A Sepsis Treatment Recommender Using LSTM Regression for Imitation Learning

Ian Pegg
UC San Diego
ipegg@ucsd.edu

Luke Wulf
UC San Diego
lwulf@ucsd.edu

Abstract

Rapid diagnosis and treatment is crucial for patients with sepsis, a leading cause of mortality in intensive care units. Currently, there is no consensus within the medical community for a sepsis treatment protocol. Previous studies that have attempted to address this problem using machine learning techniques. These studies use reinforcement learning, leading to inherently biased models. We propose a hybrid imitation-learning approach. First, predicting whether treatment is required using boosting and ignoring patient history; next predicting prescription dosage using a long short-term memory regression. Such an approach will be less biased than the reinforcement learning approach, and has the potential to be fine-tuned using apprenticeship learning to achieve state of the art performance.

1. Introduction

Sepsis is a severe infection leading to life-threatening organ failure. The management of its treatment is critical to minimize loss of life for patients in this condition. Despite its severity, sepsis has no treatment protocol consensus, and several implemented protocols have failed to demonstrate any outcome benefit [1].

Other authors have attempted to address these issues using reinforcement learning models [2][3]. However, as identified by Gottesman et. al. [4], reinforcement learning in medical applications is fraught with problems. We will redress some of those problems using a two-step imitation learning approach. Imitation learning is a technique in which the behavior of an actor is replicated by a model, frequently used in automated diagnosis from medical images [5]. With this approach, our model will first determine whether treatment is required, and in the second step, will determine the dosage amount if any was required. This model will learn typical clinical treatment strategies in a way that is inherently sub-optimal, but significantly less biased than the reinforcement learning strategies.

Following the pattern established by [2] and [3], we target vasopressor prescription as our label. Vasopressors are a class of drugs applied to restore and maintain blood pressure in patients with sepsis [6]. Patients will receive other essential treatments such as antibiotics and fluids, but these are out of the scope of this study.

We used the MIMIC-III dataset [7] to train and evaluate our model. Code for the project can be found in our repository [1].

2. Related Work

Existing work applying machine learning to the treatment of sepsis has focused on improving upon doctors' prescriptions using reinforcement learning (RL) in an attempt to learn optimal treatment strategies [2][3].

In RL, the goal is to maximize the total reward over the complete sequence:

$$R = \sum_{t=0}^{T} r_t \tag{1}$$

where r_t is the reward function at time step t.

These works use importance sampling (IS) to evaluate their models. The importance sampling estimator V^{π_e} is given by:

$$\hat{V}^{\pi_e} = \frac{1}{N} \sum_{n=1}^{N} w^{H_n} R^{H_n} \tag{2}$$

where H_n is the clinical history of patient n, π_m is the model's treatment strategy, and R is from equation 1.

The weights w^{H_n} are given by:

$$w^{H_n} = \prod_{t=0}^{T_{H_n}} \frac{\pi_m(a_t^{H_n} | s_t^{H_n})}{\pi_c(a_t^{H_n} | s_t^{H_n})} \tag{3}$$

[1] https://github.com/Ian-Mint/treatment_recommender

where π_c is the clinician treatment strategy, T_{H_n} is the number of time steps and the π functions represent the probability of action a given state s.

In this paper, we will address the following criticisms of RL in the treatment of sepsis [4]:

1. Learned treatment strategies have a tendency to recommend minimal treatment for patients with acute sepsis. RL requires the presence of negative examples, and in the absence of such data for patients with acute sepsis who received no treatment, the model learns to avoid aggressive treatment for the patients that need it most.

2. Models will tend to over-prescribe. In order to make these problems more tractable, models are given limited options for treatment. Now, prescription is the model's only recourse, so when it recognizes a patient that requires treatment, it takes the only action available to it: treatment prescription.

3. Considering equation 3, if the model's treatment strategy is very dissimilar from the clinician's, the weights will go to zero. So, the model will be incapable of learning a superior treatment strategy unless it is similar to that of the clinician.

Komorowski et. al.[3] included MIMIC-III data for adult patients meeting the criteria for septic shock. They extracted a set of 48 features including demographics and Elixhauser score [8]. These features were reduced to 750 clusters using k-means. Time-series data was split into 4-hour time intervals. They used a 90-day survival criteria as a reward function for their Markov decision process (MDP). The goal of the model is to choose the best treatment among those taken by the clinicians. IS evaluation, equation 2, demonstrated the model consistently outperforming clinicians.

