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Learning and recommending treatments using electronic medical records☆,☆☆

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ABSTRACT

Treatment directly affects patient health status. In recent years, the fast development electronic medical records (EMRs) has provided valuable resources for solving healthcare issues, especially learning and recommending treatments. However, most of the related studies are limited in exploiting various patient information, handling varying-length treatment records, capturing different kinds of treatment patterns and interpreting the recommendation mechanism. This research proposes three methods, one for learning and two for recommending treatments, to overcome the above drawbacks. All methods adopt a mixed-variate restrict Boltzmann machine to represent different kinds of patient records. The treatment learning method captures significant changes in prescription indication to split varying-length records flexibly and organizes sequences of prescription drugs into regimen trees to reveal many more different kinds of treatment patterns. The two treatment recommendation methods illustrate different ideas that can improve the treatment recommendation mechanism by combining the treatments derived from patient groups and neighbor patients. Our experimental evaluation was conducted on three acute disease cohorts extracted from the MIMIC III database. The obtained results show that the proposed methods are able to provide different kinds of treatment patterns and yield competitive efficacy with better interpretability as compared to relevant studies.

1. Introduction

Treatment and diagnosis are two important aspects of health informatics research. While many data-driven models for diagnosis prediction have been intensively developed over the past decades [2–4], few have addressed the treatment learning and recommendation [5–7] due to the following challenges. First, predicting a disease code is typically based on some static features, whereas learning and recommending treatments often involve longitudinal features reflecting patient health's progress. Mixed types of static and longitudinal features are not easy to feed traditional machine learning methods and therefore make the treatment-related tasks more challenging to tackle. Besides, patients often suffer multiple diseases or syndromes that a straightforward combination of well-defined treatment of each disease may not work effectively.

Despite the above challenges, addressing treatment-related tasks is a growing need. In the US, it was reported that during their treatment, about 7% of patients experienced adverse drug reactions, one of the leading causes of death. Moreover, in different healthcare organizations, treatments for multiple diseases often vary depending on physicians' personal experience and constraints on the amount of medical resources. As a result, learning treatment patterns and recommending treatment for new patients become emerging needs to improve the quality of treatment, minimize accidental faults that lead to adverse drug reactions, assist inexperienced physicians in grasping treatment patterns among various treatments given in their organization as well as help healthcare managers manage medical resources thoroughly.

Along with the emergence of EMRs-based healthcare mining [8], several studies have been carried out to deal with treatment learning and treatment recommendation. However, most of them underestimate the following issues. First, although tackling the treatment-related tasks requires many kinds of patient information, those studies mostly used small subsets of features. Second, few data-driven models have paid attention to incorporating

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medical domain knowledge to address some challenges inherent in longitudinal records. For example, few focused on identifying implicit treatment periods in prescription records, an important step that may highly affect learned treatment patterns. Third, related works mainly focus on mining frequent treatment patterns while many other meaningful patterns have not been derived yet, for example, pairs of drugs that are infrequently prescribed together. Lastly, most of the current data-driven models for treatment recommendation tasks are black-box models with hard-interpretable recommendation mechanism under the healthcare perspective. Hence, it is difficult to convince physicians about the rationality of developed models.

The objective of this work is twofold. First, we aim to propose a treatment learning method [1] which addresses the first three challenges. Our learning method divides a patient cohort into clusters named sub-cohorts, of which treatment patterns over periods are discovered subsequently. The proposed learning method is featured with the ability to transform mixed-type patient information into homogeneous representation by adopting a mixed variate restricted Boltzmann machine (MV.RBM) [9]. To address the varying-length records, our method calculates an accumulated score characterizing the change of prescription indication for each timestamp and determines the timestamps with significant change as the beginning of new treatment periods. For each treatment period of every sub-cohort, we also build a regimen tree where each path highlights a sequence of prescription drugs which are often prescribed in the sub-cohort. Through our experiments, the constructed regimen trees are able to not only fully capture drug use frequency in sub-cohorts but also reveal more different kinds of patient treatment patterns than the common approaches used in the literature.

Second, we propose novel methods to suggest top M prescription drugs for new patients. To tackle the fourth challenge, we take into account the neighbor patients' typical treatments resulted by solving the treatment learning task. The underlying intuition is that a new patient's treatment can be synthesized from prescription records of neighbor patients. In particular, we consider the efficacy of neighbor-based methods using two different approaches. One selects top frequent prescription drugs among neighbors' typical treatments and the other estimates the possibility of every drug in these treatments for ranking and recommendation purposes. The experimental evaluation shows that our neighbor-based methods can achieve similar efficacy in terms of precision and are better interpreted in comparison with state-of-the-art recommendation systems for solving the same task.

In short, the main contributions of our work are summarized as follows.

1. First, we develop a genetic treatment learning method to utilize different kinds of patient records. Our work adopts a mixed variate restricted Boltzmann machine (MV.RBM) to learn a homogeneous representation of mixed-type patient features.
2. Second, we exploit a medical domain factor, which is drug indication. The incorporated knowledge is promising for identifying treatment periods and understanding the symptoms underlying each frequent treatment patterns.
3. Third, we derive treatment patterns in the form of regimen trees which not only reflect usage frequency of prescription drugs in patient groups but also reveal many more different kinds of patterns.
4. Fourth, we propose two neighbor-based treatment recommendation approaches that yield competitive results and better interpretability compared to hard domain interpretable approaches.

2. Related work

2.1. Treatment learning problem

Two typical approaches often used in the literature to derive treatment patterns are the probabilistic-based approach and the frequency-based approach.

