Computing Network-Based Features from Physiological Time Series: Application to Sepsis Detection

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***Abstract*— Sepsis is a systemic deleterious host response to infection. It is a major healthcare problem that affects millions of patients every year in the intensive care units (ICUs) worldwide. Despite the fact that ICU patients are heavily instrumented with physiological sensors, early sepsis detection remains challenging, perhaps because clinicians identify sepsis by using static scores derived from bed-side measurements *individually*, i.e., without systematically accounting for potential interactions between these signals and their dynamics.**

In this study, we apply network-based data analysis to take into account interactions between bed-side physiological time series (PTS) data collected in ICU patients, and we investigate features to distinguish between sepsis and non-sepsis conditions. We treated each PTS source as a node on a graph and we retrieved the graph connectivity matrix over time by tracking the correlation between each pair of sources' signals over consecutive time windows. Then, for each connectivity matrix, we computed the eigenvalue decomposition. We found that, even though raw PTS measurements may have indistinguishable distributions in non-sepsis and early sepsis states, the median $\widehat{\mu}$ of the eigenvalues computed from the same data is statistically different ($p < 0.001$) in the two states and the evolution of $\widehat{\mu}$ may reflect the disease progression. Although preliminary, these findings suggest that network-based features computed from continuous PTS data may be useful for early sepsis detection.

I. INTRODUCTION

Sepsis is clinically defined by the presence of both an infection and a resultant maladaptive inflammatory response [1], [2]. It is a progressively injurious process that typically leads to acute organ dysfunction and tissue hypoperfusion ("severe sepsis"), and eventually to hypotension conditions that are refractory to proper fluid resuscitation ("sepsis shock") [1], [2]. Sepsis affects over 18 million people every year worldwide and results in 1400 deaths every day [3]. In the sole U.S., severe sepsis and sepsis shock affect almost a million people every year and remain the most common cause of death in intensive care units (ICUs), with a mortality rate ranging between 28% and 50% [3], [4].

Sepsis is typically initiated by specific bacterial products (e.g., lipotechoic acids, lipopolysaccharide, or oligosaccharides) introduced in the patient's circulation, which trigger an inflammatory cascade that eventually manifests with stereotypical clinical symptoms (e.g., abnormal temperature, heart rate, and respiration rate, drop in fluid output) [5], [6]. Clinical criteria have been proposed to identify sepsis, severe sepsis, and septic shock but, despite the effort, sepsis remains difficult to diagnose and even the more severe forms are often misdiagnosed [1], [2]. This difficulty likely stems from (i) an inability to recognize when a patient is transitioning from a non-septic state to a septic state, which may occur well before that the clinical symptoms become apparent, and (ii) the challenge of distinguishing sepsis from a systemic inflammatory response syndrome secondary to a non-infectious etiology [7]. Perhaps more importantly, the diagnosis of sepsis currently depends on 30 physiologic and laboratory variables (e.g., blood pressure, heart rate, temperature, oxygenation, pH, and fluid balance) that clinicians manually integrate into a single cumulative risk score (e.g., APACHE II, MODS, SOFA, MEWS, or REMS), which usually modulates *after* that the clinical symptoms have become apparent [8]–[10]. As a result, many patients with sepsis are either never diagnosed or have a late diagnosis which delays life-saving therapies.

Time, in fact, is essential to the efficacy of anti-septic treatments. The chance of surviving for patients with septic shock decreases by 7.6% for each hour that effective antimicrobials are delayed [11], while an early goal-directed therapy (i.e., a combination of early diagnosis, timely initiation of antibiotics, and resuscitation to hemodynamic goals [12]) may significantly improve the clinical outcomes of the patients and reduce the mortality rate by over 45% [11], [13]–[17].

We hypothesize that the transition from the non-septic state to the septic state is "hidden" within the physiological time series (PTS) data that are continuously collected from ICU patients through bedside instrumentation. Furthermore, we hypothesize that interactions between simultaneously acquired PTS measurements may reveal early stages of the septic condition.

