Early Prediction of Sepsis from Clinical Data Using Artificial Intelligence

R Murat Demirer
Uskudar University
Industrial Engineering Department
İstanbul, Turkey
murat.demirer@uskudar.edu.tr

Oya Demirer
Arel University
Electrical-Electronic Engineering Department
Istanbul, Turkey
oyademirer@arel.edu.tr

***Abstract*— Sepsis is a major cause of death in the world. World Health Organization estimates 30 million people developing sepsis and 6 million people die from sepsis each year; an estimated 4.2 million newborns and children are affected. The mortality rate is highest in septic shock in poor and developing countries. Early prediction of sepsis is critical for improving sepsis outcomes. The late prediction of sepsis in non-sepsis patients is a challenging problem. The aim of this study is to develop an artificial intelligence-based early warning and therapeutic decision support system which reduces sepsis-associated hospital mortality. We propose two compatible Boolean switchable Partially Observable Markov Decision Processes (POMDP) under a general risk-sensitive optimization criterion with finite time horizon. It is based on Spectral analysis of unevenly sampled (missing) observations with Demographics, Vital Signs, and Laboratory values for the patient. The policy is a common mixture of sepsis and non-sepsis beliefs on own utility functions which favors to achieve Pareto Optimality from this high dimensional belief space.**

Keywords*— *Sepsis, Artificial Intelligence, Decision Support, Lomb-Scargle Periyodogram, POMDP , Deep Learning

I. INTRODUCTION

Sepsis is life-threatening organ dysfunction. As an international definition, infection is defined as an irregular host response. Septic shock is a subset of sepsis. Circulatory, cellular and metabolic abnormalities are at greater scale, and therefore the risk of death is getting larger. According to World Health Organization (WHO) data, 27,000,000 cases of sepsis develop annually.

Sepsis is an emergency-oriented clinical-based disease that can be prevented through early warning. SIRS is a normal immune response to any infection and most people do not need hospital or antibiotics. By using the criteria defined in the SEPSIS-1 and SEPSIS-2 standards, the response to post-operative inflammation for diagnosis of sepsis is confused with all infections without primary hypothermia, endocrine, autoimmune disorders and pulmonary disorders and long-term inflammatory response (e.g urinary tract infections) and makes early diagnosis difficult. It is of vital importance to differentiate sepsis-based inflammation very early and then to implement optimal treatment strategies in the intensive care treatment strategy.

978-1-7281-1013-4/19/$31.00 ©2019 IEEE

It is important to develop an early warning model in real-time based on open utility functions as averages of sequential "policies" implemented by the stochastic distribution of relative time lags as joint phase spectrum values in the intensive care patients who were not fully observable.

The deep learning approach for the physiological parameters do not change over time which gives a black-box representation of the sepsis model. Methods such as deep learning cannot be enough to identify a patient's risk of sepsis and make a positive or negative prediction of sepsis for every time interval. This approach depends on a very large number of labelled datasets, which are tuned with the large number of hyperparameters for a specific hard task. We proposed Partially Observed Markov Decision Process (POMDP) based on what we challenge to predict sepsis approximately 6 hours,$t_{optimal}$ before the clinical prediction of sepsis in which measurements are not fully observed.

Currently used emergency medical scoring systems are general and result-oriented i.e. APACHE II, SAPS II, SOFA, MEWS and SCS scores are instantaneously calculated. These scoring systems include Modified Early Warning Score (MEWS), National Early Warning Score (NEWS), Systemic Inflammatory Response Syndrome (SIRS) criteria, Rapid Organ Failure Assessment (qSOFA), Sequential Organ Failure Assessment (SOFA) score, Acute Physiological and Chronic Health Assessment (APACHE II) score is as diverse as the Simplified Acute Physiological Score (SAPS) score, Mortality Prediction Model (MPM0) score. 2016 SCCM / ESICM has defined qSOFA as an assessment score for patients outside the ICU to facilitate the identification of patients at risk of death from sepsis [1]. In a meta-analysis, it was reported that qSOFA is superior to SIRS for the diagnosis of sepsis and qSOFA is a better predictor of in-hospital mortality [2]. The SOFA score is approved by the Critical Care Association (SCCM) and the European Intensive Care Association (ESICM) as a tool to facilitate the identification of patients at risk of death from sepsis [3].

