PROBLEM SUMMARY AND LITERATURE REVIEW

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1 Problem Definition and Introduction

Patients' body conditions will change with time. These changes depends on doctors' treatments and patients' former states. If a patient changes from a bad state to a good state because of a treatment from doctors, he gets a positive reward. The process is like markov decision process. I want to find the doctors' optimal treatment policy to let a treatment process have the best reward.

2 Challenges of the Problem

The problem has some challenges as follows:

1. In a patient's trajectory, we have the chart, examination and treatment moments of him. However, the moments of the patients are not recorded in a regualr time period. we can't set up a constant time period to separate the patients' states. Therefore, we should learn our problem based on **continuous markov process**.

2. In a markov decision process, we should define the state, the action and the reward. The state transition probability given the action, the action policy, the reward probability given the current state are necessary for us to construct a model. However, we don't know the probabilities for a disease. Many parameters are involved to build a model-based model. What's more, it is hard to define a general reward function for each state from the patients' Electronic Health Record(EHR), which is even a tough thing for knowledge experts. The only reward we have is the **final-time reward**. If the patient is dead when he leaves ICU, the reward is -1; If the patient is recovered, the reward is 1.

3. The training data is collected during randomized trials by the exploration policy. It is difficult to control the exploration or to acquire further data to evalute policies, which means we can't apply optimal policy we learned on the patients to see the results. **Therefore, we can't do on-policy learning.**

3 Important Former Works and Possible Solutions

In this section, I present some related papers to solve the challenges mentioned in last section and propose my possible solutions.

1. How to define a continuous markov decision process accommodating the treatment process:

   (a) Scientists in Reinforcement Learning have already set a continuous markov process framework. [1] extended the applicability of well-know reinforcement learning methods developed for discrete-time MDP's to the continuous-time domain in forms of semi-markov decision process. [2] proposed a options framework baesd on Semi-MDPs and showed its applications in AI by learning and planning with options. The option means a sequence of actions. For example, if we want to open the door, we first walk towrad the door, then span the door handler and open the door as last. The opening-door option is comprised of these actions [3] presented a process-Continuous Time Hidden Markov Decision Process,which can be used to model the robotic systems and gave an algorithm to estimate the policy gradient of continuous time HDMP. However, the paper only evaluates the method on a tabular probability, which can not be expanded.

   (b) The Possible Solution:
   [4] presents an efcient EM-based learning methods for CT-HMM models with discrete states to learn the disease progression without decision-making. It reformulated the estimation problem in terms of an equivalent discrete time-inhomogeneous hidden Markov model. Therefore, we may add in action terms to build the Continuous time markov decision process to learn the treatment regimes.

2. Intermediate Reward Or Final-Time Reward
   Traditional methods to learn treatment policies are all based on intermediate reward functions to optimize the cumulative reward in the process. Some people have proposed some menthods with only the final-time reward to learn the action policy.

   (a) [5] procides a framework that translates the problem of maximizing the expected future return exactly into a problem of likelihood maximization **with the only final-time reward needed**. [6] derives a new expectation maximization algorithm, using forward and backward messages, for policy optimization in linear Gaussian Markov decision processes, where the reward function is parameterized by a exible mixture of Gaussians.

   (b) These two papers above seem to be interesting, but they have the same weakeness that the state transition probability and the reward probability are prior knowledge. Thus, their frameworks are not learning ones, but maximization ones. In treatment processes, it is almost impossible for us to know the probability model of the disease. We have to learn the trsnsition probabilities first, perhaps using the methods in [4] and then apply them to the frameworks mentioned above to learn the optimal policy.

   (c) And there are many papers about healthcare based on the data from Sequential, Multiple, Assignment Randomized Trials(SMART), created by Susan Murphy. In SMART Clinical Trials, each participant moves through stages of treatment (usually one to three). At each stage, each participant is randomized among prespecified treatments. In this way, the transition is easy to be obtained [7].

3. Off-Policy Learning via Fitted Q Iteration and Importance Sampling
   Traditional RL approaches use online learning, in which the agent interacts with the environment dynamically and updates its policy after taking action. However, in each many medical domains, it is not possible to train an agent entirely online. The observation features from patients we have are obtained through a exploration policy. Therefore, in the healthcare related area, people always do off-policy learning via fitted q iteration and sampling.

