CS282: Semester Project

The goal of this semester-long project is for you to apply reinforcement learning techniques to make an impact on a real problem: managing sepsis in intensive care units. This document describes the problem, the data, and several concrete directions for your semester long project. The project deliverables are described in the syllabus.

Introduction: The Challenge of Sepsis

Sepsis, which corresponds to severe infections associated with organ dysfunction, is a major health issue. It represents the third leading cause of death worldwide, the main source of mortality in intensive care and the single most expensive medical condition treated in hospitals (Cohen et al., 2015; Torio & Andrews, 2013). It claims the lives of around 150,000 and 215,000 people in Europe and the US, respectively, each year (Angus et al., 2001; Artero, Zaragoza, & Miguel, 2012; Vincent et al., 2006). It has been estimated that it costs more than $20 billion per year to US tax payers and £2 billion to the UK (Torio & Andrews, 2013; Vincent et al., 2006).

Formally, sepsis is characterized by the presence of a suspected infection (which itself is defined by a prescription of antibiotics and the sampling of bodily fluids for microbiological culture) combined with evidence of organ dysfunction, defined by a Sequential Organ Failure Assessment (SOFA) score greater or equal to 2 (Seymour CW, Liu VX, Iwashyna TJ, & et al, 2016; Singer M, Deutschman CS, Seymour C, & et al, 2016). Septic shock is a severe form of sepsis, defined by the presence of a persistent hypotension (low blood pressure) despite adequate fluid resuscitation requiring vasopressors (medications that squeeze blood vessels, in particular arteries), and blood lactate greater than or equal to 2 mmol/L.

The physiopathological sequence of events in sepsis is overall well recognized. Sepsis is caused by bacteria penetrating the body. These entities, when detected by a particular type of cells of the immune system called macrophages, will lead to a massive release, locally and in the bloodstream, of cytokines, which are pro-inflammatory molecules. Cytokines are responsible for intense vasodilation, increased capillary permeability and decreased systemic vascular resistance. Myocardial dysfunction may also occur and worsen blood circulation. All together, these insults explain that a key clinical feature of patients in the early phase of sepsis is relative (via systemic vasodilation) or absolute (via vascular leakage) hypovolemia (inappropriately low blood volume). Hypovolemia is a serious condition, especially in frail patients, and can manifest itself through a wide range of features including tachycardia, hypotension, metabolic acidosis, kidney failure, perturbed clotting, respiratory distress or altered consciousness (Dellinger et al., 2013; Vincent, 2008). Hypovolemia and sepsis lead to rapid death if left untreated. Let us simply remember that pneumonia was by far the primary cause of death before the discovery of antibiotics (Dowling, 1972). **Thus, an important goal for patient's with sepsis—and the objective of our projects—is help the patient survive this severe immune response while the infection itself is being fought and treated.**

Although the mortality of sepsis and septic shock has improved in the last 30 years, it remains unacceptably high, at around 20 to 50% (Marik, 2015; Martin, 2012; Mayr, Yende, & Angus, 2014; Vincent et al., 2010). While the Surviving Sepsis Campaign provides general guidelines for treating groups of patients, no tool is currently available to individualize the treatment of sepsis, while a more personalized medicine has been hoped for (Dellinger et al., 2013; Vincent, 2016). While the benefits

of a targeted and early aggressive management of sepsis are well established, several key clinical questions remain unanswered, particularly with regards to the exact timing for initiating or stopping several invasive interventions, such as mechanical ventilation, sedative drugs, vasopressive agents, intravenous fluids, or renal replacement therapy (Acheampong & Vincent, 2015; Asfar et al., 2014; Beck et al., 2014; Beloncle, Lerolle, Radermacher, & Asfar, 2013; de Oliveira et al., 2015; Malbrain et al., 2014).

The most important aspect of treating a patient with sepsis is the control of the source of infection with antibiotics, and if needed surgery (to drain an abscess or remove an infected gall bladder, for example). However, the patient must also survive until the infection and the body's response is under control. Thus, a cornerstone of the early management of a septic patient is the restoration of an adequate blood volume to normalize tissue perfusion, through the administration of intravenous fluids (to increase blood volume) and/or vasopressors (to reduce relative hypovolemia). Prescribing the correct dose remains difficult, and currently relies on clinician expertise using clinical signs, blood tests and, when available, haemodynamic monitoring (cardiac ultrasound or various medical devices). Unfortunately, physicians may be wrong in their assessment up to 50% of the time (Mackenzie & Noble, 2014). The balance between underfilling and overfilling is delicate and fast-evolving (Michard, 2011) and both conditions can lead to severe adverse outcomes (Figure 1). Underfilling may lead to multi-organ failure, while overfilling may harm the cardio-respiratory system (pulmonary oedema), the kidneys, the coagulation, or lead to peripheral oedema. To add complexity, infusing vasopressors in an underfilled patient may squeeze empty blood vessels and restore macro-circulation hemodynamic parameters (blood pressure) whilst actually worsening end-organ perfusion (Kipnis & Vallet, 2010). **To summarize, the clinical questions surrounding the management of these medications in sepsis are numerous: what is the right balance between fluid and vasopressors? What is the right time for initiating vasopressors? What is the correct volume of intravenous fluid to administer during initial resuscitation? What blood pressure and fluid balance should be targeted?**

