Predicting intervention onset in the ICU with switching state space models

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Abstract

The impact of many common intensive care unit interventions have not fully quantified, especially in heterogenous patient populations. We train unsupervised switching state autoregressive models on vital signs from the public MIMIC-III database to capture patient movement between physiological states. We compare our learnt belief states to static demographics and raw vital signs in the prediction of five ICU treatments: ventilation, vasopressor administration, and three transfusions. We show belief states yield high-quality prediction in all tasks even when predicting interventions 4 or 8 hours ahead of their onset. Our results are competitive with existing work while using a substantially larger and more diverse cohort of 36,050 patients. While custom classifiers can only target one specific clinical event, our model learns physiological states which can help with many interventions. Our learning of robust patient state representations presents an exciting path towards future evidence-driven adminsitration of key clinical interventions.

1 Introduction

Patients in the intensive care unit (ICU) receive a myriad of interventions to control and respond to their rapidly changing physiological conditions. The quality of their care depends on clinical staff combining large amounts of heterogeneous clinical data to understand the severity of their illness - also called acuity. However, while ICUs continue to expand their role in acute healthcare delivery [39], only 10 of the 72 ICU interventions evalued in randomized controlled trials helped critically ill patients survive.[28]. Adverse events in ICU patients are often preceded by a period of physiologic deterioration on the order of hours, and a lack of early recognition of physiologic decline can play a major role in the failure to rescue patients.

In this work, we evaluate unsupervised patient reprentations on the task of predicting an impending need for an intervention in the ICU. Early prediction is an important task in the ICU setting, as early prediction can ensure that both hospital staff and patients are prepared for interventions. This is especially true if the interventions involve the patient losing their ability to participate in decisions about their care. We use the publicly-available MIMIC III database [14] to create latent patient representations without discriminative training, and subsequently target early prediction of common ICU interventions: vasopressors administration, mechanical ventillation, and transfusions.

Previous work on early prediction has focused on training discriminative classifiers for specific outcomes or specific subpopulations. For example, [11] trained models to predict time to septic shock onset, and [20] attempted to predict hypotensive episodes using hand-engineered aggregates. In this work, we use a general unsupervised approach to learn the physiological state of the patient. This leads to good performance on several prediction tasks, and our unsupervised features consistently improve performance results for the onset of five different interventions.

Based on these results, we believe that intervention predictions can be made based on unsupervised patterns learned from a much broader ICU cohort, without significant manual cohort and feature design. Our specific contributions are:

1. Creating an unsupervised representation from a large cohort of ICU patients useful for a variety of tasks;
2. Evaluating our features on five distinct ICU intervention tasks - each of which has associated clinical risk; and
3. Investigating the validity of the latent states on intervention tasks, based both on the weights associated with our chosen intervention tasks and post-hoc analysis of the commonly emitted phsyiological data from the states.

2 Background and Related Work

Broadly, our work stands out from previous modeling efforts for its focus on an unsupervised model of patient dynamics which we show can generalize across interventions, rather than an intervention-specific model.

2.1 ICU Interventions

We evaluate our unsupervised belief states on the prediction of five ICU treatments: ventilation, vasopressor administration, and three transfusions. An important question for each these interventions is when they will be given and when they can be stopped. Mechanical ventilation is commonly used when a patient requires assistance for breathing. However, ventilation has many potential complications, leading clinicians to try and predict the earliest time that a patient can resume spontaneous breathing [45]. Further, small changes in the timing and setting of the ventilation can make large differences in patient outcomes [38]. Vasopressors are also commonly used in the ICU, but few controlled clinical trials have documented improved outcomes from their use [24], and it may even be harmful in some populations [5]. Transfusions are used in many medical conditions, but have been associated with immunological reactions and infection. For example, red blood cell transfusions have previously been associated with increased mortality in certain populations [23], and fresh frozen plasma transfusions have been associated with increased risk of developing acute lung injury [25]. There is a further question about the efficacy of transfusions - e.g., in the case of prophylactic use of plasma [37] and platelet transfusions [36]- and best way to combine various blood products [12].