Deep neural network models that have been implemented so far can capture common patterns acquired from thousands of patients in a supervised training approach. Then, this supervised neural network approach ignores personalized sepsis dynamics and requires huge training sets apriori. However, in this challenging decision-making problem, data

are complex, multimodal, discordant, noisy and incomplete, and each patient progresses a different sepsis dynamic in different comorbidity, age and sex at every state of the disease which require unique treatment strategy.

There is no consensus on which of the scoring systems used for sepsis diagnosis and treatment is more effective and accurate. They all scoring systems do not consider both the patient's past observations apriori and after treatment interventions. We design a utility function, U^j $(j = 1,2)$ that rewards early predictions and penalizes late predictions as well as false alarms from sequences of different states to real space, $\mathbb{R}$. We automatically aim to identify a patient's risk of sepsis and make a positive or negative prediction of sepsis for every time interval. We make positive or negative predictions of utility functions $(U_{TP}(s,t), U_{FN}(s,t))$ for sepsis $j = 1$ or $j = 2$ as utility functions $(U_{FP}(s,t), U_{TN}(s,t))$ for non-sepsis patient for every time instant t during the progression of states. s denotes the patient. We give positive and negative predictions for obtaining the highest utility score for the patients.

The probabilistic distribution of spectral values with different beliefs (Sepsis/Non-sepsis) are obtained from the Lomb-Scargle periodogram which is more superior than deep learning algorithm. Our spectral model is based on POMDS-Markov process in which patient states are controlled by treatment on the state transitions that cannot be measured exactly.

Early detection and antibiotic treatment of sepsis are modeled by POMDS model for improving sepsis outcomes in times to treatment represented as hidden states S_1, S_2, S_3, S_4, where each hour of delayed treatment has been associated with roughly an 4-8% increase in mortality [4]. S_1 denotes clinical suspicion of infection at a time, t_{early} after admission to hospital and S_4 denotes the state of patient at a late time, t_{late} to be discharged from the hospital or died.

II. PARTIALLY OBSERVED MARKOV DECISION PROCESS (POMDP MODEL)

The data for each patient will be contained within partially observed Markov decision processes (POMDP) each by representing vital signs, laboratory values both based on a single hour's worth of data and demographics. (Figure 1).

TABLE I. VITAL SIGNS

HR	Heart Rate (beats per minute)
O2SAT	Pulse Oximetry (%)
TEMP	Temperature (Deg C)
SBP	Systolic BP (mm Hg)
MAP	Mean Arterial Pressure (mm Hg)
DBP	Diastolic BP (mm Hg)

Laboratory values are like vital signs which are based on hourly basis (like Glucose, HCO3-Bicarbonate, FiO2-Fraction of inspired oxygen, PaCO2, SaO2, Alkaline Phosphatase, Blood Urea Nitrogen, Lactate, Magnesium etc.).

We denote e.g. S_1 state with Lomb-Scargle spectral values of sequence $\{s_1, s_2, \dots s_{early}\}$. Subsequences are denoted by subscripted inequalities e.g. $\bar{s} = s_{\leq early}$ stands for $\{s_1, s_2, .., s_{early}\}$ as a whole sequence. We can define expectation value of S_1 as in the following equation

$$\mathbb{E}[S_1] = \sum_{\bar{s}} \mathbb{P}(\bar{s}).\bar{s} \qquad (1)$$

Sepsis or non-sepsis j's outlook as a POMDP, $\mathcal{D}^j = (\mathcal{S}^j, \mathcal{A}, T^j, U^j, \mathcal{O}, \Omega^j, n)$ which represents

- $\mathcal{S} = (S_1, S_2, S_3, S_4)$ set represents hidden states anchored on a set of special time points. $\{t_{early}, t_{optimal}, t_{sepsis}, t_{late}\}$ denote before and after timestamp of intravenous (IV) antibiotics and/or blood cultures (A_1).
- $\mathcal{A}$ represents actions of the IV antibiotics and blood cultures.
- T^j represents the conditional probabilities for sepsis or non-sepsis patient as indexed $j = 1,2$ which will govern patient's state transitions, $\mathbb{P}^j(s_{i+1}|s_i a_i)$ after IV treatments. This probability distribution depends on observations after IV or blood culture administration.
- We define a score (utility function) $U^j(s(t))$ for prediction, i.e., in a variable s and time t. j represents Sepsis/Non-sepsis utility function from observed sequences of patient's states. This is based on the clinical data provided, automatically identify a patient's risk of sepsis and make a positive or negative prediction of sepsis for every time interval. The probabilities above 0.5 indicates positive predictions and probabilities below 0.5 to indicates negative predictions,

$$U^j(s(t)) = \begin{cases} U_{TP}\,, (+)\text{prediction at time n for sepsis patient} \\ U_{FN}\,, (-)\text{prediction at time n for sepsis patient} \\ U_{FP,}\ (+)\text{ prediction at time n for non\_sepsis patient} \\ U_{TN}, (-)\text{ prediction at time n for non\_sepsis patient} \end{cases} \qquad (2)$$