In the probabilistic-based approach, a variety of probabilistic models has been proposed to learn patterns of clinical pathways or treatments. Huang et al. [10] extracted treatment patterns through latent variables generated from a probabilistic topic model capturing the link between patient features and treatments. Lu et al. [11] modeled the diagnosis, contextual information and medications by a multiple channel LDA approach. The authors assumed that a latent health status group structure generated the co-occurrences among diseases and medications. Xu et al. [12] developed a topic model which exploited billing information and prescription records to discover the execution path of clinical pathways. Park et al. [13] proposed a disease-medicine topic model summarizing prescription records from insurance data. Recently, Yao et al. [14] have developed a topic model which describes the generating process of prescription records from traditional Chinese medicine in books. The main drawback of the studies following this research stream is that they regularly employed many hyperparameters which were assumed to follow some distributions without justification from medical domain knowledge. This limitation, therefore, weakens the interpretation of the developed models considerably.

In the frequency-based approach, treatment patterns are typically derived based on prescription drugs' frequencies [15–17]. Lin et al. [15] constructed dependency graphs taking into account the frequency of clinical processes. Hirano et al. [16] mined typical treatment processes based on occurrence and transition frequency maps. Most recently, Sun et al. [17] proposed a similarity measure among prescription records to divide them into clusters and discover frequent drugs among core patients of each cluster as treatment patterns. Although the studies following this approach yield better interpretable models, most of them are restricted to frequent treatment patterns. As a result, different kinds of treatment patterns regarding the association of drug use could not be discovered easily, for instance, pairs of drugs that are unlikely to be delivered for a patient-group or drugs should be given in conjunction with other must use drugs.

2.2. Treatment recommendation problem

Deep learning recently has shown great promise in solving healthcare issues. Pham et al. [18] proposed Deepcare, a dynamic neuron network based on LSTM model, to predict future medical outcomes. Their approach was designed for multitasking, including modeling disease progression, recommending necessary intervention, and predicting future risks. Zhang et al. [19] treated the treatment recommendation as a decision making problem where a recurrent decoder was used to model label dependencies. Le et al. [20] developed a memory-augmented neuron network to predict sequences of medications and procedures. The memory-augmented network was featured with dual controllers where one encoded medical history data, and the other decoded treatment sequences. More recently, Jin et al. [7] have addressed the treatment sequence prediction by a multifaceted LSTM model designed for different types of electronic medical records (EMRs).

Despite the outstanding performances obtained in many applications, the deep learning approach for healthcare still suffers limitations concerning model interpretability. Most of the current models have not paid attention to integrate medical domain

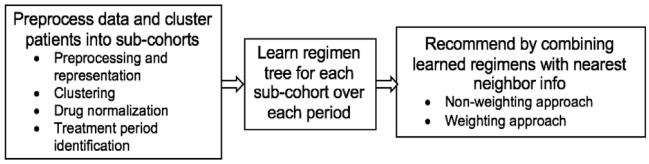

Fig. 1. An overview of our methods.

knowledge, an important factor that makes data-driven model convincing to physicians. Additionally, the treatment recommendation mechanism of the developed models under this approach may not be fitted with human intuition. Consequently, deep learning-based models for treatment recommendation problem become uneasy to be explained from the healthcare perspective.

Another approach to tackle the treatment recommendation problem is reinforcement learning (RL) based algorithm. In this research direction, most studies represented outcomes and treatments as sequences of states and actions. RL-based algorithms are then often employed to find optimal treatment sequences. Liu et al. [21] proposed a deep reinforcement learning approach to optimize dynamic treatment regimens from medical registry data. The authors predicted possible clinical procedures via a supervised learning step and estimated the long-term value function of dynamic treatment via a deep reinforcement learning model. Nemati et al. [22] investigated the optimal usage of heparin by deep reinforcement learning combining with a hidden Markov model. Recently, Wang et al. [6] have developed an approach which combines supervised learning and reinforcement learning to find optimal dynamic treatments using published real-world EMRs.

Studies following this approach are typically conducted for clinical trials with available treatment outcomes. In real-world data, for instance, prescription records, treatment outcomes are often expressed through daily nursing notes or laboratory indicators. However, identifying the corresponding outcomes for every doctor's order in the clinical context is challenging as it may require deep domain knowledge to extract relevant information. Consequently, this drawback makes the implements of reinforcement algorithms seem to be impractical with EMRs data.

A common drawback of the above works is that most of them used diagnosis codes or small subsets of relevant features due to the unavailability of data and the difficulty in feeding mixed-type data to machine learning methods. Our methods tackle this issue by collecting and making use most of the relevant information that is necessary for learning and recommending treatments.

3. Proposed methods

3.1. Overview

Fig. 1 describes an overview of our methods for learning and recommending treatments. The first phase focuses on preprocessing data and clustering patients into sub-cohorts. This phase consists of preprocessing and representing mixed-type EMRs, clustering patients, normalizing prescription drugs and identifying treatment periods. The second phase constructs regimen tree where treatment patterns are revealed for each patient sub-cohort over each period. The last phase utilizes neighbor patients' learned regimens resulted from the previous phase to recommend treatment for new patients. We present the details of all phases in the following subsections.

3.2. Data preprocessing and patient clustering

3.2.1. Data preprocessing and representation

In the literature, many studies have been conducted for representing patient records [23–25]. However, most of these studies mainly focus on diagnosis/procedure or medication codes. In our studies, we collect two sets of training patients' medical records. One consists of non-treatment data, i.e., laboratory exams (indicators), demographics, nursing notes serving for the sub-cohort construction and the other is treatment data, i.e., prescription records, serving for the derivation of treatment patterns. Since longitudinal features are not fully available for new patients from the early days of their admission, we only collect initial values of longitudinal non-treatment features of training patients. Our data collection's strategy assumes that similar care plans can be used for patients who share initial signs, symptoms, or indicators.

We encode categorical features as one-hot encoding vectors and normalize numerical features to zero-mean unit-variance. For text data, we extract the initial features by cTAKES [26], a well-known tool designed for clinical text processing. Its primary function is to identify clinical terms in a given text and link them to concepts in the Unified Medical Language System (UMLS) [27], a large ontology constructed for the biomedical domain. Not only does cTAKES normalize discovered clinical terms, but it also allows identifying semantic types of these terms. We are interested in terms with meaningful semantic to represent training and testing patients. Therefore, we extract the clinical terms of which semantic type is about signs/symptoms or diseases.