2.2 Clinical Modelling

Current ICU practice evaluates patient acuity using scoring systems like SAPS II[19], SOFA[40], or APACHE[17]. However, these scores tend to be based on static periods of patient data (often the first 24 hours after admission) and do not incorporate evolving clinical information. Such scores are also evaluated at a single end point, such as in-hosptial mortality or mortality 28 days post-discharge. Single risk scores are unable to capture the different ways in which a patient may be ill.

One common approach in clinical machine learning is to implicitly capture time within the feature space using concatenation during some phase of the model learning. This can be done using statistical aggregation of variables over different time ranges [13; 15], creating multiple models for outcome evaluation at different timepoints [6; 9], or developing models that reduce timeseries data into a smaller space[10; 4].

While discrete states allow interpretion of learned state sequences in terms of separable stages of health, several authors have used continuous latent states popularized by linear dynamical systems models, also known as "Kalman filter" models. Some [30] have used switching factorial LDS models for infant care, but focused on identifying measurement errors like disconnected probes. Others [3] employed an LDS model for prediction of patient mortality, but did not consider any actionable interventions. Neither did [21], who developed a high-order switching autoregressive LDS model also for mortality prediction with a reduced variable and patient set from MIMIC. Recently, [18] developed a non-linear deep architecture for training Kalman filter models with an application on counterfactual inference of the impact of different drugs for diabetes. Some work has focused on discrete observations rather than continuous clinical data [22]. None of these approaches, however, evaluate how well the approach could predict actionable interventions.

Other work has attempted to predict the intervention onset in the ICU, but to date these have all been focused on smaller ICU populations or involved targeted outcome training. [16] developed a logistic regression model to predict the need for blood transfusion in 1007 coronary artery bypass graft patients, and obtained a training set AUC of 0.86 on their training set (no test set ACU was reported). More recently, demographic and admission variables from 1,016 trauma patients were used to train a backpropagation neural network to predict the number of units of PRBC, FFP, and platelets transfused for each patient over verious time spans (during the first 2 hours, 6 hours, 24 hours, etc.) for a best mean absolute error of 7.02 blood product units.[43] For vasopressor use, [6] used a subset of the MIMIC II patients receiving fluid resuscitation (2944 adult ICU patients), and attempted to predict subsequent vasopressor administration within 2 hours using a general model and two disease-based models. The general patient model achieved an AUC of 0.79 ± 0.02, and the disease-models had AUCs of 0.82 ± 0.02 for pneumonia and 0.83 ± 0.03 for pancreatitis. [34] trained an ensemble fuzzy modeling to predict the need of vasopressors administration in septic shock patients (the same dataset as [6]) and obtained an AUC of 0.85 ± 0.01 in the general population. [44] developed a switching-state autoreressive model on 4,331 patients who were administered vasopressors, and achieved an AUC of 0.88 ± 0.0061 with a 4 hour gap on 15,695 ICU patients.

3 Data

All data comes from the publicly-available MIMIC-III database [14]. This dataset contains static and dynamic information for nearly 60,000 patients treated in the critical care units of the Beth-Israel Deaconess Medical Center (BIDMC) in Boston between 2001-2012. Our experiments use MIMIC-III version 1.4, released in September 2016.

3.1 Cohort Selection

Our cohort consisted of adult patients over the age of 15 (we leave the question of whether adult and pediatric patients have similar physiological states to future work). We also excluded patients with less than 6 hours or more than 360 hours of data to avoid fundamentally sicker patients, and focus instead on those with good chances of recovery due to interventions. These exclusion criteria are much less stringent than those used in previous work as we are attempting to model [13; 15]. After filtering by these criteria, we achieved a final cohort of 36,050 patients.