Studies [18]–[20] have shown that a combination of non-linear features computed out of different PTS sources and multivariate logistic regression can separate sepsis and non-sepsis states. However, because each source is processed independently from the others, large sets of training data are required to achieve sufficient classification accuracy. In this paper, instead, we investigate the effectiveness of network-based features from PTS measurements to distinguish between sepsis and non-sepsis conditions. We tested our approach by using data from two patients in the MIMIC II (Multiparameter Intelligent Monitoring in Intensive Care II) database [21], [22]. First, we envisioned the patient as a *networked dynamic system*, wherein sepsis not only affects the functionality of individual components (e.g., cardiovascular system or respiratory system), but also dysregulates

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the interactions between these components [5], [6]. The dysregulation is one of the mechanisms that initiates sepsis and affects the dynamics of multiple PTS features simultaneously (e.g. heart rate, blood pressure, and respiratory rate). Second, by following the approach in [23]–[27], we computed graph theory-based statistics to model a patient's PTS dynamics. Each type of PTS source was considered a node on a graph, and edges between nodes were weighted by how correlated the signals were in a given window of time. The connectivity matrix of the graph and its set of eigenvalues were then tracked over time by sliding the window and the median value $\widehat{\mu}$ of the eigenvalues in each window was estimated and used to characterize the sepsis and non-sepsis state.

Preliminary results indicate that, even though the distributions of raw PTS measurements in non-sepsis and sepsis states were indistinguishable when viewed individually, the distributions of $\widehat{\mu}$ computed from the same data clearly distinguishes these two states. This suggests that network-based features extracted from PTS data may be useful for real-time detection of transitions into sepsis states.

II. METHODS

A. Patients from the MIMIC II Database

We tested our approach on two patients (ID: s10653 and s11342) from the MIMIC-II database [21], [22]. Subjects s10653 (female, 87y) and s11342 (female, 44y) were monitored in ICU several weeks before developing sepsis and then after the sepsis diagnosis. The clinical pattern of these patients was characterized by a first stay in ICU due to severe cardio-pulmonary deficits along with hepatic or kidney failure (up to two days), a following amelioration of the clinical conditions and release from the ICU, and then a later return to ICU because of a deterioration of the general conditions and diagnosed sepsis. For each patient, we used continuous PTS measurements collected after the diagnosis (s10653: 15.2 h; s11342: 59.4 h) and in the latest pre-sepsis stay of the subjects in ICU (s10653: 38.2 h collected 6 weeks before the diagnosis of sepsis; s11342: 14.3 h collected 8 weeks before the diagnosis of sepsis).

B. PTS measurements

Each PTS signal was acquired with a different sampling rate and equipment and then low-pass filtered (anti-aliasing) down-sampled to 1 Hz, and stored in the MIMIC II database. For each condition, we used seven signals: HR (heart rate computed from the ECG signal), RR (respiration rate), S_pO_2 (saturation of peripheral oxygen), PP (heart rate estimated from a peripheral pulsatile signal), P_d, P_s, and P_m (diastolic, systolic, and mean arterial blood pressure, respectively), where the blood pressures were measured non-invasively and averaged over consecutive, non-overlapping, 1 min-long windows. See [21], [22] for further details about the dataset. Each PTS signal was high-pass filtered (4th order Butterworth filter, cutoff frequency: 0.04 Hz) to remove the DC component and normalized by removing the mean and dividing by S.D. Missing samples (e.g., Fig. 1*a-d*) were reconstructed via linear interpolation. Note that other normalization methods (e.g., division by S.D. of the physiologic range of the PTS signals for healthy subjects) may produce different results. The dynamics of the resultant normalized signals, however, will remain unaffected.

C. Network Data Analysis

For each patient, we considered the vector-valued series

$$\eta(t) \triangleq [HR\ RR\ S_pO_2\ PP\ P_m\ P_s\ P_d]^T \quad (1)$$

given by estimating the high-pass filtered, normalized PTS signals once every second t (i.e., sampling rate: 1 Hz). Each signal was divided into consecutive, overlapping windows (window length: 30 s; overlap: 25 s) and, for each window $k = 1, 2, \ldots$, a connectivity matrix $A(k)$ was constructed based on the zero-lag cross-correlation coefficients

$$A_{ij}(k) \triangleq \frac{1}{M} \sum_{m=0}^{M} \eta_i((k-1)\Delta + m)\eta_j((k-1)\Delta + m) \quad (2)$$

where η_i and η_j are the component i and j of the vector (1), respectively, M is the number of samples in the window (i.e., M=30), and Δ=5 s is the lag between consecutive windows. The choice of the window size in this particular example was due to the limited duration of the dataset. Note that the correlation coefficient $A_{ij}(k)$ varies between +1 (i.e., perfect correlation) and -1 (i.e., perfect anticorrelation), and it is 0 when the two components are completely uncorrelated [29].

For each patient, we computed the importance (a.k.a., "centrality" [28]) of each PTS component in (1) over time by performing the eigenvalue decomposition of the matrices A_k, $k = 1, 2, \ldots$ [29], and tracking the leading eigenvector (a.k.a. "eigenvector centrality" [EVC] [28]) and the vector of eigenvalues, $\Lambda_k \triangleq [\lambda_1 \ldots \lambda_7]^T$, $k = 1, 2, \ldots$.