   (a) [8] investigated the use of batch reinforcement learning techniques(also means fitted q iteration) to learn the optimal treatment policy from studies of simulation. Fitted a iteration define continuous states and action spaces, taking

suffcient use of training datas. It can be implemented by extremely randomized trees [9] or neural network [10]. That is the fact that the test set was collected under a given(exploration) policy, thus the target policy cannot be applied on this test set.The solution in the paper is to use a form of rejection sampling to select only those segments of the test set which are consistent with the target policy. However, the weakness of the paper is that its reward function is special for Epliepsy simulation problem. And the action is only the different frequency of the silmulation.

(b) [11] also learn the optimal policy by fitted q-iteration, because it uses the complete set of transitions each time that updates the estimation of the optimal Q-function. The problem of the paper is like that mentioned aboove. The state and action space are special to the disease.

(c) [12] presents the importance sampling methods in different versions and show how they can be applied on Off-policy learning. The evaluation via importance sampling is based on value function approximation and find a trade-off between bias and variance. However, it is evaluated through simulation.

(d) Based on the former paper, I think what I should do is to find a more general framework to define the state, action and reward. Recently, I'm reading [13], which summarized Q-learning and A-learning methods on dynamic treatment regimes

4 Other Related Works

1. HIDDEN-MODE MARKOV DECISION PROCESSES:
   it works on non-stationary MDP environments. It proposes a hidden-mode markov decision process model, assuming that environmental changes are always confined to a small number of hidden modes. And it models the HM-MDP via the more general POMDP model.
   [14]

2. MODEL-FREE REINFORCEMENT LEARNING AS MIXTURE LEARNING:
   it describes a Stochastic Approximation EM algorithm for likelihood maximization that, in the tabular case, is equivalent to a non-bootstrapping optimistic policy iteration algorithm like Sarsa(1) that can be applied both in MDPs and POMDPs. The proposed model can be viewed as a generalization of the stochastic shortest path reformulation of an innite-horizon MDP. [15]

3. DEEP PATIENT: AN UNSUPERVISED REPRESENTATION TO PREDICT THE FUTURE OF PATIENTS FROM THE ELECTRONIC HEALTH RECORDS:
   The paper presents a novel unsupervised deep feature learning method to derive a general-purpose patient representation from EHR data that facilitates clinical predictive modeling. In particular, a three-layer stack of denoising autoencoders was used to capture hierarchical regularities and dependencies in the aggregated EHRs of about 700,000 patients from the Mount Sinai data warehouse.The deep patient representation was evaluated by predicting patients future diseases-modeling a practical task in clinical decision making. [16]

4. FORECASTICU: A PROGNOSTIC DECISION SUPPORT SYSTEM FOR TIMELY PREDICTION OF INTENSIVE CARE UNIT ADMISSION:
   ForecastICU is rst trained in an ofine stage by constructing a Bayesian belief system about how trajectories of physiological data streams of the patient map to a clinical status. After that, ForecastICU monitors a new patient in real-time by observing her physiological data stream, updating its belief about her status over time, and prompting an alarm whenever its belief process hits a predened threshold (condence). Using a real-world dataset obtained from UCLA Ronald Reagan

Medical Center. [17]

5 Insights About All Events On Patients In MIMIC Database

I have already extracted **10000 patients** data in all events from the MIMIC database by Python and reorganized a patient's trajectory as an example to show the results. Codes and data are uploaded onto Github(https://github.com/yzy1995/MIMIC). The details of the database are as follows:

1. The number of different items for all events except labevents:
   12478 different items for all events in the whole database

2. CHARTEVENTS:
   5561 different chartevents items in the whole database
   It is different for different patients(subjectid).There are **hunderds of** items for each patient
   The charttime of the term is discrete, recording the value in periods.

3. OUTPUTEVENTS:
   1155 different outputevents items in the whole database
   It is different for different patients. As for the patients I have queried, the items for each patient are **less than ten**.
   There is no property of the output in the database, just the amount of the output.