The encoded non-treatment data is mixed of numerical, binary or categorical data types. Such heterogeneous input vectors are often difficult to feed clustering methods. To this end, we employ a MV.RBM, a powerful unsupervised representation model, to transform encoded input vectors into a homogeneous representation. MV.RBM is an extension of the RBM model developed for heterogeneous input units. In the MV.RBM architecture, the data type of the input layer is designed for not only binary units, but also numerical, categorical or ordinal units. Let $\mathbf{v} = (v_1, v_2, \ldots, v_N)$ denote the set of visible units and $\mathbf{h} = (h_1, h_2, \ldots, h_K)$ denote the set of hidden units. MV.RBM defines a more deliberate energy function which covers the case of other data types in addition to binary data. The energy function of MV.RBM is given as follows.

$$E(\mathbf{v}, \mathbf{h}) = -(\sum_i G_i(v_i) + \sum_k b_k h_k + \sum_{ik} H_{ik}(v_i) h_k)$$

where $b_1, b_2, \ldots, b_K$ are bias parameters of hidden units, $G_i(v_i)$ and $H_{ik}(v_i)$ are type-specific functions.

The functions $G_i(v_i)$, $H_{ik}(v_i)$ and corresponding $P_i(v_i|\mathbf{h})$ for each kind of data are given in Table 1. The inference step for model parameters $\theta = (a, b, w)$ can be found in [9].

Assuming input features are mutually independent given their latent factors, Fig. 2 demonstrates how to feed non-treatment features to MV.RBM. Without losing generality, we suppose demographic features take either numerical, binary or categorical values while indicator features take numerical values. For text data, we extract UMLS terms describing signs/symptoms or diseases and represent them by one-hot encoding vectors.

3.2.2. Patient clustering

We utilize the latent states of a trained MV.RBM as representation vectors of encoded input. These vectors then can be easily fed into well-known clustering methods. Based on a survey about hierarchical clustering methods for binary vectors [28], we use the hierarchical clustering with Hamming distance and the complete linkage to cluster representation vectors of training patients as it was reported to give low error rate when being used in combination with symmetric distances.

Table 1
The type specific functions [9]. a_i, a_{im} are input bias parameters, w_{ik}, w_{imk} are input-hidden weighting parameters. Those with extra subscript m are dedicated for categorical features.

	$G_i(v_i)$	$H_{ik}(v_i)$	$P_i(v_i\|\mathbf{h})$
Binary	$a_i v_i$	$w_{ik} v_i$	$\frac{\exp(a_i v_i + \sum_k w_{ik} h_k v_i)}{1+\exp(a_i + \sum_k w_{ik} h_k)}$
Gaussian	$-v_i^2/2\sigma^2 + a_i v_i$	$w_{ik} v_i$	$\mathcal{N}(\sigma_i^2(a_i + \sum_k w_{ik} h_k),\ \sigma_i)$
Categorical	$\sum_m a_{im}\delta_m[v_i]$	$\sum_{m,k} a_{imk}\delta_m[v_i]$	$\frac{\exp(\sum_m a_{im}\delta_m[v_i]) + (\sum_{m,k} w_{imk}\delta_m[v_i]h_k)}{\sum_l \exp(a_{il} + \sum_k w_{ilk} h_k)}$

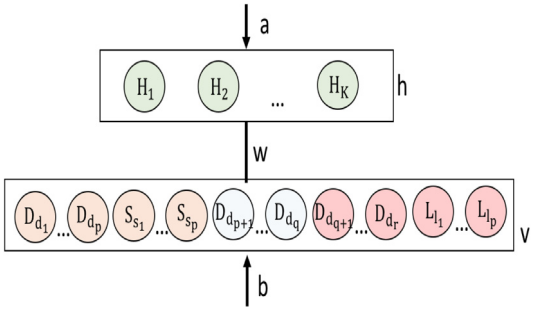

Fig. 2. A MV.RBM for patient records. The orange, blue and pink circles in the input layer represent for binary, categorical and continuous input units. The circles with labels D, S, L indicate demographic, sign/symptom and laboratory indicator features, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

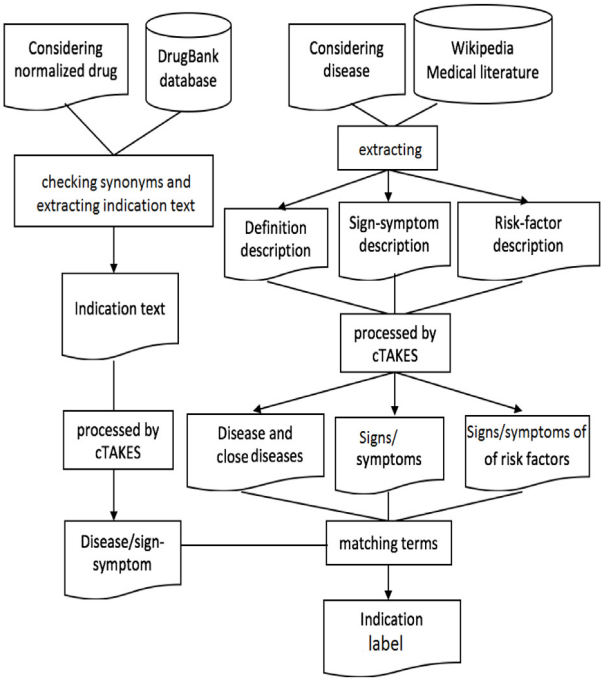

Fig. 3. An overview of the indication labeling framework.

3.2.3. Drug normalization and indication labeling

As physicians usually prescribe patients the same ingredient drugs under various names, we use cTAKES and DrugBank database to select the most UMLS term, namely normalized drug, for each original prescription drug. Besides normalizing drug name, labeling prescription drugs' indication is one of the most important steps which assists the subsequent tasks. Drugs with indication labels are useful not only in measuring the change of prescription indication but also in interpreting treatment patterns of patient sub-cohorts.

