NON-INVASIVE SEPSIS PATIENT CLASSIFICATION USING LEAST SQUARES SUPPORT VECTOR MACHINE

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Abstract: Sepsis is a systemic inflammatory response to serious infection. Without proper identification and treatment at its early stage, this syndrome can deteriorate within hours to a more devastating state. In this paper, it was hypothesized that early identification of sepsis stages can be achieved through the evaluation of patients' autonomic neural activity by means of power spectral analysis. Least squares support vector machine (LSSVM) was utilized to classify sepsis patients into systemic inflammatory response syndrome (SIRS) and severe sepsis groups, based on the measured normalized low-frequency (LFn) components of heard period (RRi) and pulse transit time (PTT) time series. Polar-like transformation of LFn pair of RRi and PTT provides another two distinctive features into the construction of input space. Age factor was also used as an attribute in sepsis classification. The performance of the proposed LSSVM with two different kernels: cubic-polynomial and Gaussian radial basis function (RBF), was evaluated using 5-fold cross-validation technique. From the study, LSSVM with RBF kernel was found to be an effective classifier in the identification of sepsis syndrome progression, with the classification accuracy, sensitivity, and specificity: 93.32%, 99.87%, and 79.29% respectively.

1 INTRODUCTION

Sepsis has been defined as the systemic response to severe infection in critically ill patients. Systemic inflammatory response syndrome (SIRS), severe sepsis, and septic shock represent the increasingly severe stages of the same sepsis syndrome. Delays in the identification of sepsis progression and the administration of proper treatments to the patient resulted in the increase of mortality rate and prolonged hospital stay (Rivers et al., 2001). However, early detection and immediate interventions to halt the progression of sepsis may greatly improve the outcomes of the sepsis patients (Rivers et al., 2005). The guidelines for sepsis diagnosis (Figure 1) defined in 1991 during the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference have given us clear definitions of SIRS, sepsis, and severe sepsis (Bone et al., 1992), and these definitions were strictly followed in this paper. It was hypothesized that early identification and differentiation of sepsis stages: i.e., SIRS and severe sepsis, may be achieved through the evaluation of sepsis patients' autonomic neural activity by the use of support vector machine (SVM). The analysis was based on the cardiovascular data collected from 33 patients at risk of sepsis, who were presented to the Emergency Department of the Prince of Wales Hospital from August 2006 to January 2007.

2 METHODS

The protocol used in this study was approved by the Prince of Wales Hospital Human Research Ethics Committee (HREC). It was conducted according to the Australian national guidelines concerning ethical research involving human subjects, as well as the World Medical Association Declaration of Helsinki. Informed verbal consent was obtained from eligible

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Systemic inflammatory response syndrome (SIRS): the systemic inflammatory response to a variety of severe clinical injuries. The response is manifested by two or more of the following conditions:

- temperature > 38 °C or < 36 °C.
- heart rate > 90 bpm.
- respiratory rate > 20 breaths per minute, or $PaCO_2$ < 32 mmHG.
- white blood cell count > 12,000/cu mm, < 4,000/cu mm, or > 10% immature (band) forms.

Sepsis: SIRS with confirmed evidence of infection.

Severe Sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. The perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Figure 1: Definition of SIRS, sepsis, and severe sepsis given by (Bone et al., 1992).

individual adult patients at risk of sepsis, and verbal assent from patient's next of kin prior to the study. 33 Patients fulfilling SIRS and severe sepsis criteria given in Figure 1 were enrolled into the study and no exclusion was based on sex or age. Before the initiation of any intravenous interventions, the patients were connected to PowerLab 16/30 using 3 electrocardiography (ECG) electrodes, infra-red ear lobe plethysmograph (PPG), pulse transducer, and oximeter pod, with data collected via a Bio Amp®. To meet the recommended measurement standards described in the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, the signals were sampled at 1000 Hz with a time duration of not less than 5 minutes (Malik et al., 1996).

2.1 Power Spectral Analysis

Power spectral analysis was used to break down every repeating wave in cardiovascular time series into a series of sine waves of different frequency. This technique allowed non-invasive evaluation of autonomic nervous system activity either at central or peripheral sites. The spectral analysis algorithm used in this study was summarized in Figure 2(a), covering the phases of: initial low-pass filtering, detections of ECG R-waves and PPG peaks, generation of pulse transit time (PTT) and R-R intervals (RRi) time series, and finally the pre-processing of cardiovascular signals. Figure 2(b) illustrates the definitions of both RRi and PTT features, together with an example of PTT time series generation.