Intervention	Num Positive	Num Control
Vasopressor	9,983	27,951
Red blood cell transfusion	25,592	12,342
Fresh frozen plasma transfusion	4,035	33,899
Platelet transfusion	36,563	1,371
Mechanical Ventilation	18,872	19,062

Table 1: The total counts of positive and control patients in our cohort for each of our 5 possible interventions.

3.2 Data Types and Pre-processing

For each patient n in our N patient cohort, we extracted three arrays from the MIMIC-III dataset: a timeseries of clinical observations x_n, a timeseries of clinical intevention labels y_n, and static observations s_n.

Per-timestep clinical observations - x_n. The clinical variable array $x_n = [x_{n1}\ x_{n2}\ \dots\ x_{nt}\ \dots x_{nT_n}]$ consisted of 18 of vitals and lab variables at each timestep t. These clinical variables x_n were then standardized via z-scoring, so that 0 represents the mean.

Seven nurse-verified vital signs, heart-rate (hr), mean arterial blood pressure (meanbp), peripheral capillary oxygen saturation (spo2); fraction of inspired oxygen (fio2), temperature (temp), spontaneous respiration rate (resp), and urine output (urine) were taken from the nurse-validated vital sign trends found in MIMIC III. These signals are produced by bedside monitors once per second, but often stored only once every 560 minutes based on nurse-validated confirmation in the clinical information system.

Ten signals, creatinine, glucose, bicarbonate, hematocrit (hct), lactate, magnesium, platelets, potassium, sodium, white blood cell count (wbc) were taken from the laboratory measurements. These data are produced when blood samples are sent to the laboratory by the clinical staff.

Per-timestep intervention labels - y_n. We examine five ICU interventions: mechanical ventilation, vasopressor adminsitration, red blood cell transfusion, fresh frozen plasma transfusion, and platelet transfusion. The intervention labels $y_n = [y_{n1}\ y_{n2}\ \dots y_{nt} \dots y_{nT}]$ indicated whether each of the interventions were performed at time t. Intervention variables were post-processed to recover continuous segments of administration and non-administration based on the recommendations of the MIMIC II team and the BIDMC clinical staff: ventilation gaps were interpolated for gaps of fewer than 8 hours, vasopressors for gaps fewer than 4 hours, and transfusions for gaps fewer than 2 hours.

Static observations - s_n. The patient's static vector s_n contained the patient's demographic information: age at admission, admitting weight, admitting height, body mass index (BMI), gender and first ICU service type (MICU,

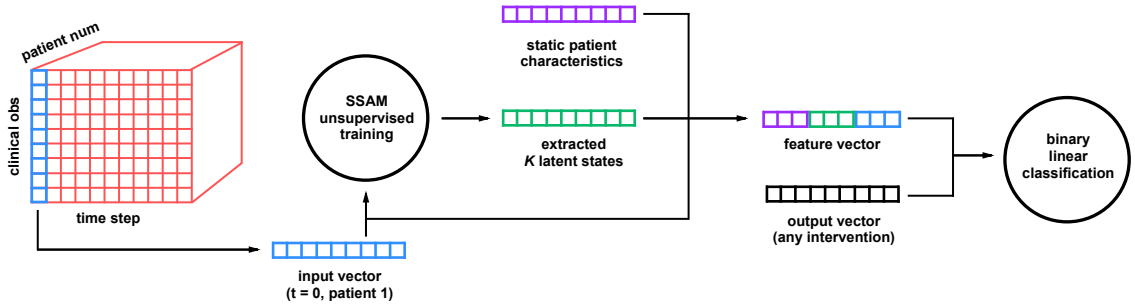

Figure 1: Illustration of data processing pipeline. (1) We extract vital signs and lab results (x_n) are extracted from the database for a filtered selection of patients. (2) A switching-state autoregressive model is used the model the time series, generating belief states b_n (the probability of each state at each time). (3) Static features are extracted for all patients (s_n) - these are based on admission data and do not change over the course of the subject's stay. (4) Given three possible sets of features for each timestep t and patient n - s_n, x_{nt}, and b_{nt} - we train a classifier to predict the per-timestep outcome of interest y_{nt} (e.g. vasopressor administration). Our system predicts the outcome y_{nt} using features from either the immediately previous timestep $f_{n,(t-1)}$, or some further delay $f_{n,(t-d)}$.