For every normalized drug dr, we identify which diseases or symptoms are treated by dr and classify dr's indication to one of the three following groups, namely primary group, symptom group or risk factor group. The primary group includes drugs to treat at least one of the considering diseases or their close diseases. The symptom group is a set of drugs to treat typical symptoms of the considering diseases while the risk factor group is determined as a set of drugs to treat risk factors that may cause the considering diseases.

Fig. 3 illustrates the idea of labeling prescription drugs' indications. We collect from Wikipedia and biomedical literature relevant texts describing the definitions, typical symptoms and risk factors of the considering diseases. These texts are then processed by cTAKES to extract UMLS terms of which semantic types are about symptoms or diseases and then are matched with those of the considering normalized drug.

3.2.4. Treatment period identification

Prescription records are complex and varying-length objects. In the literature, they are often split by fixed intervals of treatment periods [17,29]. In our work, we address the longitudinal property of prescription records flexibly by a domain-based approach. The main idea is inspired by the observation that a patient is possibly in a new treatment period whenever there is a significant change in prescription drugs' indications. To characterize the strength of indication changes in prescription records, we construct an accumulated score for each timestamp that considers prescription drugs which are new, recently stopped or redelivered with changed dosage. Based on the drugs' indication labels, we count on the numbers of drugs among the above drugs of which the indication belongs to the primary, symptom, or risk factor group. The accumulated score aggregates these quantities weighted by their importance in treating the considering diseases. We assign the weights in decreasing order of primary, symptom, or risk factor group.

The notations to be used for the treatment period identification algorithm are explained as follows. We denote $dr_j^{p,t} = \{name, startdate, enddate, dosage\}$ to characterize every drug dr_j prescribed for patient p at specific timestamp t by its normalized drug name, starting date, ending date of usage, and dosage. Let $\Theta^p = \{dr_j^{p,t}.name\}$ be the set of drugs given to the patient, $T^p = \{dr_j^{p,t}.startdate\}$ be the ordered set of prescribed dates, and PD, SD, RD be the sets of primary drugs, symptom drugs, risk factor drugs which have been identified in the previous section, respectively. The detailed algorithm for scoring changes in prescription drugs' indications for a patient p at the timestamp t is presented in Algorithm 1. For readability, we remove the superscript p, t, j and use Set notations in the pseudocode.

3.3. Treatment learning

This section describes our approach of the construction of regimen trees which allow discovering many more different kinds of treatment patterns. We note that the regimen trees take into account normalized prescription drugs with indication labels only. Information regarding dosage, route, chronological order among drugs in each period is supposed to be decided by physicians.

Algorithm 1: Scoring prescription records

Data: Θ, T
Result: return *scores* as a list of accumulated scores
Initialize U as an empty set ; ▷ set of recently delivered drugs
Initialize *scores* as an empty list ;
$aScore := 0$; ▷ the accumulated score
for *each* $t \in T$ **do**
  $D := \{dr \mid \forall dr \in \Theta \wedge dr.startdate == t\}$; ▷ delivered drugs on date d
  $N := \{dr \mid \forall dr \in D \wedge dr.name \notin U.name\}$; ▷ newly delivered drugs
  $DC := \{dr \mid \forall dr \in D, \exists dr' \in U$ such that $dr.name == dr'.name \wedge dr.dosage <> dr'.dosage\}$; ▷ dosage-changed drugs
  $S := \{dr \mid \forall dr \in U \wedge dr.name \notin D.name \wedge dr.enddate < t\}$; ▷ recent stopped-use drugs
  for *each* $dr' \in U$ **do**
    if $\exists dr'' \in D$ *such that* $dr'.name == dr''.name$ **then**
      $dr' := dr''$; ▷ update U with redelivered drugs
  $U := (U \setminus S) \cup N$; ▷ update U with newly delivered drugs
  $CD := N \cup DC \cup S$; ▷ considering drugs for calculating scores
  $CPD := CD.name \cap PD$; ▷ considering primary drugs
  $CSD := CD.name \cap SD$; ▷ considering symptom-healing drugs
  $CRD := CD.name \cap RD$; ▷ considering risk factor-healing drugs
  $aScore = aScore + |CPD| \times weight_{main} + |CSD| \times weight_{symp} + |CRD| \times weight_{risk}$;
  Add *aScore* to *scores*

At a considering node, we extract prescription records of patients who were prescribed by nodes along the path from the root until the considering node. The next unlabeled child node is labeled with the most frequent prescription drug apart from those linked with the parent nodes. Determining the drug label of the next child node follows the same mechanism, but we exclude prescription records of patients who were treated by labeled nodes on the same level. We continue this procedure recursively until the number of patients treated with drugs from the root until the considering node is fewer than some threshold. For each node, we also save the ID of the patients who were treated by the set of drugs from the root until that node.

It is of interest to note that each patient p in a treatment period is treated by nodes on a unique path named treatment path in a regimen tree. This property is utilized for the treatment recommendation task presented in the subsequent section. We denote d, ν, Γ, δ_ν, $\delta_{\nu+}$, ϵ, Υ, $\Lambda[\delta_\nu]$ as the current depth of the constructing regimen tree, the constructing node, the constructing regimen tree, the treatment path from the root until ν, the treatment path from the root until the next unlabeled child node of ν, the threshold to stop constructing regimen tree at the considering node, the high of the regimen tree, the patient IDs of patients who were treated by drugs on δ_ν, respectively. Let further define

- Ω_{δ_ν} be the current patient-drug interaction matrix corresponding to treatment path δ_ν.
- Ω_{δ_ϕ} be the initial interaction matrix where

$$\begin{cases} \omega^{kj}_{\delta_\phi} = 1; \text{ if patient } p_j \text{ was treated with drug } dr_k \\ \omega^{kj}_{\delta_\phi} = 0; \text{ if patient } p_j \text{ was not treated with drug } dr_k \end{cases}$$

- $\Omega^k = (\omega^{ij})$ be the interaction matrix of patients who were treated with drug k where i s.t $i \neq k$ and j s.t $a_{kj} = 1$.
- $\Omega^{-k} = (\omega^{ij})$ be the interaction matrix of patients who were not treated with drug k, where i s.t $i \neq k$ and j s.t $a_{kj} = 0$.

