large dataset, the leave-one-out cross validation method was used for training and testing.

For each individual patient, a collection of features based on entropy are built as follows. First, selected VS of a certain length (i.e. 3 days VS) are aligned by time and filled in for missing values with the k-nearest neighbor imputation method. Next, given a slice window size L, the VS within a moving window of length L are sorted in bag and are represented by permutations. Such collection

of permutations makes an alphabet, where the frequency of each "word" (permutation pattern) is calculated. With a vector of instantiation of parameter α in the equation (2), a set of entropy values are calculated for the window size L. Then the second step is repeated for different parameter values for L. So far, a group of new features are created for individual patients, which are different measurement of their physiological status complexity. With those features, various kinds of classification methods are applied to predict outcomes of clinical interest.

Tables 2a and 2b show confusion matrices and overall accuracy for predicting mortality and 3-month GOSE. The a priori knowledge is that 13.3% died in hospital, and 58.3% have unfavorable 3-month GOSE. Using early VS as defined above, a classification tree built upon permutation entropy achieved 62.50% in true positive rate (91.67% in overall accuracy) in predicting death, and 82.86% in true positive rate (76.67% in overall accuracy) in predicting unfavorable cases for 3-month GOSE, which are all higher than the a priori. This suggests that the permutation entropy is capable of classifying patients of different physiological status, and can handle imbalanced class distribution. On the other hand, the permutation entropy also demonstrates good performance of prediction using early VS. This has potential clinical importance in providing medical care providers with timely prognostic information.

Table 2: Confusion matrices for classification trees built upon features created by permutation entropy on the testing set.

(a) In-hospital mortality

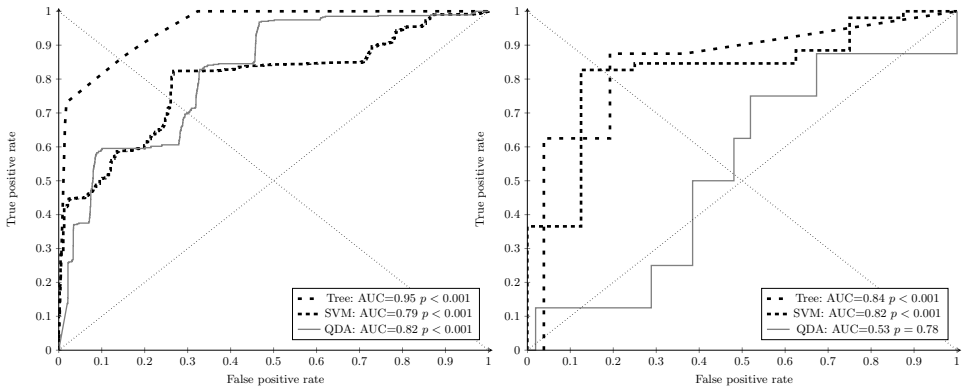
Predicted / True	First 1 day		First 2 days		First 3 days	
	(A)	(D)	(A)	(D)	(A)	(D)
(A)live	94.23%	5.77%	86.54%	13.46%	96.15%	3.85%
(D)ead	62.50%	37.50%	75.00%	25.00%	37.50%	62.50%
Overall	86.67%		78.33%		**91.67%**	

(b) 3-month GOSE

Predicted / True	Last 3 days		Last 2 days		Last 1 day	
	(G)	(B)	(G)	(B)	(G)	(B)
(G)ood	68.00%	32.00%	44.00%	56.00%	52.00%	48.00%
(B)ad	17.14%	82.86%	37.14%	62.86%	48.57%	51.43%
Overall	**76.67%**		55.00%		51.67%	

We then applied two other different learning methods, the support vector machine (SVM) and the quadratic discriminant analysis. The ROC AUC is employed to assess the performance of different classifiers. As noted above, ROC graphs depict the tradeoff between sensitivity and specificity for each classifier in both training and testing data sets, and the AUC measures the probability of

the classifier assigning a higher score to the positive than to the negative case, if one positive and one negative case were to be randomly drawn. Figures 2a and 2b show the in-hospital mortality prediction on the training and testing sets, using the first three days' VS. Figures 3a and 3b compare prediction power of three classifiers for 3-month GOSE using the last three days' VS. Note that the classifier built by the classification tree has the best discrimination for mortality prediction on both the training and the testing sets. The classification tree also has good discrimination capability on the 3-month GOSE outcomes.