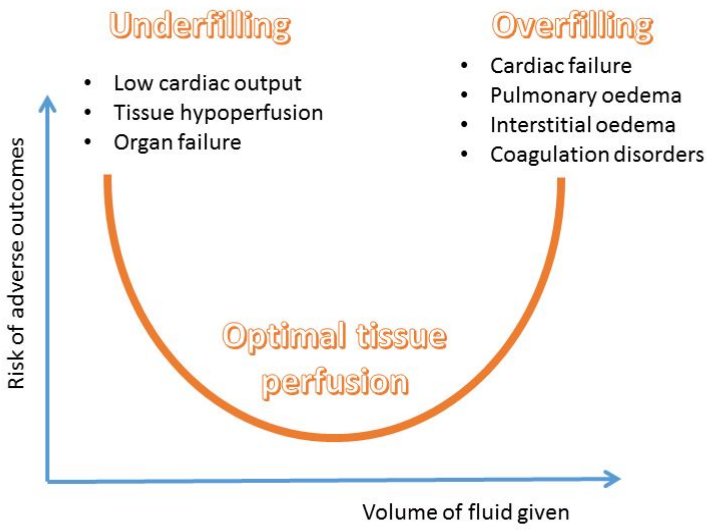

Figure: The relationship between fluid resuscitation and outcome, showing the balance between under and overfilling. Adapted from Dr Levrat, www.reannecy.org.

There are several other factors that are important in managing patients with sepsis, in addition to management of fluids. The overall incidence of acute kidney injury in intensive care patients ranges from 20 to 50%, of which 45–70 % is associated with sepsis (Doi, 2016). If the renal function decreases too much, the patient requires dialysis – also called renal replacement therapy. The mortality of these patients reaches 60–80%. The optimal timing for initiating RRT is mostly unknown. Some physicians advocate an early initiation in an attempt to try and clear the blood from a fraction of the cytokines and improve the inflammatory syndrome, but the evidence is unclear. **Thus, another important question is when and whether to initiate RRT.**

Finally, around 50% of patients with sepsis require mechanical ventilation, because of respiratory failure (in general due to a pneumonia), altered consciousness or often in an attempt to reduce the patient's oxygen consumption (the diaphragm consumes up to 20% of cardiac output in sepsis (Magder, 2009)). It is in general only initiated in sedated patients, so sedation and mechanical ventilation can be modeled together. **As with the previous interventions, it is an open question as to when to initiate sedation and ventillation.**

Initiating any of these interventions (mechanical ventilation, sedative drugs, vasopressive agents, intravenous fluids, or renal replacement therapy) is always a difficult question at the bedside since they are associated with many complications, and will impair patient prognosis if given when not needed. This is where the enormous potential of this research lies. If we are able to identify with enough confidence which patients will benefit from these interventions, then we can limit the harm to patient caused by the treatment itself while improving the survival of these patients.

Description of the Dataset

The table below lists the 48 variables that are available to you. They include demographics, premorbid status, vital signs, laboratory values, fluid balance and interventions of interest: medications received (intravenous fluids, vasopressors, sedation), mechanical ventilation, renal replacement therapy. Acronyms are defined in the caption at the bottom. Units are the units that the measurement is supposed to be in, but you may find that the actual measurement is in different units (including metric/customary issues and which order of magnitude e.g. percents or proportions).

Category	Items	Type
	Bloc: numbering of time step, per ICU stay Icustay_id: unique ICU stay identifier Charttime: time corresponding to the lower bound of each time step, in posix time.	
Demographics	Age (days) Gender Weight (kg)	Cont. Binary Cont.