medical care unit; SICU, surgical care unit; CCU, cardiac care unit; CSRU, cardiac-surgery recovery unit). Missing values for weight, height and BMI were imputed using the patient's single nearest neighbor according to $L1$ distance to other patients. All other values were fully present.

4 Methods

Given a cohort of N patients each with associated data $\{x_n, y_n, s_n\}_{n=1}^N$, we propose a two-stage analysis pipeline: unsupervised modeling followed by supervised prediction of interventions. First, we employ a switching state space model to discover useful temporal patterns within observed patient trajectories $\{x_n\}_{n=1}^N$. The goal here is to discover a latent representation which is compact yet usefully captures the key dynamic trends found in patient data. Second, we using trained belief states to predict intervention onset.

Switching state space models. Switching state space models are widely-used for unsupervised probabilistic modeling of time-series. The simplest possible models are classic hidden Markov models [32], which assume each observed sequence x_n with length T_n can be generated in two steps. First, generate a hidden state sequence $z_n = [z_{n1} \dots z_{nT_n}]$ via a first-order Markov chain over a discrete state space of size K. The parameters of this stage are the starting-state probability vector π_0 and transition probability vectors $\{\pi_k\}_{k=1}^K$ for each possible state. We sample the discrete state assigned to the first timestep ($t = 1$) as: $z_{n1} \sim \text{Cat}(\pi_0)$. Then, each successive discrete state is draw from the appropriate Markov transition probability: $z_{nt} \sim \text{Cat}(\pi_{z_{nt-1}})$. Second, given the state sequence z_n we generate each observation $x_{nt} \in \text{R}^D$ from an *emission* model with state-specific density F with parameter ϕ_k: $p(x_{nt}|z_{nt} = k, \phi_k) = F(x_n|\phi_k)$.

Auto-regressive state space models. Many extensions have focused on *auto-regressive* emission models which use previous observations as well as current state to parameterize the emission model. If each observation is a multivariate real vector, a first-order AR emission model can generate the observations at timestep $t = 1, 2, \dots T_n$ via the model

$$x_{nt}|x_{nt-1}, z_{nt} = k \sim \mathcal{N}(x_{nt}|A_k x_{nt-1} + \mu_k, \Sigma_k) \tag{1}$$

Bayesian inference for such autoregressive models has been explored previously by several authors [31; 7]. This construction assumes either a known observation x_{n0} for the very first time-interval $t = 0$ of any sequence, or perhaps a generative model $p(x_{n0}|\phi_0)$ for this starting observation.

Training state space models. Several training procedures are possible for learning switching-state autoregressive model parameters $\pi_0, \{\pi_k, \phi_k\}_{k=1}^K$ from data $\{x_n\}_{n=1}^N$. The most popular include Markov chain Monte Carlo sampling methods [35] and variational optimization methods [42]. We follow a standard variational Bayesian approach for training our HMMs [2] using continuous auto-regressive emission models. To verify robustness, we also confirmed that training using the pipeline of [44], which discretizes x and applies a naive Bayes emission model, leads to similar results.