Two major oscillatory components (i.e., low frequency, LF (0.035 - 0.15 Hz) and high frequency, HF (0.15 - 0.45 Hz) were derived. HF of RRi provided an index of parasympathetic modulation of heart function, whilst the LF component represented both sympathetic and parasympathetic modulation on the heart (Mainardi et al., 1997). Despites of the dubious capability of PTT in blood pressure estimation, PTT variability does reflect blood pressure variability to some extent (Payne et al., 2006). These spectral components have to be normalized in proportion to the total power of the time series by excluding the very-low frequency components (< 0.035Hz).

2.2 Nonlinear Support Vector Machine

SVM was first derived by Vapnik from the statistical learning theory framework (Vapnik, 2000), and its use in medical decision-making and human physiological analysis is now increasing rigorously due to its robust and solid mathematical foundation. In this paper, a variant of the original SVM, i.e., least squares SVM (LSSVM) was used for the classification of sepsis patients. The main difference between LSSVM and standard SVM relies on their training approaches where LSSVM involves the solution of linear equations, while SVM requires the solution of a quadratic programming problem (Suykens and Vandewalle, 1999), which is computationally more expensive and complex.

Using "T" as the notation for vector transposition and given that $\{y_k, x_k\}_{k=1}^N$ is a set of N training data points, where $x_k \in \mathbb{R}^n$ is k-th input vector, and $y_k \in \mathbb{R}$ is k-th output vector, the equality constraint of LSSVM is given as follows:

$$y_k[\mathbf{w}^{\mathrm{T}} g(x_k) + b] = 1 - \xi_k, \text{ for } k = 1, ..., N \quad (1)$$

where, $g(.)$ is a nonlinear function that maps the input space into a high-dimensional space, $\mathbf{w}$ is an n-dimensional vector, b is a bias term, and ξ represents non-negative slack variables.

Subject to the equality constraint in (1), the coefficients $\mathbf{w}$ and b can be obtained through the minimization process of the following optimization function:

$$Q(\mathbf{w}, b, \xi) = \frac{1}{2}\mathbf{w}^{\mathrm{T}}\mathbf{w} + \frac{c}{2}\sum_{k=1}^{N} \xi_k^2 \quad (2)$$

By introducing the non-negative Lagrange multiplier α_k and using c as the margin parameter that determines the trade-off between maximization of the margin and minimization of the classification error, the Lagrangian, $\mathfrak{L}$ is defined from (1) and (2) as follows:

$$\mathfrak{L}(\mathbf{w}, b, \xi; \alpha) = Q(\mathbf{w}, b, \xi) - \mathfrak{C} \quad (3)$$

where, $\mathfrak{C} = \sum_{k=1}^{N} \alpha_k (y_k(\mathbf{w}^{\mathrm{T}} g(x_k) + b) - 1 + \xi_k)$

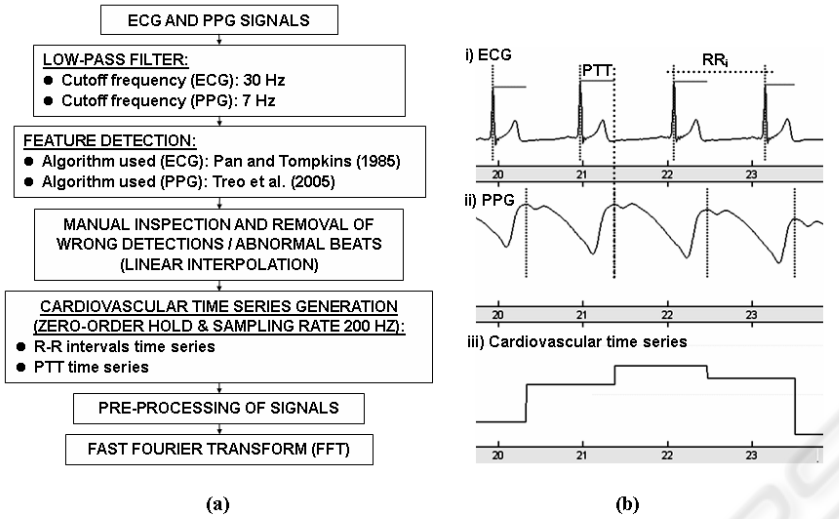

Figure 2: (a)Flow chart of signal processing prior to power spectral analysis. (b)Feature detection and cardiovascular time series generation.