The case $U(s(t)) = (1/\gamma)e^{\gamma s(t)}$ is a risk sensitive function with the parameter,$\gamma \neq 0$ which creates an exponential family for belief compression for POMDP model.

$$U^{-1}(\mathbb{E}[U(S)]) \approx \mathbb{E}X - \frac{1}{2} l_U(\mathbb{E}S) Var[S] \qquad (3)$$

The Utility function U is given by $U(j,s) = U^j(s)$.

- $\mathcal{O}$ represents the set of periodogram (LSP) values from sequences of patient states which are not uniformly sampled.
- The observation probabilities Ω of the physiological variables

$$\mathbb{P}\big(o_i \big| (j_{I_u(\bar{s})}, s_i\big) = \mathbb{P}\big(B = j_{I_u(s)}\big)\mathbb{P}^{j_{I_u(\bar{s})}}(o_i|s_i) \qquad (4)$$

- Ω^j represents the conditional probabilities Sepsis/non sepsis,j believes that governs the patient's spectral observations, $\mathbb{P}^j(o_i|s_i)$ based on states.

One might model the AI based decision support model as maximizing the expected value, given its spectral observations of some utility function, $U^{j_{I_u(\bar{s})}}(s,t)$ of the patient that equals to a weighted mixture sum of sepsis (convex) non-sepsis (concave) Utility functions U^1 and U^2[6].

$$w^1U^1 + w^2U^2 \tag{5}$$

At each time point, i, the AI machine will have a policy $\pi_i$for each sequence of Lomb-Scargle periodogram values based on observations $o_{\leq i}$ and past IV and blood culture order actions $a_{<i}$. Machine policy architecture shown by green color in figure 1 is a distribution of past actions $a_{<i}$ based on observations before IV treatment ($\pi_i(-|o_{\leq i}a_{<i})$ to generate an action a_i with probability $\pi_i(a_i|o_{\leq i}a_{<i})$.

The probability of sepsis or non-sepsis beliefs with all outcomes $(\bar{s},\bar{o},\bar{a})$for any state $\bar{s} \in (\mathcal{S}^j)^n$, outcomes and actions include whole spectral sequences until the time n.

$$\mathbb{P}^j(\bar{s},\bar{o},\bar{a},\pi) = \mathbb{P}^j(s_1)\prod_{i=1}^{n}\mathbb{P}^j(o_i|s_i)\,\pi(a_i|o_{\leq i}a_{<i})\,.\,\mathbb{P}^j(s_{i+1}|s_ia_i) \tag{6}$$

The policy shown in green color is common to both sepsis and non-sepsis based POMDPs models which are governing the probabilities and expectations. POMDP model enlarges the state space by the conditional distributions of the unobservable states (S_1,S_2,S_3) given the observable past distributions.

III. Pareto Optimal Policies

A. *Compatible POMDPs for Sepsis and Non-sepsis Conditions*

The decision support model has two compatible POMDPs, D^1 *and* D^2. The policy for Sepsis may be viewed as a policy for the non-sepsis. They have the same set of IV therapeutics,$\mathcal{A}$ and observations,$\mathcal{O}$ and the same number of discrete time steps, n. Two compatible POMDPs are governing the probabilities and expectations of a patient with utility functions U^j, and policy π for all probability distributions of spectral measurements until the discrete time,n.

$$\mathbb{E}^j[U^j;\pi] = \sum_{\bar{s}\in(\mathcal{S}^j)^n} \mathbb{P}^j(\bar{s},\pi)U^j(\bar{s}) \tag{7}$$

This utility functions reward classifiers for early predictions of sepsis ($j=1$) and penalizes them for late/missed predictions and for predictions of sepsis in non-sepsis patients (j=2). A policy is a Pareto Optimal for a compatible sepsis and non-sepsis pair of POMDPs (D^1,D^2) for the decision-making architecture. Optimality seeks expectations with the highest utility score for the patients in the data.