Raghu et. al. [2] set up their data in much the same way as Komorowski et. al.[3], using 48 features from patients meeting the criteria for septic shock in the MIMIC-III database. Again, data were chunked into 4-hour time interval, and 90-day survival was used as the criteria for the reward function. Raghu et. al. also found results outperforming the clinician treatment strategy.

3. Dataset

MIMIC-III is a relational database containing patient care information from intensive care unit (ICU) stays at the Beth Israel Deaconess Medical Center. The de-identified data is associated with over 40,000 patients who were admitted to the ICU between 2001 and 2012. All charted information is contained in the database: fields like time of admission, blood pressure, diagnosis, and free-text notes. Figure 1 provides a graphical representation of the dataset, including information about how the data was collected and processed.

From nearly 60,000 ICU admissions, patients contracted sepsis in a little over 4,000 cases. Among these patients, the median age was 68, 55% of the patients were male, and 5% of the patients were newborns.

4. Method

Using the MIMIC-III database, we will extract pertinent ICU stay features to learn how doctors prescribe and administer vasopressors. This problem is two-fold; we will be need both binary classification and value prediction to correctly administer vasopressors in a responsible manner.

Our method will be split into three parts: Extracting a usable training set from MIMIC-III, using static analysis to identify the need for vasopressors, and predicting the dosage of the prescription. The goal of these methods is to create a two-part model that can accurately mirror a clinician's response to a sepsis patient's vasopressor treatment requirements.

4.1. Data Cleaning and Processing

The dataset was downloaded following the MIMIC approval process [2] and compiled to a Postgres database using tools published by the project [3].

With this database, we first identified those patients with diagnosis codes corresponding to mild sepsis, severe sepsis, and septic shock. We started by isolating these cases and identifying the similarities in their ICU stays, prescriptions, and treatments. By parsing through the patient's sequential data, we identified vital signs, laboratory measurements, and categorical features present in 80% or more of the sepsis cases. The features we identified in this manner were then normalized before being provided as inputs to our model.

Following the pattern of related works [2][3], we collected our time-series data into four-hour intervals – averaging quantities like heart rate and accumulating quantities like fluid intake. Quantities such as laboratory and vital signs measurements were interpolated by propagating the last known measurement across time steps where such data was missing. In this manner, our model was presented with the same measurements a real clinician would be.

4.2. Static Analysis

In the binary classification experiments we will be using statistical learning models to identify whether or not a patient will need to be treated with vasopressin. The models have been selected as they excel in the binary classification problem and are easily implemented with the scikit-learn