Algorithm 2 demonstrates the detailed algorithm of the regimen tree's construction for a patient sub-cohort over a specific period.

Algorithm 2: Procedure for the construction of a regimen tree

`Tree`$(d, \nu, \Gamma, \Omega_{\delta_\nu}, \Lambda)$
if Ω_{δ_ν} *is* $\emptyset$ *or* $d == \Upsilon$ **then**
  return
$k := \arg\max_i \sum_{j=1}^{n} a_{ij}$; ▷ find the most frequent prescription drug
$\Gamma[\delta_\nu, k] :=$ "$\nwarrow$";
$\delta_k := \delta_\nu \cup k$;
$\Omega_{\delta_k} := \Omega^k_{\delta_\nu}$; ▷ treated by drug k
$\Omega_{\delta_{\nu+}} := \Omega^{-k}_{\delta_\nu}$; ▷ not treated by drug k
$\Lambda[\delta_k] := \{j$ s.t $\omega^{kj}_{\delta_\nu} = 1\}$; ▷ tracing variable
if $|\Lambda[\delta_k]| < \epsilon$ **then**
  `Tree`$(d, \nu, \Gamma, \Omega_{\delta_k}, \Lambda)$;
else
  `Tree`$(d+1, k, \Gamma, \Omega_{\delta_k}, \Lambda)$;
  `Tree`$(d, \nu, \Gamma, \Omega_{\delta_{\nu+}}, \Lambda)$;
return ;

3.4. Treatment recommendation

This section presents interpretable methods aiming to assist physicians in recommending treatment for a new patient p based on his K neighbors' treatments. Our proposed approach utilizes the resulting regimen trees to find the K associated treatment paths of the neighbors. Each treatment path is considered as a set of typical drugs to treat one of the K neighbors and is supposed to contribute to the formation of treatment of p. It is worth noting that to capture the variant of treatments of similar patients, the K neighbor patients and their associated treatment paths can belong to different sub-cohorts.

Suppose $p_1, p_2, \ldots, p_K$ are the K nearest neighbors of patient p. Let $\delta^{p_k} = \{dr_1^{p_k}, dr_2^{p_k}, \ldots, dr_M^{p_k}\}$ denote the set of drugs linked with the treatment path of patient p_k. The associated treatment paths $\delta^{p_1}, \ldots, \delta^{p_K}$ and the distances $d^p_{p_1}, d^p_{p_2}, \ldots, d^p_{p_K}$ are then utilized to recommend top M drugs for p. Let $C = \{dr_1, dr_2, \ldots, dr_j\}$ be the set of distinct drugs named candidate drugs jointed from $\delta^{p_1}, \ldots, \delta^{p_K}$. We propose the two following approaches to rank the candidate drugs.

3.4.1. Non-weighting approach (NWTR)

The intuition underlying this approach is that prescription drugs delivered to many neighbors are likely to be used for a new patient. Therefore, for every candidate drug dr in C, we compute its path frequency $freq^p_{dr}$, i.e., the number of treatment paths containing dr, as one of the criteria for recommendation. Drugs with higher path frequency indicate that they are prescribed for a greater number of neighbor patients and hence, have a higher chance to be recommended. The formula of $freq^p_{dr}$ is provided below.

$$freq^p_{dr} = \sum_{i=1}^{K} I(dr \in \delta^{p_i}) \tag{1}$$

To solve the case dr has the same path frequency with other drugs, we consider a distance priority metric d^p_{dr}, another measure which considers the distance from test patient to the neighbors whose treatment paths contain dr. The greater the sum of the

inverse distance from these neighbors to p, the higher priority the drug is recommended. We provide the formula of d^p_{dr} as follows.

$$dist^p_{dr} = \sum_{i=1}^{K} I(dr \in \delta^{p_i}) \times \frac{1}{d^p_{p^i} + c} \quad (2)$$

where c is a constant to avoid zero division issue happening when $d^p_{p^i} = 0$.

Algorithm 3 provides the pseudocode describing the procedure to recommend prescription drugs for new patient p in a period using non-weighting approach. It is noted that H^{train} is a matrix consisting of representation vectors of training patients.

Algorithm 3: Recommending prescription drugs for new patient p in a specific treatment period using non-weighting approach.

Data: Λ, θ, v^p, H^{train}
Result: return top M recommended drugs
Compute $h^p = P(h|v^p, \theta)$;
Compute similarity between h^p and each training patient's representation vector $h^{p'}$ in H^{train};
Select the K most similar patients $p_1, p_2, ..., p_K$;
Trace associated treatment paths $\delta^{p_1}, \delta^{p_2}, ..., \delta^{p_K}$ through tracing variable Λ ;
$C = \bigcup_{i=1}^{K} \delta^{p_i}$;
for *each* $dr \in C$ **do**
    Compute $freq^p_{dr}$ by Eq. (1);
    Compute $dist^p_{dr}$ by Eq. (2);
Return top M drugs sorted by ($freq^p$, $dist^p$);

3.4.2. Weighting approach (WTR)

The non-weighting approach takes into account the frequency of candidate drugs among K treatment paths. This approach, however, seems to work effectively only if the K neighbors are reliable neighbors, i.e., their treatments are highly relevant to p's treatment. In case the prescription drugs of K neighbors are considerably different from p, we propose a more deliberate approach by estimating a hitting weight to each node on the K treatment paths. Given a node on a treatment path, its hitting weight is measured based on the number of times that node was prescribed for some neighbors among training patients weighted by the distance similarity from the patient of that node to those neighbors.