$$\mathbb{E}^2[U^2;\pi] \geq \mathbb{E}^2[U^2;\pi'] \text{ or } \mathbb{E}^1[U^1;\pi] \geq \mathbb{E}^1[U^1;\pi'] \tag{8}$$

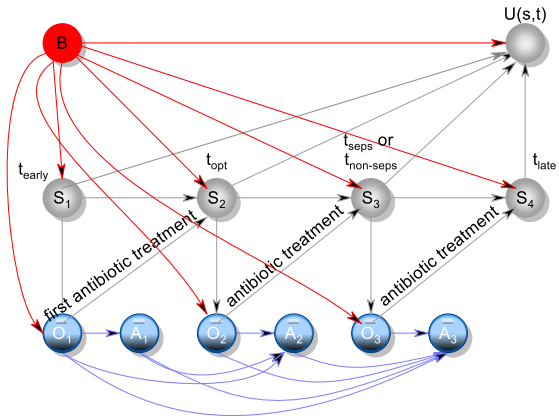

Fig. 1. POMDP Architecture for sepsis and non-sepsis spectrum conditions

We finally define a POMDP mixture with parameters $D^j = (\mathcal{S}^j,\mathcal{A},T^j,U^j,\mathcal{O},\Omega^j,n)$ denoted as $D = w^1D^1 + w^2D^2$. For sake of simplicity $j = j_{I_u(\bar{s})}$.

A new POMDP architecture works by flipping a (w^1,w^2) weighted Boolean random SepsisLabel $(B=j)$ variable and then running D^1or D^2 according to a SepsisLabel whether $j=1$ if $t \geq t_{sepsis} - 6$ hours otherwise $j=2$ if $t < t_{sepsis}$-6 [7]. Given any policy π, the expected payoff is

$$\mathbb{P}(B=1).\mathbb{E}(U|B=1;\pi + \mathbb{P}(B=2).\mathbb{E}(U|B=2;\pi) = w^1\mathbb{E}^1(U^1;\pi) + w^2\mathbb{E}^2(U^2;\pi) \tag{9}$$

where $w^1 + w^2 = 1$ and $t_{sepsis} = \min(t_{suspicious}, t_{SOFA})$ the onset time of sepsis is the earlier of $t_{suscipion}$ and t_{SOFA} as long as $t_{suspicious} - 24 \leq t_{SOFA} \leq t_{suspicion} + 12$ hours [7].

$\mathbb{B}$ Boolean random variable implies how belief dynamics is being progressed and it must be optimized by two beliefs in either $\mathbb{P}^1$, U^1 or $\mathbb{P}^2, U^2$. $l_U(s) = -\frac{U''^{(j)}(s)}{U'^{(j)}(s)}$ is the Arrow-Pitt function of absolute risk aversion. If U^j is concave, the variance is subtracted in non-sepsis condition and POMPDP decision maker is risk seeking. If U^j is convex in non-sepsis condition, the variance is added and the POMDP is risk averse. B denotes the Boolean variable depending on Arrow-Pitt function, so then $\mathbb{P}\left(B = j_{I_u(s)}\right) = w^j$

IV. Expectations of the POMDP Architecture Based on Periodograms with Missing and Irregular Values

A physiological variable is denoted by a positive sequence $(s_1, s_2 \ldots s_n)$ from x_{t_i} irregular measurements, like HR, blood pressure etc. [Table.1]. $\bar{s}$ defines the whole sequence for the physiological variable up to time, n. A measured value at a given frequency in a sequence is denoted by a modified

version of the periodogram for each frequency value. υ corresponds to a policy with maximum expectation,π and other policy as second maximum expectation, π' with the frequency up to n. Observation [8].

$$s_\upsilon = \frac{1}{2}(a_\upsilon^2 + b_\upsilon^2) \tag{10}$$

where

$$a_\upsilon = \frac{\sum_{i=1}^{n} x_{t_i} \cos[2\pi\nu(t_i - \tau)]}{\sqrt{\sum_{i=1}^{n} cos^2[2\pi\nu(t_i - \tau)]}} \tag{11.a}$$

$$b_\upsilon = \frac{\sum_{i=1}^{n} x_{t_i} \sin[2\pi\nu(t_i - \tau)]}{\sqrt{\sum_{i=1}^{n} sin^2[2\pi\nu(t_i - \tau)]}} \tag{11.b}$$

with τ defined

$$\tan(2\pi\upsilon) = \frac{\sum_{i=1}^{n} \sin(4\pi\upsilon t_i)}{\sum_{i=1}^{n} \cos(4\pi\upsilon t_i)} \tag{12}$$