[2] https://mimic.physionet.org/

[3] https://github.com/MIT-LCP/mimic-code

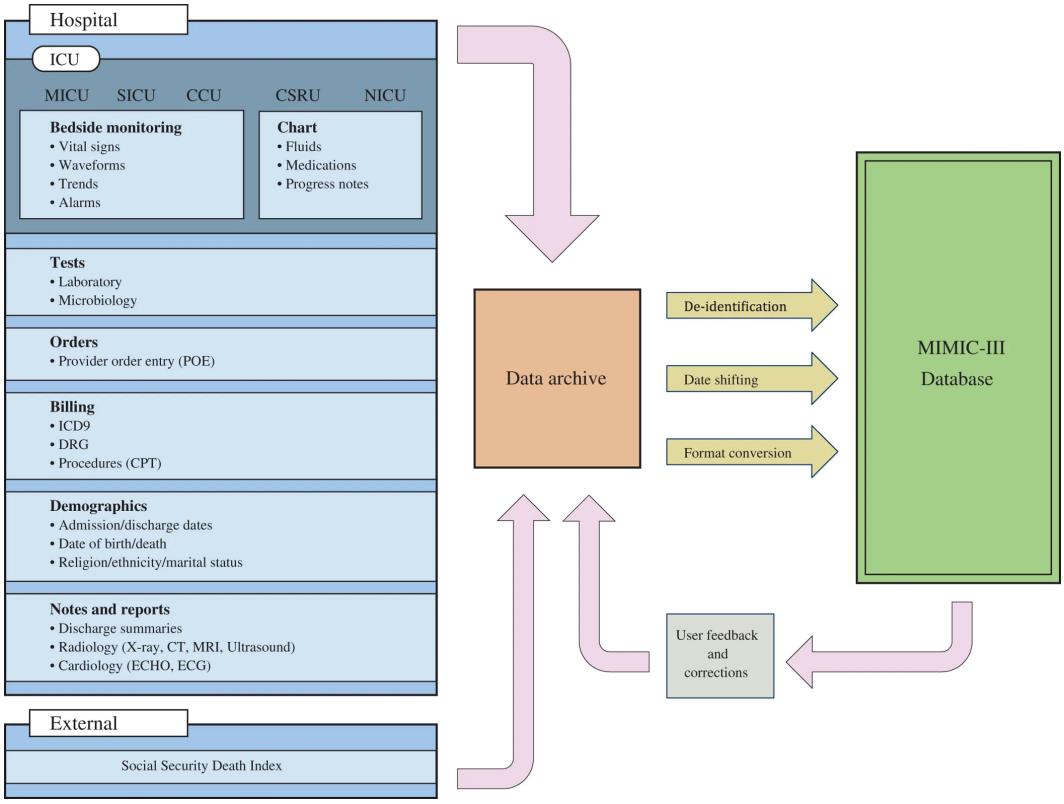

Figure 1. MIMIC-III dataset [7]

python library. The models we have chosen for our experiment are:

- *Linear Regression*: Fitting a hyperplane to classify samples using MSE as the loss function.
- *Logistic Regression*: Fitting a logistic curve to classify samples. With this model, non-linear decision boundaries can be found. Traditionally, logistic regression a simple and effective binary classifier.
- *Support Vector Machine*: Fitting a maximum-margin hyperplane to classify data points. We will be using the linear kernel with soft-margin for computational ease.
- *AdaBoost*: Ensemble learning model where many weak learners work in unison to come to a non-linear decision function. The ensemble approach will prove useful to create a more robust classifier.

4.3. LSTM

First proposed by Hoschreiter & Schmidhuber [9], long short term memory (LSTM) neural networks are based on recurrent neural networks (RNN), but are capable of maintaining longer term memories than traditional RNNs. LSTMs are used in state of the art implementations of caption generation [10], machine translation [11], speech recognition [12], and are generally useful in sequence-to-sequence machine learning problems.

Given an input sequence $\mathbf{x} = (x_1, \ldots, x_T)$, a LSTM finds the hidden sequence $\mathbf{h} = (h_1, \ldots, h_T)$ and output sequence $\mathbf{y} = (y_1, \ldots, y_T)$ by iterating over $t = 1, \ldots, T$:

$$h_t = \mathcal{H}(W_{xh}x_t + W_{hh}h_{t-1} + b_h) \tag{4}$$
$$y_t = W_{hy}h_t + b_y \tag{5}$$

where the b_i are bias terms, and W_{ij} denote weights from layer i to j.

The function $\mathcal{H}$ in equation 4 is implemented as follows:

$$i_t = \sigma(W_{xi}x_t + W_{hi}h_{t-1} + W_{ci}c_{t-1} + b_i) \tag{6}$$
$$f_t = \sigma(W_{xf}x_t + W_{hf}h_{t-1} + W_{cf}c_{t-1} + b_f) \tag{7}$$
$$c_t = f_t c_{t-1} + i_t \tanh(W_{xc}x_t + W_{hc}h_{t-1} + b_c) \tag{8}$$
$$o_t = \sigma(W_{xo}x_t + W_{ho}h_{t-1} + W_{co}c_t + b_o) \tag{9}$$
$$h_t = o_t \tanh(c_t) \tag{10}$$

where σ is the sigmoid function and i, f, o are the input, forget, and output gate respectively. c is the memory cell, the key feature giving LSTM its useful properties. Figure 2 provides a graphical representation of this model.