More in details, we split training patients into several subsets where each subset is considered as a sub-testing set and the rests are sub-training set. For each patient in the sub-testing sets, we query his K' neighbors $p_1, p_2, \ldots, p_{K'}$ and their associated treatment paths $\delta^{p_1}, \ldots, \delta^{p_{K'}}$. For each patient p_j in the sub-training set, let S^{p_j} be the set of patients who have p_j as one of their K' neighbors. We calculate a hitting-score $hit^{\delta^{p_j}}_{dr}$ for each drug dr on the treatment path δ^{p_j} of training patient p_j as follows.

$$hit^{\delta^{p_j}}_{dr} = \sum_{p_k \in S^{p_j}} d^{p_j}_{p_k} \times I(dr \in \delta^{p_k})$$

In the above formula, every time drug dr was used to treat a patient p_k in S^{p_j}, we add to the hitting score $hit^{\delta^{p_j}}_{dr}$ a reward equaling to the distance $d^{p_j}_{p_k}$. The meaning is that when p_j and p_k are far neighbors and dr has been found in the treatment of p_k, it is added more weight than the closer neighbors as a compensation for the possibility of "incorrectly" identifying close neighbors. The term "incorrectly" means that although those far neighbors are considerably different in terms of non-treatment-based features, they are very similar in terms of treatment-based features. In case p_j and p_k are close neighbors and dr has been found in the treatment of p_k, we add a relatively small award equaling to their distance to the hitting score as there is a high possibility that dr can be found in the treatment of p_k.

Algorithm 4: Recommending prescription drugs for new patient p in a specific period using weighting approach.

Data: Λ, θ, v^p, H^{train}
Result: return top M recommended drugs
Randomly split training set into sub-training and sub-testing sets ;
Initialize all nodes in the regimen trees with 0 hitting score;
for *each pair (sub-training , sub-testing)* **do**
    for *each p in the sub-testing* **do**
        Select K' most similar patients $p_1, p_2, ..., p_{K'}$ among sub-training patients ;
        Trace associated treatment paths $\delta^{p_1}, \delta^{p_2}, ..., \delta^{p_{K'}}$ through tracing variable Λ ;
        for *each* δ^{p_i} **do**
            for *each dr in* δ^{p_i} **do**
                If p was treated with dr $hit^{\delta^{p_j}}_{dr} = hit^{\delta^{p_j}}_{dr} + d^p_{p^i}$
Compute $h^p = P(h|v^p, \theta)$;
Compute similarity between h^p and each training patient in H^{train};
Select K most similar patients $p_1, p_2, ..., p_K$;
Trace associated treatment paths $\delta^{p_1}, \delta^{p_2}, ..., \delta^{p_K}$ through tracing variable Λ ;
$C = \bigcup_{i=1}^{K} \delta^{p_i}$;
for *each* $dr \in C$ **do**
    Compute $\overline{hit^p_{dr}}$ Eq. (3);
Return top M drugs sorted by $\overline{hit^p_{dr}}$;

After calculating the hitting scores for all nodes in the regimen trees, we perform the procedure for ranking recommendation drugs for testing patient p. For each candidate drug dr in the set C, we compute an average hitting score $\overline{hit^p_{dr}}$ weighted by the distances from the test patient to neighbors whose treatment paths include dr. The formula of $\overline{hit^p_{dr}}$ is given below.

$$\overline{hit^p_{dr}} = \frac{1}{\sum_{i=1}^{K} I(dr \in \delta^{p_i})} \sum_{i=1}^{K} I(dr \in \delta^{p_i}) \times hit^{\delta^{p_i}}_{dr} \times d^p_{p^i} \quad (3)$$

Algorithm 4 summarizes the main steps of the treatment recommendation method using the weighting approach.

4. Experimental evaluation

4.1. Evaluation metric

Let M, T, n, $\hat{D}^{\pi_j}_p$, $D^{\pi_j}_p$, π_j denote the number of recommended drugs, the test set, i.e., set of new patients, the number of treatment periods, the set of recommended drugs for the testing patient p in period π_j and the set of actual prescription drugs for p in period π_j, respectively.

We use precision, recall, and $F1$ score, the three well-known evaluation metrics, to evaluate the efficacy of the proposed treatment recommendation approaches. The formulas of these metrics are given as follows.

$$recall@M = \frac{1}{|T| \times n} \sum_{p \in T} \sum_{j=1}^{n} \frac{|\hat{D}^{\pi_j}_p \cap D^{\pi_j}_p|}{|D^{\pi_j}_p|}$$

$$precision@M = \frac{1}{|T| \times n} \sum_{p \in T} \sum_{j=1}^{n} \frac{|\hat{D}^{\pi_j}_p \cap D^{\pi_j}_p|}{M}$$

Table 2
Top 5 primary ICD codes among patients with single admission.

Primary ICD 9	Name	Number of patients
41401	Coronary atherosclerosis of native coronary artery	3430
0389	Unspecified septicemia	1805
41071	Myocardial infarction	1654
4241	Aortic valve disorders	1122
51881	Acute respiratory failure	945

Table 3
Statistic about the datasets used in our experimental evaluation.

	Myocardial infarction	Septicemia	Respiratory
Number of patients	1654	1805	945
Number of processed patients	1330	1359	658
Number of prescription drugs	1038	1238	1047
Number of normalized drugs	558	630	537
Number of drugs with relevant indication labels	244	190	100

$$F1@M = \frac{2 \times precision \times recall}{precision + recall}$$

4.2. Dataset

Our experiments were conducted on MIMIC [30], a real-world publicly available EMRs database which consists of approximately 60000 admissions of patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012.

Table 2 reports the top five single admission cohorts of patients who have the same first diagnosis ICD. We extracted records of the patients with acute diseases, i.e., the second, the third, and the fifth cohort. For short, we name the three cohorts as the septicemia, myocardial infarction, and respiratory cohort.

It is noted that patients who were prescribed fewer than three days were excluded in our experiments. Clinical features with the number of presented patients fewer than 5% or greater than 95% of the total number of patients in each cohort were also eliminated. Table 3 presents an overview of the datasets before and after preprocessing.