Feature extraction using state space models. Given a trained state-space model, which is defined by the parameters $\pi_0, \{\pi_k, \phi_k\}_{k=1}^K$, we can represent each observed time-series by its associated *forward-looking belief* sequence $[b_{n1}, \dots b_{nt} \dots b_{nT_n}]$, where each time-interval-specific vector b_{nt} gives the probability that each possible state is used:

$$b_{nt} = [b_{nt1} \dots b_{ntK}], \quad \text{s.t. } b_{tnk} \geq 0, \sum_{k=1}^K b_{ntk} = 1, \text{ and } b_{ntk} \triangleq p(z_{nt} = k | \pi_0, \{\pi_k, \phi_k\}_{k=1}^K\}, x_{n1}, \dots x_{nt}) \quad (2)$$

This quantity can be easily computed using dynamic programming [32], with runtime cost $O(T_n K^2)$. We deliberately choose to use the forward-looking belief in Eq. (2), rather than the full-sequence belief $p(z_{nt} = k | x_{n1} \dots x_{nT_n})$, because in our ICU application we need to make predictions as time unfolds, rather than retrospectively.

We consider the task of *onset prediction* for interventions such as putting the patient on a ventilator or administering vasopressor drugs. This is a binary classification task, where at each one-hour interval of the patient's stay in the hospital, we must predict whether to apply the intervention (positive event) or not (negative event). We treat each of our 5 interventions as a separate event, and train a separate classifier for each.

The number of hours in advance an accurate prediction can be made is a critical consideration for planning hospital staffing and preparing patients both physically and mentally. We thus specifically study performance at various levels of *delay* d between the target timestep t where intervention y_{nt} might occur and the earlier timestep $t-d$ where features $f_{n(t-d)}$ (either observations x or beliefs b) are extracted. Larger values of delay d have more difficult predictions. We consider delay values of 1, 2, 4, and 8 hours, where the interval between each of our timesteps is one hour.

Onset Definition. We assemble an evaluation dataset from our full cohort of data for N patients. If sequence n contains no positive instance of the intervention, we use the entire sequence. Otherwise, we include only timesteps until the first positive example. Sequences with positive examples which occur too soon (within the first 6 hours) were discarded, so that all training examples represent patients with sufficient time inside the ICU before intervention occurred. These criteria prevents our classifier from being trained or evaluated during situations where its decisions about whether to intervene are not even needed.

Assembling all timesteps meeting this criteria generally creates a very unbalanced dataset with many more negative than positive examples. We can rectify this by appropriately modifying the cost function of our classifier to weight each class' examples according to the inverse of the class frequency in the training set.

Classifier Training. Our onset classification pipeline for intervention c at delay of d hours consumes as input the tuple $\{f_{n(t-d)}, y_{ntc}\}$ for each timestep t in the evaluation dataset. The feature vectors $f_{n(t-d)}$ represent the *delayed* input vectors provided to the classifier, while the binary labels y_{ntc} for the specific intervention c in question.

Given this data, we consider 5 possible random splits of the data, where each patient's data belongs to a single split. For each split, we train a Logistic Regression binary classifier using a cost function which imposes L2 shrinkage penalties on the weight parameters and accounts for unbalanced class weights. We use nested cross-validation to identify the cost parameter which maximizes area-under-the-ROC-curve (AUC) for the heldout set. Our implementation uses the popular Python library sci-kit learn [29]. For each intervention c, we report the AUC as well standard error estimates obtained by bootstrapping across the five folds.

5 Results

5.1 Quantitative Results

We compare our feature representations across increasing prediction gaps for intervention onset classification in Fig. 2. Our conclusions are itemized below:

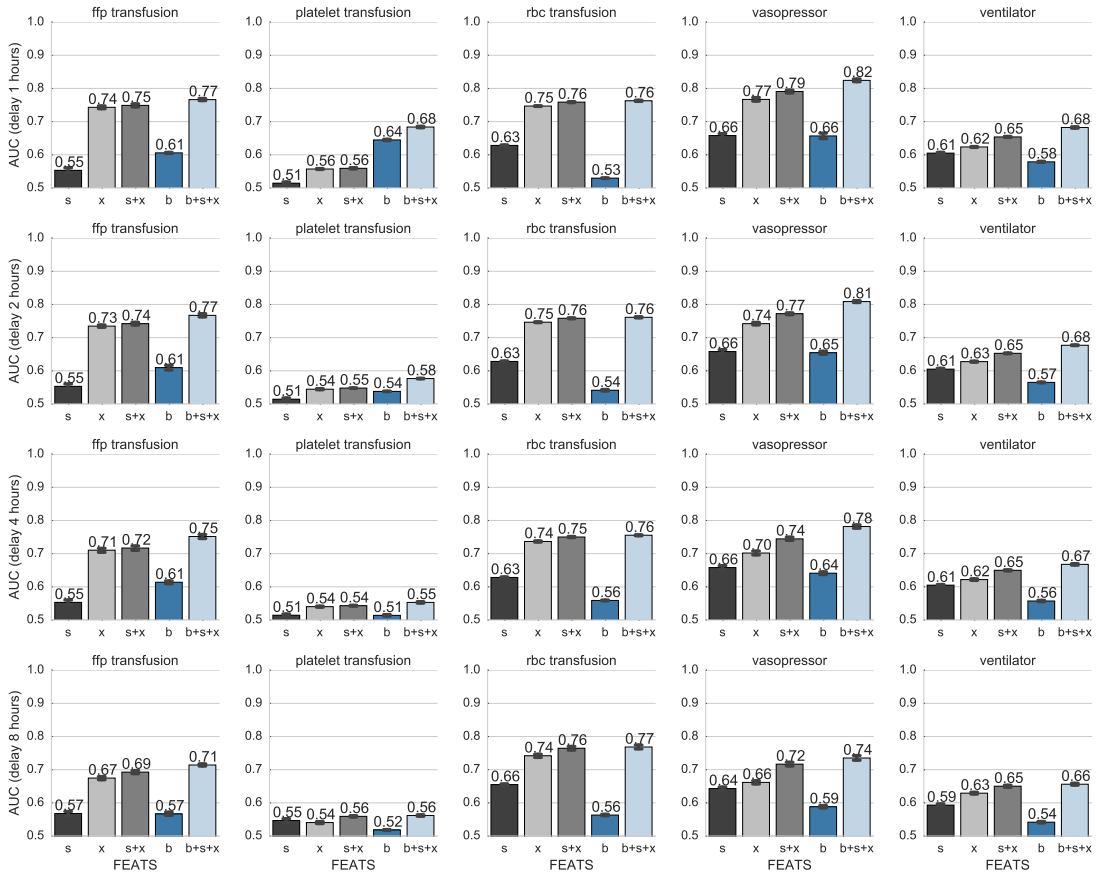

Figure 2: AUC scores for different features predicting the need to start each intervention at a delay of $d \in \{1, 2, 4, 8\}$ hours ahead of the current timestep. *Features:* Each bar color denotes one feature or feature concatenation: static observations s (10 dimensions using one-hot encoding), dynamic time-series observations x (18 dimensions), and belief state vectors b ($K = 10$ dimensions) from the switching state model in Eq. (2). *Interventions:* we conside fresh-frozen-plasma transfusion (ffp), platelet transfusion, red-blood-cell (rbc) transfusion, vasopressor administration, and ventilator intubation.

Belief features plus observations yield best performance. Using our unsupervised belief features b led to the best perfomance ($b + s + x$) as compared to the static observations s and dynamic observations x - and this improvement was noteicabley improved from other results for all interventions except red blood cell transfusions. This indicates that our unsupervised belief states are capturing important differences between patients who are never an intervention and those who are, and that they are useful for predict these needs for this and other important clinical interventions.

Additionally, while belief states alone are often not as good as the raw dynamic features x, they are still well above chance (AUC = 0.5) for all 5 interventions. We do not expect these to always perform well alone because they are trained in an unsupervised manner that *generalizes* across interventions.