4. LABEVENTS:
   729 different labevents items in the whole database
   It is different for different patients(subjectid).There are **tens of** items for each patient
   The time associated with the labevents results is the time of fluid acquisition, not the time that the values were made available to the clinical staff.
   discrete time record.

5. DATETIMEEVENTS :
   155 different datetimeevents items in the whole database
   datetimeevents contains all date measurements about patient in the ICU. For example, the date of last analysis would be in datetimeevents table.
   Many patients don't have datetimeevents item. There are **less than ten** items for those patient who have datetimeevents item.
   discrete time record.
6. INPUTEVENTSCV :
   2938 different labevents items in the whole database
   It is different for different patients(subjectid).There are **about ten** items for each patient.
   Discrete time record. We only have the start time of the inputevents.
7. InPUTEVENTSMV:
   278 different labevents items in the whole database
   It is different for different patients(subjectid).There are **tens of** items for each patient.
   We have the start and end time of the inputevents in mv databse. cv and mv are different ICU database for the inputevents.

8. MICROBIOLOGYEVENTS:
   There are three different items in the whole database: specitem, orgitem, abitem

65 different specitems
309 different orgitems
30 different abitems
Discrete time record. We only have charttime of the microbiologyevents. We have the interpretation of the results of the test. S is sensitive, R is resistant, I is intermediate, P is pending.

9. PROCEDUREEVETSMV(stored in mv database): **116** different procedureeventsmv items in the whole database
There are **tens of** items for each patient.
We have the start and end time of the procedureevents. The procedures will last for a few days.

10. The number of different icd9codes for diagnose:
14567 different icd9codes.

11. The number of different icd9codes for procedure:
3882 different icd9codes.

12. The number of different drugs for patients in the database:
4525 different drugs.
As for each patients, it depends.
We have the start and end time of the drug in the database.

6 Applications And Methods On MIMIC

The papers in this section are selected from the pubilications on MIMIC II or III database. Most of them are journal articles. The purpose of theses papers are not related to our problem, optimizing the treatment policy. The main methods they have used are **logistic model, bayesian framework and Kalman filter**. The brief abstracts of these papaers are listed as follows, in which the methods are marked in bold. We can see more papers on this website:`https://mimic.physionet.org/about/publications/`

1.THE EFFECT OF AGE AND CLINICAL CIRCUMSTANCES ON THE OUTCOME OF RED BLOOD CELL TRANSFUSION IN CRITICALLY ILL PATIENTS

By using the MIMIC II database (v2.6), a retrospective analysis of 9,809 critically ill patients, we evaluated the effect of RBC transfusion on 30-day and 1-year mortality. Propensity score modeling and **logistic regression** adjusted for known confounding and assessed the independent effect of transfusion on 30-day and 1-year mortality. Sensitivity analysis was performed by using 3,164 transfused and nontransfused pairs, matched according the previously validated propensity model for RBC transfusion. [18]

2.A DATA-DRIVEN APPROACH TO OPTIMIZED MEDICATION DOSING: A FOCUS ON HEPARIN:

We identified available clinical features which impact patient response to heparin and extracted 1,511 patients from the MIMIC II database which met our inclusion criteria. These were used to develop two **multivariate logistic regressions**, modeling sub- and supra-therapeutic activated partial thromboplastin time (aPTT) as a function of clinical features. We combined information from these models to estimate an initial heparin dose that would, on a per-patient basis, maximize the probability of a therapeutic aPTT within 48 h of the initial infusion. We tested our models ability to classifying therapeutic outcomes on a withheld dataset and compared performance to a weight-alone alternative using volume under surface (VUS) (a multiclass version of AUC). [19]

3.A PHYSIOLOGICAL TIME SERIES DYNAMICS-BASED APPROACH TO PATIENT MONITORING AND OUTCOME PREDICTION:
The objective of this study is to consider an approach to the analysis of critical care bedside monitoring that is based on the dynamical behaviors of vital sign time series. They employed a **switching vector autoregressive (SVAR) framework**. Given a collection of time series from a cohort, the proposed SVAR framework allows for simultaneous learning of the underlying dynamic behaviors or modes, and segmentation of the time series in terms of the most likely dynamic describing the time series evolution at any given point in time. [20]