4.3. Parameter setting

We set the number of hidden units in the trained MV.RBM models to 100 units since the learning error rate did not decrease significantly with a larger size of hidden units.

In the clustering step, we observed the resulting dendrograms and found that training patients were relatively well separated at a distance above 0.6. However, splitting the training patients at such distance will result in large size sub-cohorts where treatment in each sub-cohort may vary considerably. For this reason, we cut the dendrograms at a distance of 0.4 to obtain small-size clusters.

We set $\Upsilon = M$, $\epsilon = 5$ and $n = 3$. Fig. 4 illustrates a sample plot of accumulated indication changing score. In our work, all prescription records are split into three periods where the splitting points are the timestamps of which the associated accumulated scores change significantly. For the weighting parameters of indication groups in the treatment period identification algorithm, we asked for an expert's advice and assigned the weight of main group, symptom group, risk factor group to 1, 0.7, 0.5, respectively.

We varied $K = \{5, 10, 15, 20, 30, 40, 50, 80, 100, 200\}$ in both weighting and non-weighting approaches. For the weighting approach, we split the training set into five subsets and set $K' = 100$.

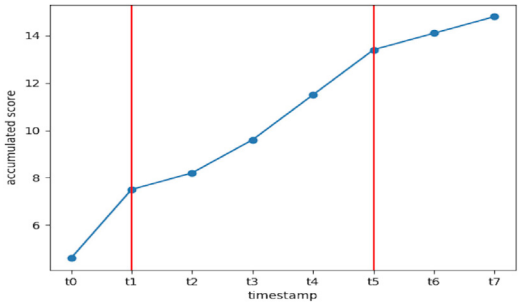

Fig. 4. A sample plot of accumulated indication changing scores of a given patient. We split the prescription records into three periods (t_0), (t_1, t_2, t_3, t_4), (t_5, t_6, t_7).

4.4. Baseline

It is noted that the methodology of our work and most of the related works are not easy to be applied to each other due to the difference in the problem settings and data collection methods. Hence, we consider our treatment recommendation problem as the top-M item recommendation problem where users are patients and items are prescription drugs. Although rich side information about patients such as patient demographics, indicators, nursing notes is available, it is not straightforward to exploit such information to leverage user preferences, i.e., how likely a prescription drug is given to a patient.

Thus, we compared the efficacy of proposed recommendation approaches to an API dedicated for implicit collaborative filtering recommender systems (ICF).[1] This API was implemented based on the idea presented in [31–33]. In the implicit feedback dataset, there is no target value, the API uses the logistic loss to fit a model that attempts to predict all the given (user, item) pairs in the training data as 1 and all others as 0.[2]

We compare the proposed approaches to the Graphlab API using the implicit alternative least square [32] solver (ICF+IALS), the stochastic gradient descent [34] solver (ICF+SGD) and the adaptive stochastic gradient descent [35] (ICF+ADA). It is noted that the above baselines are not completely black-box and can be explained in terms of mathematical viewpoint. However, it is hard to understand the treatment mechanism under the healthcare perspective since they try to find parameters that optimize

[1] https://turi.com/products/create/docs/graphlab.toolkits.recommender.html

[2] https://turi.com/products/create/docs/generated/graphlab.recommender.ranking_factorization_recommender.RankingFactorizationRecommender.html.

Table 4
Sample extracted UMLS terms by using cTAKES.

Sample text	Myocardial infarction(MI), commonly known as a heart attack, occurs when blood flow decreases or stops to a part of the heart causing damage to the heart muscle
Extracted terms	myocardial infarction, heart attack

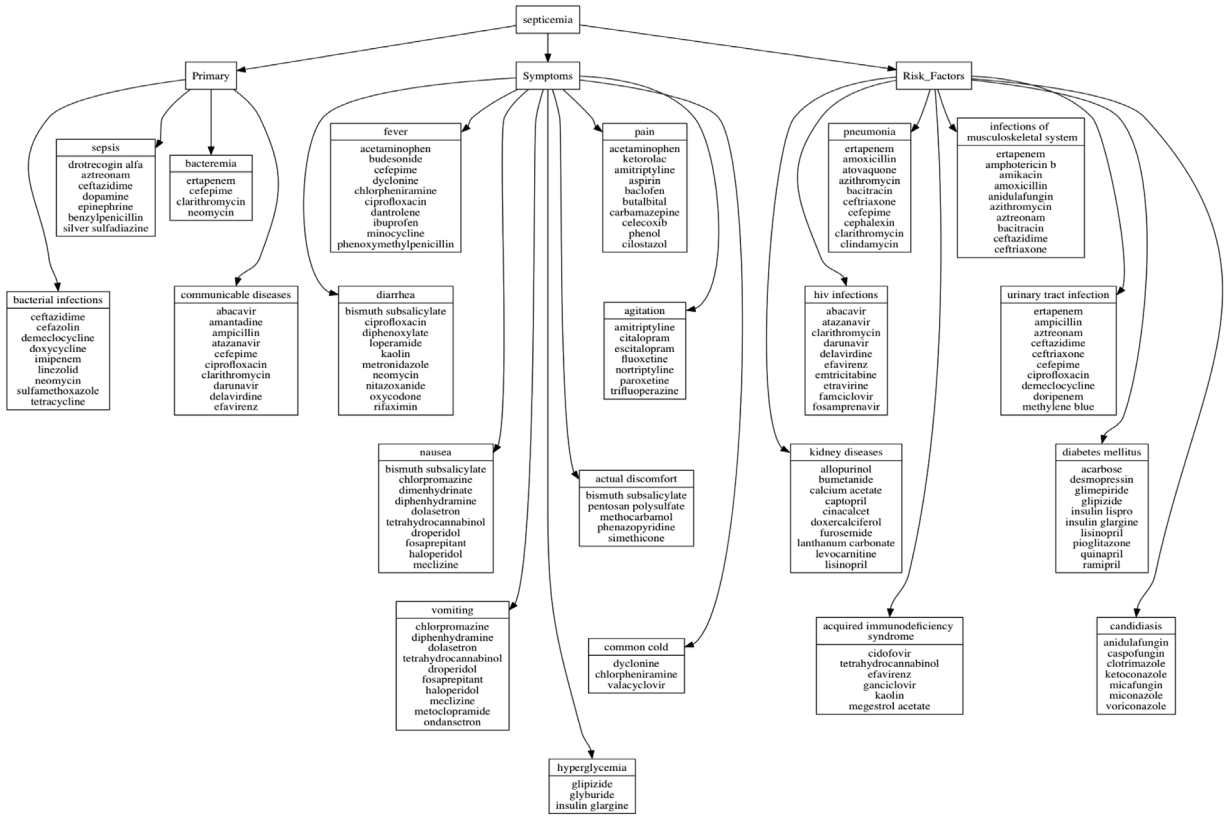

Fig. 5. Extracted typical symptoms and drugs classified in three groups of the septicemia cohort.