	Readmission to intensive care	Binary
	Elixhauser score (premorbid status)	Cont.
Vital signs	Modified SOFA*	Cont.
	SIRS	Cont.
	Glasgow coma scale	Cont.
	Heart rate, systolic, mean and diastolic blood pressure, shock index	Cont.
	Respiratory rate, SpO_2	Cont.
	Temperature	Cont.
Lab values	Potassium, sodium, chloride	Cont.
	Glucose, BUN, creatinine	Cont.
	Magnesium, calcium, ionized calcium, carbon dioxide	Cont.
	SGOT, SGPT, total bilirubin, albumin	Cont.
	Hemoglobin	Cont.
	White blood cells count, platelets count, PTT, PT, INR	Cont.
	pH, PaO_2, $PaCO_2$, base excess, bicarbonate, lactate, PaO_2/FiO_2 ratio	Cont.
Ventilation parameters	Mechanical ventilation	Binary
	FiO_2	Cont.
Medications and fluid balance	Current IV fluid intake over 4h, cumulated IV fluid intake	Cont.
	Mean and maximum dose of vasopressor over 4h	Cont.
	Urine output over 4h, cumulated urine output	Cont.
	Cumulated fluid balance since admission (includes preadmission data when available)	Cont.

Other interventions	Renal replacement therapy	Binary
	Sedation	Binary
Outcome	Hospital mortality	Binary
	90-day mortality	Binary

Table S1: Description of the variables included in the dataset. INR: International Normalized Ratio; * Modified SOFA: SOFA based on values in the current 4h time step; PEEP: Positive End Expiratory Pressure; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; Sedation includes hypnotic drugs, opioids and muscle blockers; SIRS: Systemic Inflammatory Response Syndrome; Shock index: systolic blood pressure/heart rate.

Suggestions for Semester-Project Directions

In the first section, we outlined how several interventions have the potential of improving patient survival, but also the potential for severe harm if used at the wrong time. Below we discuss concrete directions for semester-long projects. You may choose from any of these directions (and refine them); if you wish to purse a different direction please first discuss with the staff to ensure that we expect the direction to have technical and/or clinical value.

Technical Questions: These questions focus on core reinforcement learning questions that have the potential to assist in the management of sepsis. You can view them as extensions of the models from Homework 3.

- **What is the best state representation?** In Homework 3, you used the simplest form of state representation: discrete clusters based only on the current observations. Are there better options? There are many directions here: Should the states be discrete or continuous? If discrete, are there better choices of clustering (to suggest one, t-SNE)? Should we be incorporating more of the history? How far back must we look? Or should we look back a variable amount? Are all variables important, or can we ignore some of them? Can you validate whether your choices help satisfy Markov assumptions?
- **Are there advantages to using an explicit hidden state model?** The clustering approach to grouping states is implicitly a hidden state model, in the sense that we assume that the dynamical system evolves over clusters, and clusters emit observations. Are there advantages to explicitly using a POMDP or RNN?
- **How can we best combine model-based, model-free, and direct policy learning approaches?** All these approaches have their advantages and disadvantages. How can we combine them to get the best of all?
- **How should we handle missing data?** The current data set has missing values imputed. Does the choice of imputation method affect the policies and outcomes? What is the value of multiple Gaussian Process imputation, similarly to (Prasad, Cheng, Chivers, Draugelis, & Engelhardt, 2017)? What if we do not perform any imputation (e.g. use a mixture model rather than a clustering model for defining the state)?
- **Can shaping rewards help get better policies?** Our primary outcome is mortality within 90 days, but as you saw, that option makes the reward signals very sparse. To address this problem, intermediate rewards could be assigned along the way, during the course of a patient stay. One possibility is to assign reward signals to a severity score, such as the SOFA score,

provided in the dataset. Does incorporating these intermediate rewards help create a policy that has improved mortality outcomes?

- **Can we optimize for multiple objectives?** While mortality is the primary outcome, it would be ideal to also minimize the length of stay to reduce costs as well as exposure risk. What are the trade-offs?

Scientific Questions: These questions focus on important clinical questions for sepsis management. You might end up making only minor extensions to the technical machinery from Homework 3, but answer specific clinical questions.

- **Can we optimize over a broader set of medical interventions?** The various interventions that could be evaluated with this dataset are: Vasopressor and intravenous fluid therapy (can be assessed together or separately), Mechanical ventilation and sedation (same comment), Renal replacement therapy. Some of these interventions can be modeled as either discrete or continuous. Can you create a model that provides recommendations across the whole of this action space?
- **How can we managing patients with AKI (Acute Kidney Injury) and sepsis?** This is a subset of patients that may require different kinds of management.
- **Inverse RL: What are clinicians trying to optimize?** Can we estimate the reward value assumed by physicians when making their decisions? In particular, the clinicians have dual objectives of 1) making their patients reach survival quickly and 2) making them avoid death. In a data set of this size, it is also important to note that their may be subgroups of clinicians (e.g. experience vs. inexperienced). Even if care provider identifiers are given in the data, it is highly unreliable. However, it may be possible to identify subgroups of clinicians who behave similarly, especially if we make certain assumptions (e.g. clinicians tend to make similar decisions for similar patients).

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