4.CUSTOMIZED PREDICTION OF SHORT LENGTH OF STAY FOLLOWING ELECTIVE CARDIAC SURGERY IN ELDERLY PATIENTS USING A GENETIC ALGORITHM:
Objective:To develop a customized short LOS (length of stay)(¡6 days) prediction model for geriatric patients receiving cardiac surgery, using local data and a computational feature selection algorithm. We applied a GenAlg to computationally select features for prediction of short LOS. GenAlgs are optimization routines that attempt to find a set of features that maximizes a user-defined fitness function. [21]

5.EMPIRICAL RELATIONSHIPS AMONG OLIGURIA, CREATININE, MORTALITY, AND RENAL REPLACEMENT THERAPY IN THE CRITICALLY ILL:
The paper wants to investigate the empirical relationships among creatinine, oliguria, in-hospital mortality, and receipt of renal replacement therapy (RRT).Using MIMIC II, we extracted data from 17,227 critically ill patients with an in-hospital mortality rate of 10.9. The 14,526 patients had **urine output measurements**. Various combinations of creatinine/urine output thresholds and observation periods were investigated by **building multivariate logistic regression models** for in-hospital mortality and RRT predictions. [22]

6.DYNAMIC DATA DURING HYPOTENSIVE EPISODE IMPROVES MORTALITY PREDICTIONS AMONG PATIENTS WITH SEPSIS AND HYPOTENSION.:
OBJECTIVES:To determine if a prediction rule for hospital mortality using dynamic variables in response to treatment of hypotension in patients with sepsis performs better than current models.
They developed a prediction algorithm for hospital mortality in patients with sepsis and hypotension requiring medical intervention using data from MIMIC II. We extracted 189 candidate variables, including treatments, physiologic variables and laboratory values collected before, during, and after a hypotensive episode. Thirty predictors were identified **using a genetic algorithm** on a training set (n=1500) and validated with **a logistic regression model** on an independent validation set (n=613). The final prediction algorithm used included dynamic information and had good discrimination (area under the receiver operating curve=0.82) and calibration (Hosmer-Lemeshow C statistic=10.43, p=0.06). [23]

7.A DATABASE-DRIVEN DECISION SUPPORT SYSTEM: CUSTOMIZED MORTALITY PREDICTION:
We hypothesize that local customized modeling will provide more accurate mortality prediction than the current standard approach using existing scoring systems. Mortality prediction models were developed for two subsets of patients in MIMIC, and for the subset of patients 80 years old in a cardiac surgical patient registry. **Logistic regression (LR), Bayesian network (BN) and artificial neural network (ANN)** were employed. The best-fitted models were tested on the remaining unseen data and compared to either the Simplified Acute Physiology Score (SAPS) for the ICU patients, or the EuroSCORE for the cardiac surgery patients. Local customized mortality prediction models performed better as compared to the corresponding current standard severity scoring system for all three subsets of patients: **patients with acute kidney injury** (AUC = 0.875 for ANN, vs. SAPS, AUC = 0.642), **patients with subarachnoid hemorrhage** (AUC = 0.958 for BN, vs. SAPS, AUC = 0.84), and **elderly patients undergoing open heart surgery** (AUC = 0.94 for ANN, vs. EuroSCORE, AUC = 0.648). [24]

8.MODEL-BASED NONINVASIVE ESTIMATION OF INTRACRANIAL PRESSURE FROM CEREBRAL BLOOD FLOW VELOCITY AND ARTERIAL PRESSURE:
Our model-based approach to continuous estimation and tracking of intracranial pressure (ICP) uses routinely obtainable time-synchronized, noninvasive (or minimally invasive) measurements of peripheral arterial blood pressure and blood flow velocity in the middle cerebral artery (MCA), both at intra-heartbeat resolution. Our algorithm produced patient-specific ICP estimates with no calibration or training. Using 35 hours of data from 37 patients with traumatic brain injury, we generated ICP estimates on 2,665 non-overlapping 60-beat data windows. [25]