Prediction quality drops slightly with increasing delay, but still remain well above chance even 8 hours ahead. Our best feature set for vasopressors achieves above 0.8 AUC for 1-hour ahead predictions, and remains above 0.7 AUC for 8-hours ahead predictions. Similarly, our best features achieve achieve AUC above 0.65 for ventilator intubation and above 0.7 for fresh frozen plasma and red-blood-cell transfusions across all delay values (1, 2, 4, and 8 hours).

There is no direct comparison for our results for most of the interventions as prior work has all focused on very small datasets, or has not reported test set AUCs. The best result for vasopressor onset prediction was obtained by [44] AUC of 0.88 $\pm$ 0.0061 with a 4 hour gap. While this model was evalued on a total patient cohort of 15,695 ICU patients, their model was trained on the subset of 4,331 patients who were administered vasopressors. Our model uses a larger, more general cohort, and achieves a performance of 0.78 without a biased focus on vasopressor patients.

5.2 Qualitative Results.

The goal of this work was to create unsupervised respresentations of multi-dimensional physiological signals, and examine how they relate to important ICU interventions. One interesting question is whether there are indentifyable or interpretable known clinical states that may correspond to our learned reppresentations. We investigate this by examining the belief states for interpretibility post-hoc, and identifying belief states that enriched for particular outcomes.

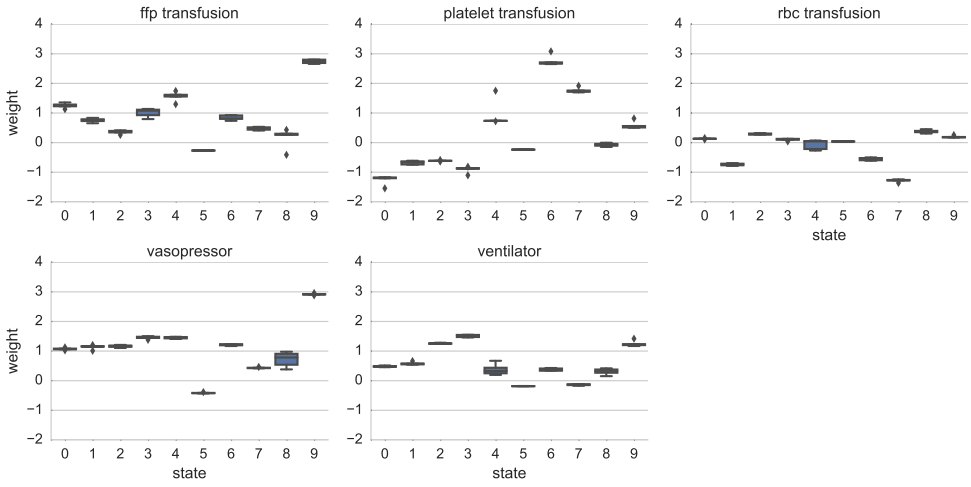

Figure 3: Learned classifier weights for each belief state under each separate intervention task, using fixed delay of 1 hour. The learned set of $K = 10$ hidden states is indexed by an integer from $0, 1, \ldots 9$. Large weight values indicate a state's presence will cause the logistic regression classifier to raise the probability of the intervention.

Fig. 3 shows the weight coeficients which the trained logistic regression model associated with each of the 10 belief states, along with error bars drawn from separate training across 5 possible folds of the dataset. For example, we show that belief state 3 is strongly associated with needing mechanical ventilation (weight = 1.51), state 9 is associated with a need for vasopressors (weight = 2.92) and a fresh frozen plasma transfusion (weight = 2.74), and belief state 6 is associated with platelet transfusions (weight = 2.76). We emphasize that our belief states were learned with an unsupervised switching state model, so there was no discriminative signal driving these associations.