In SVM, kernel function is required to lift the input space into a high-dimension feature space. Given the general kernel function, $H(x,x') = g^{\mathrm{T}}(x) \cdot g(x')$, the polynomial kernel function with constant h can be derived as follows:

$$H(x,x') = (x^{\mathrm{T}} \cdot x' + h)^d \tag{4}$$

where, d is the polynomial order, and cubic-polynomial kernel ($d = 3$) was used in this study.

Another kernel function which is of particular interest in this study is Gaussian radial basis function (RBF) as given in the following function (5). Through RBF kernel, the dimension of the feature space can be increased to infinity due to the infinite series expansion of e^x. This ultimate increase of feature space dimension is preferred in SVM because it ensures that any given classification problem, regardless of its size or dimension, can be solved in a predictable way, especially when the discontinuities or outliers are acceptable.

$$H(x,x') = e^{-\gamma\|x-x'\|^2} \tag{5}$$

where γ is a positive parameter for controlling the radius.

3 LSSVM CLASSIFIER SETUP

A distribution plot of the normalized low frequency (LFn) components for RRi and PTT time series of both SIRS and severe sepsis patients in Figure 3 has clearly revealed that the latter has the tendency to stay closely to the origin, (0,0) as well as the $\tan(\pi/4)$ straight line, **P**. Based on this observation, two distinctive attributes, i.e., the radius, r and the angle, θ were derived by denoting LFn of PTT and RRi as x_1 and x_2 respectively:

$$r(x_1,x_2) = \sqrt{x_1^2 + x_2^2} \tag{6}$$

$$\theta(x_1,x_2) = \left| \frac{\pi}{4} - \tan^{-1}\left(\frac{x_2}{x_1}\right) \right| \tag{7}$$

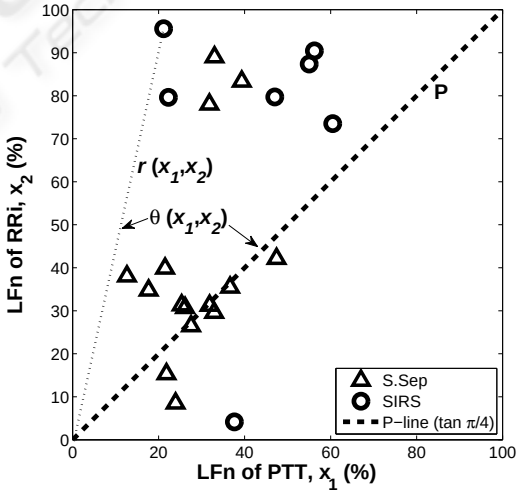

Figure 3: Distribution of severe sepsis and SIRS patients in x_2 versus x_1 plane.

$r(x_1,x_2)$ estimates the distance of the LFn pairs from the origin, while $\theta(x_1,x_2)$ measures the closeness between the LFn pairs to **P** straight line. By taking these two attributes: $r(x_1,x_2)$ and $\theta(x_1,x_2)$ into the construction of input space, it is believed that this will improve the separability of the sepsis groups.

LFn pairs of RRi and PTT, without the transformation in (6) and (7), were included also into the construction of input space as these low frequency components are potential in reflecting the sepsis stages (Annane et al., 1999; Pontet et al., 2003). Age factor is another attribute which is excellent in determining the subsequent outcomes of sepsis patients (Martin et al., 2006). The meant five-dimensional input space as stated above is shown in Figure 4(a) and 4(b), with the space dimensions restricted to only three.

To evaluate the effectiveness of LSSVM, a 5-fold cross validation technique was used in this study. This method partitioned the original sample into five sub-samples, with one sub-sample retained for validation purpose and the remaining sub-samples were used as the training data. This process was repeated until all the sub-samples were used once in the validation process. By doing this, the performance of the classifier was less susceptible to data division problem.