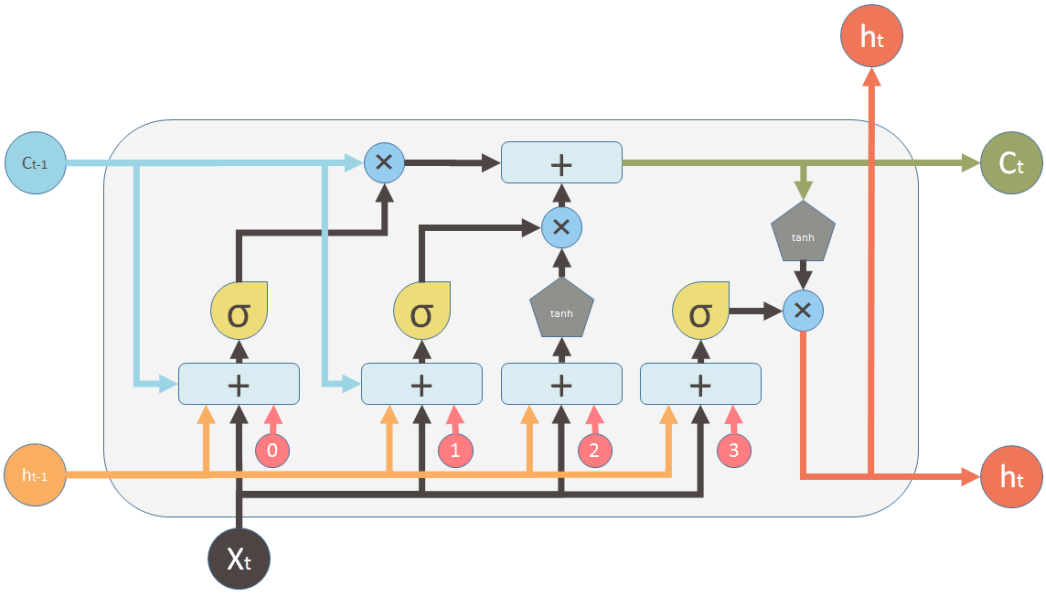

Figure 2. LSTM neural network [13]

5. Experiments

5.1. Static Analysis

For the static portion of our analysis, we used multiple statistical learning models to implement a binary classifier whose goal is the identification of patients who require the administration of vasopressors. These models were implemented using scikit-learn and python.

In this portion of the analysis, the clinical history of patients was ignored. The training set was flattened so that each four hour interval was sampled separately. Formatting the data in this manner, we have a training set of 95000 points distributed as 93% negative and 7% positive. This was then up-sampled to achieve a balanced set.

Linear discriminant analysis (LDA) was used to reduce the dimensionality of our feature space and separate the positive and negative cases. After running LDA we found the most correlating feature to a positive label to be "specific gravity of urine" and the most correlating feature to a negative label to be "urine appearance". This is a logical outcome, as both features are proxies for hydration, a state directly impacted by vasopressor administration [14]. Using the reduced features in our machine learning models, we produced the results shown in table 1.

Running the static analysis with AdaBoost proved most effective in predicting whether or not vasopressors prescription was required. AdaBoost is an ensemble learner, thus has more opportunity to learn the non-linear decision boundary of the solution. This is likely the reason it outperformed all other models presented in table 1. Supporting this conclusion is the fact that linear regression was the worst performer of the tested models.

Table 1. Static analysis results

Model	Accuracy
Linear Regression	71.04%
Logistic Regression	81.26%
SVM	83.22%
AdaBoost	83.71%

5.2. Time Series Analysis

For the time-series portion of our analysis, we employed a LSTM network implemented with tensorflow and keras in python.

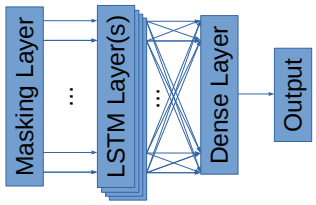

Figure 3. LSTM model with masking

First, because our data contains sequences of various length, all sequences were padded to the same length. Our model uses a masking layer to inform the next layers what (padded) data to ignore. The output of the masking layer is fed into a sequence of one or more LSTM layers. Finally, a densely connected perceptron layer provides a single output: the desired vasopressor dose. A basic representation of the network can be seen in figure 3.

Table 2. 1-layer LSTM results

Width	Sequence Length	RMS Loss $\times 10^{-3}$
8	4	0.50
4	8	0.58
16	8	0.59
32	4	0.70
64	8	0.79
16	8	0.89
16	4	0.89
4	4	1.09
16	16	1.17
32	8	1.22
16	32	1.26
8	8	1.50

Table 3. 2-layer LSTM results

Width	Sequence Length	RMS Loss $\times 10^{-3}$
8	8	0.67
4	16	0.72
32	8	0.74
8	4	0.81
32	16	0.83
4	8	0.91
4	4	1.10
16	8	1.14
16	32	1.15
16	4	1.18
4	16	1.27
8	16	1.36
32	4	1.37
16	16	1.52

For this regression model, we used RMSprop [15] as our optimizer and RMSe as the loss function:

$$RMS(w,t) = 0.9RMS(w,t-1) + 0.1\left(\frac{\partial E}{\partial w}(t)\right)^2 \tag{11}$$

$$E = \frac{1}{N}\sum_{i=0}^{N}(y_i - z_i)^2 \tag{12}$$

where E is the loss, w represents all weight vectors, t is the time step, y_i is the predicted label and z_i is the label of input i.