Because the trace of $A(k)$ is constant over k and equal to the sum of the eigenvalues in Λ_k [29], we hypothesize that (i) as the network connectivity changes because of the transition into the sepsis condition, a broad-band re-distribution of the values in the components of Λ_k occurs and (ii) the emergence of significant interactions between different PTS signals can be reflected by the median value $\widehat{\mu}_k$ of the eigenvalues in Λ_k. Hence, we tracked $\widehat{\mu}_k$ over time and we use it to characterize the non-sepsis and sepsis state. The median is chosen because, as the correlation between the PTS measurements increases (i.e., the nodes in the graph become all strongly connected), the eigenvalues of the associated connectivity matrix show a large spread, with the largest eigenvalue being significantly larger than the remaining eigenvalues [29]. Conversely, as the PTS measurements become strongly uncorrelated, the off-diagonal elements of the connectivity matrix approach all 0 and, correspondingly, the eigenvalues are all comparable in magnitude [29].

III. RESULTS

For each patient, matrices $A(k)$, $k = 1, 2, \ldots$ were 7×7, and the correspondent EVC vector and median value $\widehat{\mu}_k$ of the eigenvalues were computed and tracked over time.

Fig. 1*a-d* reports the temporal evolution of the raw PTS measurements for both patients in non-sepsis (Fig. 1*a*,*b*)

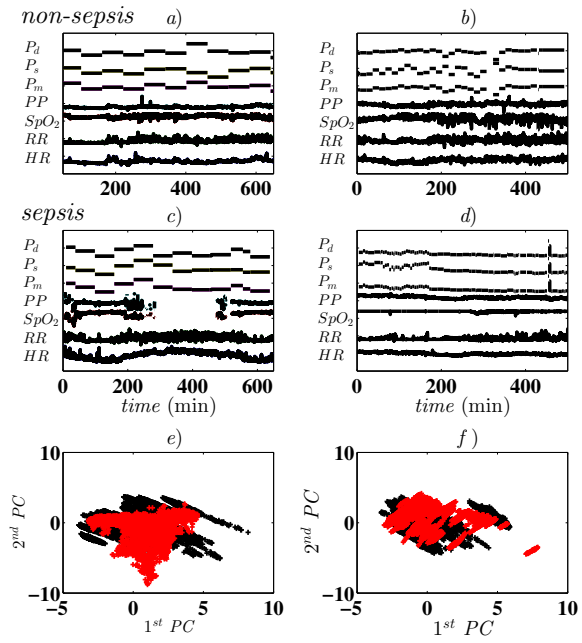

Fig. 1. *a-d*) PTS measurements for s10653 recorded 6 weeks before developing sepsis (*a*) and after the diagnosis (*c*) and for s11342 recorded 8 weeks before developing sepsis (*b*) and after the diagnosis (*d*). Time scale in *c-d*) also applies to *a-b*), respectively. *e-f*) First and second principal component (PC) of the vector of raw PTS measurements for s10653 (*e*) and s11342 (*f*) in non-sepsis and sepsis conditions (black and red points, respectively).