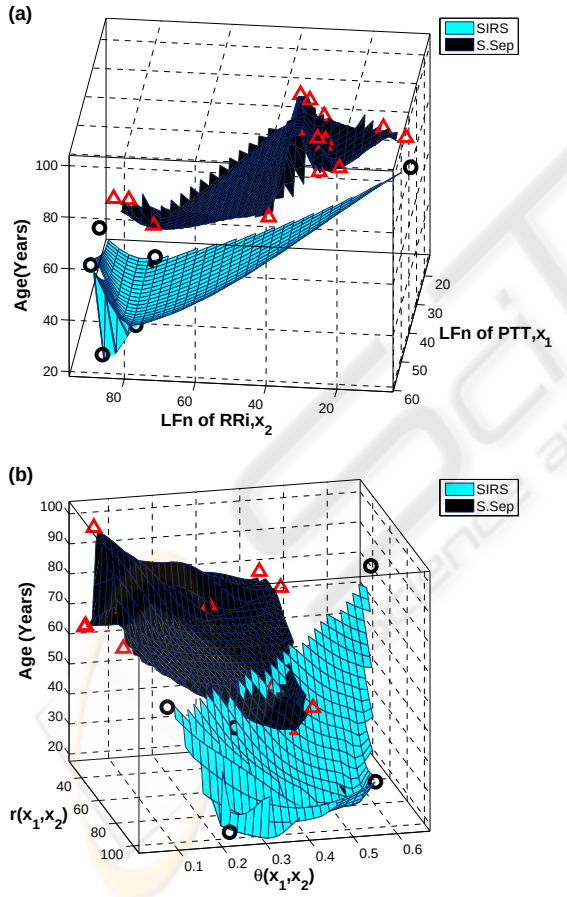

Figure 4: Different angles of view of the constructed input space with the space axis: (a) $\{x_1, x_2, \text{Age}\}$, and (b) $\{r(x_1,x_2), \theta(x_1,x_2), \text{Age}\}$, where the space dimensions are restricted to only three.

4 RESULTS AND DISCUSSIONS

The classification results of the proposed LSSVM with different input spaces and kernels are given in Table 1. It was clear that higher-dimensions of input space offered no benefit to the cubic-polynomial LSSVM, in contrast to its counterpart, RBF LSSVM which performed better with higher-dimension input space, given that the final classification results: 93.32% (accuracy), 99.87% (sensitivity), and 79.29% (specificity) respectively. This is mainly because RBF kernel lifts the dimension of the input space to infinity in feature space, such that a linear separating hyperplane can be easily generated between the sepsis groups. However, it is ironical to point out that the polar-like transformation in (6) and (7) actually discourages the performance of RBF LSSVM, especially when the dimension of the input space is low.

Despites of the excellent performance of the proposed LSSVM, a study by Li et al.(2007) has demonstrated that small-data-set learning can jeopardize the effectiveness of the SVM classification (Li et al., 2007). In this study, the number of study participant is considerably small, and this may affect the validity of the classification results shown above. In future, more participants should be enrolled into the study so that complete learning of the trend and distribution of the sepsis patients can be achieved and thus producing more convincing classification results.

5 CONCLUSIONS

A non-invasive classifier, LSSVM has been proposed and used in this study to detect sepsis continuums (i.e., SIRS and severe sepsis). Through the polar-like transformation functions, two distinctive attributes: radius and angle difference were derived and incorporated into the construction of input space. From this study, LSSVM with RBF kernel is an effective method that can be used in the classification of severe sepsis patients with the classification accuracy, sensitivity, and specificity: 93.32%, 99.87%, and 79.29% respectively. In spite of its supreme classification performance, LSSVM is relatively vulnerable to low number of training data. In future, more study participants should be enrolled into the study to further validate the effectiveness of the proposed LSSVM in sepsis patients classification.

Table 1: Classification results of LSSVM with different input space dimension and kernels.

Input Space	Kernel	Accuracy	Sensitivity	Specificity
{PTT,RRi}	Cubic-Polynomial	87.05	96.80	66.14
{r,θ}	Cubic-Polynomial	87.59	95.40	70.86
{PTT,RRi,Age}	Cubic-Polynomial	82.91	98.20	50.14
{r,θ,Age}	Cubic-Polynomial	87.86	100.00	61.86
{PTT,RRi,r,θ,Age}	Cubic-Polynomial	86.82	98.53	61.71
{PTT,RRi}	RBF	82.18	94.20	56.43
{r,θ}	RBF	78.59	88.93	56.43
{PTT,RRi,Age}	RBF	91.73	98.60	77.00
{r,θ,Age}	RBF	90.45	98.33	73.57
{PTT,RRi,r,θ,Age}	RBF	93.32	99.87	79.29

Abbreviations: Accuracy $= (TP+TN)/(POS+NEG)$, Sensitivity $= TP/POS$, Specificity $= TN/NEG$: *TP* is true positives; *TN* is true negatives; *POS* is total positives; *NEG* is total negatives.

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