The results of our experiments can be found in tables 2 and 3. These were obtained using splits the following data splits: 70% training, 10% validation, and 20% testing. It can be seen that we achieved the best performance with a sequence length of 8, corresponding to 32-hours. The optimal model was also also the simplest, a 1-layer LSTM with 4 nodes. These results indicate that there are very few features that come into play when a clinician makes a decision about vasopressor prescription, and that the past 32 hours of patient history are the most pertinent to the clinician making a decision about vasopressor prescription.

A concrete example of the model's output can be seen in figure 4. Looking at this figure, we can see a few things:

- the prescription of zero vasopressor is predicted accurately;
- when vasopressor is required, it is predicted quite accurately, and;
- vasopressor prescription is consistently underprescribed.

6. Future Work

Building on our results, there are multiple paths that could be taken to enhance this model to improve clinical utility. Both the static and dynamic models could be improved by further feature extraction. The bulk of our extraction work consisted of cleaning the dataset, and further data analysis would be beneficial in extracting more useful data to find correlating features.

In addition, the static analysis could be improved through the use of neural network models. We chose to forgo this opportunity in this project due to data limitations, however neural networks have the potential to both accurately predict vasopressor prescription, and to identify the most important features in classification.

A frequent goal in medical applications of machine learning is to produce a model that can be intuitively understood [16]. A way should be devised to make our models' decision processes more explainable. The decision process and rationale of a model is incredibly important in healthcare as a clinician must explain simply and succinctly how and why they chose a particular course of action. By improving upon the transparency of our model, it could lead to easier adoption and less learned bias.

Finally, using the baseline presented here and the steps recommended above, this model would be an excellent starting point for fine-tuning using apprenticeship learning [17]. Such models, like Deep Mind's AlphaGo [18], have achieved state of the art performance in reinforcement learning applications.

7. Conclusion

By using a hybrid approach with both static and temporal models, we can accurately predict the need for and subsequent prescription of vasopressors to a patient with sepsis.

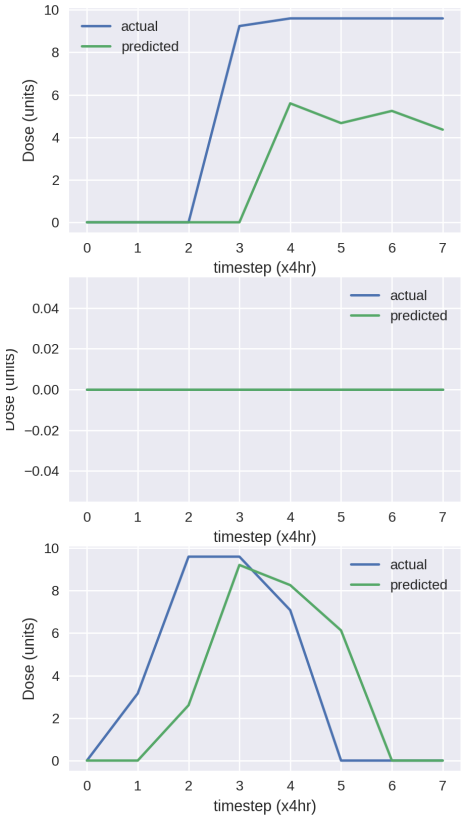

Figure 4. Example outputs of model-prescribed versus clinician-prescribed vasopressor dosages for three different 32-hour long sequences

This was achieved through the use of binary classification using AdaBoost and dosage prediction with LSTM. Particularly with the LSTM, we found that given the standard lab measurements we can predict both the timing and dosage of vasopressors with accuracy.

Most importantly, this model could be used as a starting point for apprenticeship learning, with the potential to exceed human performance in sepsis treatment.

Sepsis is a condition that progresses rapidly if treatment lags. The use of models like the one we propose can supplement clinician decision making to quickly identify and act upon the symptoms of sepsis. This will correlate to shorter recovery times, lower mortality and lower ICU occupancy.

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