9.TRANSFER ENTROPY ESTIMATION AND DIRECTIONAL COUPLING CHANGE DETECTION IN BIOMEDICAL TIME SERIES:
The paper has investigated how different transfer entropy estimation methods perform in typical biomedical applications featuring small sample size and presence of outliers. They compared three transfer entropy estimation techniques using both simulated time series and respiratory recordings from lambs, fixed-binning with ranking,**kernel density estimation (KDE), and the Darbellay-Vajda (D-V) adaptive partitioning algorithm extended to three dimensions**. In the simulated experiment, sample size was varied from 50 to 200, while coupling strength was increased. In order to introduce outliers, the heavy-tailed Laplace distribution was utilized. [26]

10.A CLINICAL DATABASE-DRIVEN APPROACH TO DECISION SUPPORT: PREDICTING MORTALITY AMONG PATIENTS WITH ACUTE KIDNEY INJURY:
The paper developed mortality prediction models of ICU patients who had acute kidney injury (AKI) and compared them against the Simplified Acute Physiology Score (SAPS). We used MIMIC and **identified 1400 patients with an ICD9 diagnosis of AKI and who had an ICU stay more than 3 days**.**Multivariate regression models** were built using the SAPS variables from the first 72 hours of ICU admission. All the models developed on the training set performed better than SAPS (AUC = 0.64, Hosmer-Lemeshow p less than 0.001) on an unseen test set; the best model had an AUC = 0.74 and Hosmer-Lemeshow p = 0.53. [27]

11.A NONPARAMETRIC SURROGATE-BASED TEST OF SIGNIFICANCE FOR T-WAVE ALTERNANS DETECTION:
The paper presents a non-parametric adaptive surrogate test to mitigate the problem of TWA false detection. The proposed test makes no assumption concerning the distribution or stationarity of the noise or the TWA in the data, and therefore is robust under varying recording conditions. The purpose of this work is to devise **a robust statistical test** to assist in accurate detection of TWA, independent of the particular estimation algorithm being used. [28]

12.AN ARTIFICIAL VECTOR MODEL FOR GENERATING ABNORMAL ELECTROCARDIOGRAPHIC RHYTHMS:
We present generalizations of our previously published artificial models for generating multi-channel ECG to provide simulations of abnormal cardiac rhythms. Using a three-dimensional vectorcardiogram (VCG) formulation, we generate the normal cardiac dipole for a patient using a sum of Gaussian kernels, fitted to real VCG recordings.Switching between normal and abnormal beat types is achieved using a first-order Markov chain. Probability transitions can be learned from real data or modeled by coupling to heart rate and sympathovagal balance. [29]

13.AN INVESTIGATION OF PATTERNS IN HEMODYNAMIC DATA INDICATIVE OF IMPENDING HYPOTENSION IN INTENSIVE CARE:
Given the complexity and heterogeneity of ICU data, a machine learning approach was used in this study. **Time series of minute-by-minute measures of mean arterial blood pressure, heart rate, pulse pressure, and relative cardiac output from 1,311 records from the MIMIC II Database were used.** An HE was defined as a 30-minute period during which the mean arterial pressure was below 60 mmHg for at least 90 percent of the time. Features extracted from the hemodynamic data during an observation period of either 30 or 60 minutes were analyzed to predict the occurrence of HEs 1 or 2 hours

into the future. Artificial neural networks (ANNs) were trained for binary classification (normotensive vs. hypotensive) and regression (estimation of future mean blood pressure). [30]

14.SYNTHETIC ECG GENERATION AND BAYESIAN FILTERING USING A GAUSSIAN WAVE-BASED DYNAMICAL MODEL:
In this paper, we describe **a Gaussian wave-based state space** to model the temporal dynamics of electrocardiogram (ECG) signals. It is shown that this model may be effectively used for generating synthetic ECGs as well as separate characteristic waves (CWs) such as the atrial and ventricular complexes. The model uses separate state variables for each CW, i.e. P, QRS and T, and hence is capable of generating individual synthetic CWs as well as realistic ECG signals. The model is therefore useful for generating arrhythmias. In addition, discrete versions of the equations are presented for **a model-based Bayesian framework for denoising**. This framework, together with **an extended Kalman filter and extended Kalman smoother**, was used for denoising the ECG for both normal rhythms and arrhythmias. [31]

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