(a) Training (b) Testing

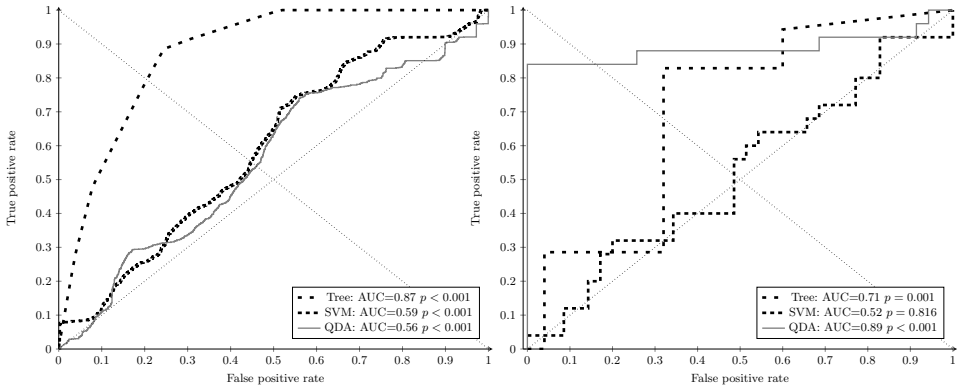
Fig. 2: ROCs of mortality classifiers built by three learning methods, using 3 days training set.

3.3 Baseline

In this section, we compare our results with other models created from clinical experience to demonstrate that permutation entropy method has stable and comparable performance.

Many empirical models have been studied and reported to estimate patients' current and future status. With computer assistance, more statistical metrics can be calculated from long duration vital signs records. Previous work by our group [12, 21] on this same dataset studied cumulated dose of ICP $>$ 20mm Hg, CPP $<$ 60mm Hg and Brain Trauma Index (BTI=CPP/ICP) as features to predict functional outcomes for patients of severe BTI, using ROC analysis and observed good predictive power for 3-month GOSE 1-4 (AUC=0.65~0.75, $p < 0.05$) [21].

To compare with features built from the permutation entropy, up to 5 features from the 5 vital signs in Table 1 were selected. Mean values of HR, SpO_2, SBP, shock index (SI=SPB/HR), and ICP were calculated using the first 3 days data for the in-hospital mortality prediction, and the last 3 days for the 3-month



(a) Training (b) Testing

Fig. 3: ROCs of 3M-GOSE classifiers built by three learning methods, using 3 days training set.

GOSE. Table 3 compares the performance of classification tree built on features from the permutation entropy and the top 3 classification trees built on subsets of features out of total $\sum_{k=1}^{5} C_5^k = 31$ combinations from the Table 1.

It can be observed that the classification tree built upon features created by the permutation entropy demonstrated better performance in terms of overall accuracy and values of AUC for both in-hospital mortality and 3-month GOSE prediction.

Table 3: Comparison between permutation entropy and baseline models on testing set.

Decision tree features	Mortality			Decision tree features	3-month GOSE		
	Accu.	AUC	p-value		Accu.	AUC	p-value
Entropy	91.67%	0.84	< 0.001	Entropy	76.67%	0.71	0.001
ICP/SPO2/HR	85.00%	0.71	0.057	SPO2/HR	68.33%	0.69	0.005
SBP	81.67%	0.82	< 0.001	SPO2/SBP/HR	65.00%	0.68	0.009
SI/SBP	80.00%	0.78	0.005	SI/SPO2/HR	63.33%	0.67	0.013

4 Conclusion

4.1 Summary

Using a large collection of continuous, automated, electronic patient VS data, we derived features to quantify the complexity of this dynamic system using

permutation entropy and found that VS features can predict in-hospital mortality and 3-month GOSE, despite a skewed dataset from relatively few instances. These features created by permutation entropy demonstrated promising results. Among 13.3% deaths (58.3% unfavorable cases), we observed 91.67% overall accuracy (62.5% for deaths) for in-hospital mortality prediction, and 76.67% in 3-month GOSE prediction (82.86% for bad outcomes). In comparison with other classifiers on the same dataset, permutation entropy predicted in-hospital mortality and 3-month GOSE with greater accuracy and area under the receiver operating characteristic curves (ROC AUC=0.84, $p < 0.001$ for mortality, and ROC AUC=0.71, $p = 0.001$ for 3-month GOSE on testing sets).

Permutation entropy is capable of capturing the essentials of dynamic systems described by time series, which can be used to create interpretable decision rules. The capability that this method displays in our study to identify within the first 12 hours of care changes in VS associate with long-term outcome, offers clinicians the potential for early interventions, which may improve outcome.

4.2 Future Work

In this study, we used features created by permutation entropy to compare the capabilities of this technique with AUC in prediction of outcome. The accuracy of the prediction models can be improved by including extra descriptive features, such as those features studied in comparison. Furthermore, patients can be categorized into refined subgroups, for which more specific models can be built by categorizing by age or types of injury.

Higher frequency data can be used to enhance early prediction. Optimal calculation of entropy requires time series of sufficient length for a reasonable estimation of ordinal pattern distribution. Using higher frequency data, such as waveform data, permutation entropy may be able to create features to describe the system complexity in earlier time series, such as the first 12 hours in the hospital.

4.3 Clinical Implication

Access to valid clinical prognosis is important in the first 72 hours of care among a group of patients typically hospitalized for several weeks. However, the overall mean time to death for people who died of TBI in our system is 24 hours [6]. Our long-term goal in this work is to provide the critical care team with access to valid clinical prognosis in the first 12 hours after hospital admission and even, if possible, during pre-hospital care and transport, maximizing the potential for timely therapeutic interventions that can save lives and, more importantly, improve long-term clinical outcome.

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