To develop more intuition about the belief states, we also examine the emissions from each belief state. For each state k, we select timesteps with a significant belief mass ($b_{ntk} > 0.3$) and averaged the values of the associated raw observations x_{nt}. As shown in Figure 4, belief state 9 has an increased lactate level, as well as a lowered SpO2 and bicarbonate level. Given these values, one possibilty is that belief state 9 is capturing a general physiological decline as increased lactate has previously been associated with increased mortality [27] and proposed as a biomarker for physiological stress [26], and lowered bicarbonate levels have been associated with acute hyperventilation [1]. Its possible that further investigation of this state would demonstrate its correlation with other negative outcomes -

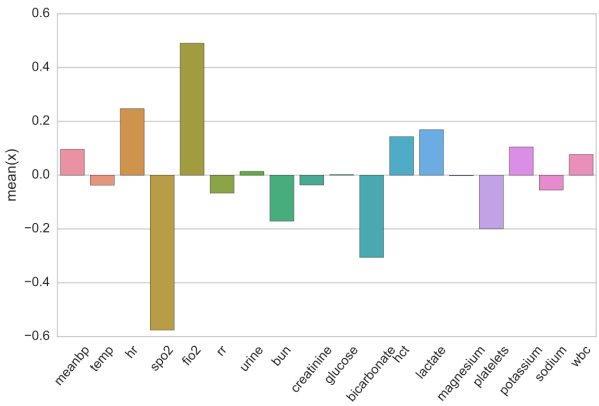

Figure 4: Average value of dynamic features x_{nt} assigned to timesteps strongly associated with state index 9. Note that these values are z-score standardized per variable. State 9 had very low observed spo2 and bicarbonate levels as compared to other states. Lactate levels were the highest observed across all states - no other state had significant positive lactate z-scores.

perhaps even with eventaul mortality.

Belief state 4 had a significantly increased white blood cell count and glucose level; previous work has suggested that high white blood cell counts are associated with worsening insulin sensitivity - which can predicts the development of Type 2 Diabetes.[41] While we did not focus on the identification of chronic disease sub-populations in this work, focusing on individuals from those populations would be an interesting extension for future consideration. We also noted that state 8 had a significantly increased urine output and descreased temperature; this could be indicative of cold-induced diuresis in patients recieving therapeutic hypothermia post srugery.[33] Its possible that our states are capturing specific treatments like therapeutic hypothermia becuase they present very distinctive emission profiles.

6 Discussion and Conclusion

As intensive care units play more expansive roles in acute hospital care, understanding the benefits and pitfalls of common clinical interventions is critical. This is especially important as ICU staff are required to make constant decision about patient treatment in real-time but the impact of many common interventions have not been fully quantified - especially in heterogenous populations. Electronic health records that record patient vital signs and clinical intervention signals offer an opportunity to study patient need for, and response to, these interventions.

We trained unsupervised switching state autoregressive models on patient vital signs, and compared our learnt belief states to static demographic features and the raw vital signs themselves in the prediction of five ICU treatments. It is impressive that our belief states were able to contribute toward intervention prediction in all five settings, given the fundamental differences in the interventions. Mechanical ventilation involves a physical insertion procedure, and is an agressive intervention done when the patient is unable to breathe for themselves. Predicting a need for pressors is strongly tied to ICU status (because vasopressor use itself buys the patient an ICU admission) but administering a vasopressor does not involve a separate device being inserted. Transfusions can be administered on the floor, and combined for use in stages for different resucitation protocols. Much work currently focuses on building discriminative classifiers for a particular combination of patient cohort and prediction target. Learning robust representations of patient state without a targeted outcome could provide the foundations for exciting future work suggesting therapy paths in clinical settings.

Our work has some natural extensions for future work. While we present results on intervention prediction in the largest cohort to our knowledge, we currently focus on adult patients. In theory, our task-agnostic approaches could also be used to find physiological patterns in children as well. We also plan to evaluate our method on other important ICU intervention onset tasks, and extend to weaning tasks. Another interesting extension to our work would be the inclusion of non-Markovian transition distributions or sequence-specific binary masks for state usage [8].

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