Then $\sigma_1 = \sigma_{a_\upsilon}$ and $\sigma_2 = \sigma_{b_\upsilon}$denote the standard deviations of the sinus and cosines terms for the related physiological variables at a given frequency υ.

$$\sigma_{a_\upsilon}^2 = \frac{\sigma_n^2}{n}\sum_{i=1}^{n} cos^2(2\pi\upsilon t_i) \tag{13.a}$$

$$\sigma_{b_\upsilon}^2 = \frac{\sigma_n^2}{n}\sum_{i=1}^{n} sin^2(2\pi\upsilon t_i) \tag{13.b}$$

and then correlation between sinus and cosine terms is defined.

$$\rho_\upsilon = \frac{E[a_\upsilon b_\upsilon]}{\sigma_{a_\upsilon}\sigma_{b_\upsilon}} \tag{14}$$

σ_n^2 is the noise variance which is considered from the other policy with second expectation level at frequency. POMDP is governing the corresponding probabilities

$$P_{Sj}(\bar{s}, \pi) = \frac{1}{2\sigma_1\sigma_2\sqrt{1-\rho^2}} \exp\left[-\frac{1}{4}(\beta^+ - \gamma^+)\bar{s}\right] I_0\left(\frac{1}{4}\gamma^+\bar{s}\right) \tag{15}$$

where $I_0(.)$ is modified Bessel function of the first kind of zero, $\bar{s} \geq 0$ and

$$\gamma^+ = \frac{[2(\sigma_1^2+\sigma_2^2) - 4\sigma_1^2\sigma_2^2(1-\rho^2)]^{1/2}}{\sigma_1^2\sigma_2^2(1-\rho^2)} \tag{16.a}$$

and

$$\beta^+ = \gamma^+ + \frac{\sigma_1^2+\sigma_2^2}{\sigma_1^2\sigma_2^2(1-\rho^2)} \tag{16.b}$$

V. RESULTS

We implemented the training database of 5,000 subjects from Clinical Data in PhysioNet [7]. Each row of the table provides a collection of measurements with missing values at the same time (e.g., heart rate and oxygen level at the same time) [7]. The applications of this model will be realized in later articles.

VI. CONCLUSION

New generation AI architectural structure is incorporated into nonuniform spectrogram estimation. Therefore, this article has theoretically formed a new mathematical theory. We applied the early detection of sepsis to optimal sequential decision-making theory to achieve Pareto Optimality conditions under Sepsis/Non-sepsis beliefs with differing positive and negative utility predictions at a given time t (suspicious, optimal and late). A super human AI prediction machine will use each of those Sepsis/Non-sepsis beliefs in evaluating how well an IV antibiotic and/or blood culture therapy will serve that Sepsis/Non-Sepsis utility functions and shift the relative priority it assigns to either Sepsis or Non-sepsis's expected utilities over time with a flipping Boolean random variable, SepsisLabel. We will then be able to predict the onset time of sepsis and relative priorities of the shared control of two beliefs. Sepsis and non-sepsis beliefs increase the degree on which the machine's decisions will affect the utilities. In addition, the onset time of sepsis will be learned by the POMDP rather than explicitly specified.

REFERENCES

[1] The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 15:801.

[2] Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315:762.

[3] Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017;45:486.

[4] Christopher W. Seymour et.al , "Time to Treatment and Mortality during Mandated Emergency Care for Sepsis", N Engl J Med. 2017 June 08; 376(23): 2235–2244

[5] R. Vio, P. Andreani, "Spectral analysis of unevenly sampled signals: an effective alternative to the Lomb-Scargle periodogram", arXiv:1807.01595v1, 2018

[6] Andrew Critch, "Toward negotiable reinforcement learning: shifting priorities in Pareto optimal sequential decision-making", arXiv:1701.01302

[7] Early Prediction of Sepsis from Clinical Data: the PhysioNet/Computing in Cardiology Challenge 2019

[8] R. Vio and P. Andreani, "Spectral analysis of unevenly sampled signals: an effective alternative to the Lomb-Scargle periodogram", Astronomy &Astrophysics,2018.