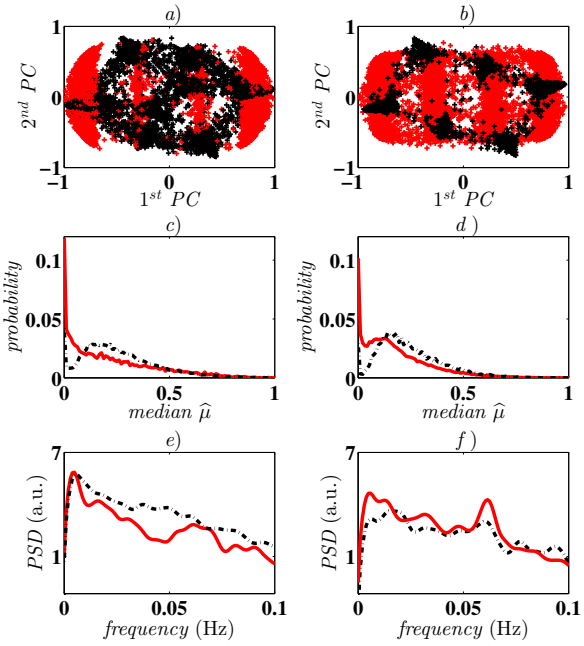

Fig. 2. *a-b*) First and second principal component (PC) of the EVC vector for s10653 (*a*) and s11342 (*b*) in non-sepsis (black points) and sepsis (red points) state. *c-d*) Probability distribution of $\widehat{\mu}_k$ in non-sepsis (black line) and sepsis (red line) state in s10653 (*c*) and s11342 (*d*). *e-f*) Power spectrum density (PSD) of $\widehat{\mu}_k$ in non-sepsis (black line) and sepsis (red line) state in s10653 (*e*) and s11342 (*f*). The PSD was computed with the Welch method (i.e., signals divided into 256 samples-long windows, 10 samples shift, each data window multiplied by a Hanning window and FFT transformed).

and sepsis (Fig. 1*c*,*d*) conditions. The PTS measurements did not show significant features in sepsis vs. non-sepsis conditions (Wilcoxon test, $p > 0.05$) as indicated by the principal component analysis [30] of the vector-valued time series $\eta(t)$ defined in (1). In both patients, the first two principal components accounted for over 70% of the variance in the data under non-sepsis conditions (s10653: 70.4%; s11342: 73.7%) and over 80% of the variance (s10653: 81.7%; s11342: 80.4%) under sepsis conditions, with no clear separation between the two states (Fig. 1*e*,*f*).

The correlation among the PST measurements, instead, had a different pattern in the two states and was captured by the EVC vector and the distribution of the eigenvalues. First, we performed a principal component analysis of the EVCs estimated over consecutive time windows and we noted that, even though the fraction of variance in the data accounted by the first two principal components was lower than for the raw PTS measurements (sepsis vs. non-sepsis: 68.1% vs. 52.9% in s10653; 67.6% vs. 58.2% in s11342), the increment of variance accounted for at the transition from the non-sepsis to the sepsis state was larger in both patients, thus suggesting that the sepsis state caused a larger rotation in the EVC space than in the raw PTS vector space. Furthermore, the first two principal components of the EVCs had a significantly different distribution (Wilcoxon test, $p < 0.05$) in sepsis and non-sepsis conditions (Fig. 2*a*,*b*), which indicates a structural change in the correlation between the different PTS sources.

The rotation of the EVC space under sepsis conditions was also associated with a change in the distribution of the eigenvalues. In particular, while the largest eigenvalue was similar in sepsis and non-sepsis conditions, the distribution of the eigenvalues was more skewed in sepsis conditions and this impacted the median value, which was lower on average under sepsis conditions. This is reflected in the overall sample probability distribution of the $\widehat{\mu}_k$ time series (Fig. 2*c*,*d*): because of the increased skewness of the eigenvalue distribution, the most likely value was $\widehat{\mu}_k = 0$ under sepsis conditions and the overall likelihood of a median value lower than 0.1 significantly increased at the transition from non-sepsis to sepsis conditions (Wilcoxon test, $p < 0.001$), thus indicating that the generalized inflammatory state was affecting multiple systems and determining an overall correlation among the different PTS sources increased. Furthermore, the temporal evolution of $\widehat{\mu}_k$ had a different pattern in non-sepsis and sepsis conditions, with the emergence of a slow oscillation (between 0.05 Hz and 0.07 Hz, Fig. 2*e*,*f*) in the latter case. This oscillation may reflect a pathological coupling between the HR, RR, and PP signals in (1), perhaps due to a baroreflex dysfunction related to hypertension (both patients were diagnosed hypertension and respiratory failure) and/or a dysregulation of the combined sympathetic and parasympathetic modulation [31], [32].

IV. CONCLUSIONS AND FUTURE WORK

Sepsis is one of the primary causes of death in the ICUs worldwide. Early detection of sepsis conditions is of

paramount importance to successfully treat septic patients but, despite numerous efforts, it remains challenging and ultimately hampered by the fact that diagnosis follows the appearance of stereotypical clinical symptoms, which may occur only at a late stage of the disease. In this paper, we explored a network-based approach to analyze bed-side PTS measurements collected in ICU patients and we showed that multivariate features extracted from these measurements may allow to distinguish between non-sepsis and sepsis state, independently of the assessment of clinical symptoms.

We plan (i) to further assess the robustness of our results on a larger set of ICU patients, (ii) to eventually explore additional measures that may determine the connectivity between the PTS sources and separate non-sepsis and sepsis state more effectively (e.g., band-limited cross-power, coherence, mutual information, average clustering coefficient, small-world parameter, etc.) , and (iii) ultimately to develop an optimal unsupervised policy for early sepsis detection based on the paradigm in [24], [25].

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