functions taking all patients and drugs into consideration. In other words, it is not easy to point out which neighbors the treatment recommendation process is based on.

We also investigate the efficacy of the recommendation task with $K = 1$ (NNTR(K = 1)), i.e., using treatment of the nearest neighbor.

4.5. Evaluation on treatment learning task

We first present intermediate results followed by an example of a resulting regimen tree and its interpretation. Table 4 gives an example of extracted UMLS terms for the definition of myocardial infarction by using cTAKES. It can be seen that the extracted terms are relevant to the myocardial infarction and its close diseases.

Fig. 5 illustrates the extracted typical symptoms and drugs for the primary group, the symptom group and the risk factor group of the septicemia cohort. Fig. 6 gives an example of a resulting regimen tree over a specific period of the septicemia sub-cohort. It is noted that the prefix "m","s", "r" indicates the associated prescription drugs are primary, sign/ symptom or risk factor drugs, respectively. The suffix number in each node, named node frequency, indicates the number of patients who were prescribed by drugs on the path from the root node until that node excluding the drug with higher prescription frequency on the same level of that drug and those with greater node frequency on the same level of parent nodes.

The sample regimen tree can be interpreted as follow. We start from the root node. The risk factor drug vancomycin is the most prescription drug which was prescribed for 26 patients. Among the patients who were treated with vancomycin, the primary drug metronidazole is the most prescription drug that was prescribed for 16 patients. Among the patients who were not treated with vancomycin, insulin lispro is the most prescription drug. It was prescribed for 6 patients. The remaining nodes in the tree can be explained similarly. We note that in some nodes, the mass balance of prescription drug frequency between a parent and its child nodes may not be held since there are some drugs we could not find their associated indication and the lacking nodes belong to such drugs.

It can be noticed that the set of drugs {VANCOMYCIN, METRONIDAZOLE, FUROSEMIDE, INSULIN LISPRO, ACETAMINOPHEN, ASPIRIN} is the sequence of drugs that were prescribed with high node frequency. This set can be considered as the primary treatment pattern of the sub-cohort.

In the indication labeling section, we can recognize not only the indication group of a prescription drug but also the signs/ symptoms treated by that drug. This property allows interpreting in depth the discovered treatment pattern sets. For example, the risk factor drugs metoprolol, furosemide, insulin lispro mainly cure the infection of the musculoskeletal system, kidney diseases and diabetes, respectively. The symptom drugs acetaminophen, aspirin play a role in relieving pain symptoms. Combining the above supporting domain knowledge, one can infer that most

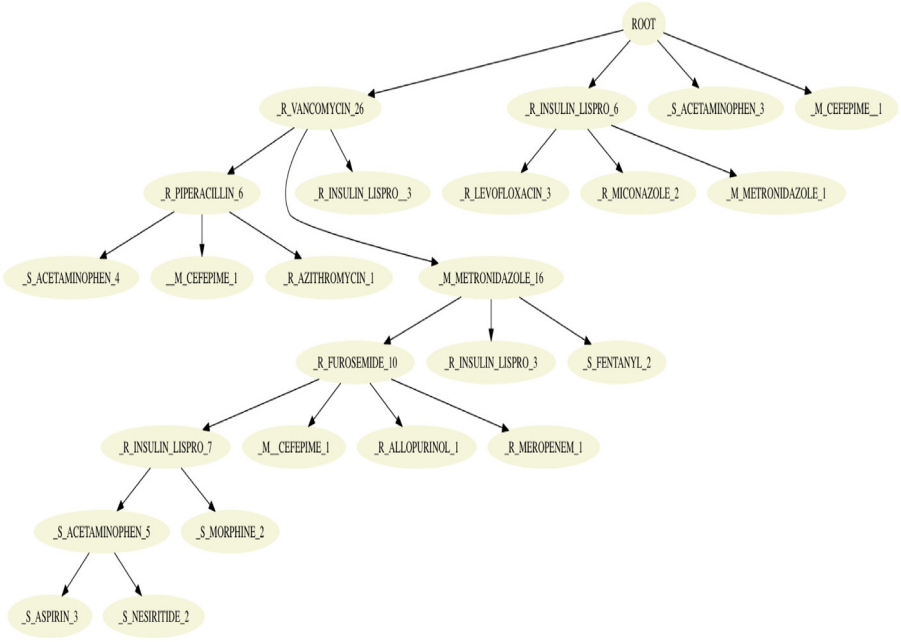

Fig. 6. An example of a resulting regimen tree.

Table 5
A qualitative comparison between our proposed treatment learning method and the related works.

Feature	Our work	Related works
Using different kinds of patient info	Yes	Limited
Domain incorporation	Yes	Limited
Addressing the treatment period identification	Yes	No
Understanding disease and drug relation	Yes	No
Treatment patterns reveal frequent pattern drugs	Yes	Yes
Treatment patterns reveal drugs used in conjunction with other drugs	Yes	Limited
Understanding symptoms underlying the treatments	Yes	Limited

of the patients in the sub-cohort of sample regimen tree also suffer from the musculoskeletal system issue, kidney diseases and diabetes; the risk factor that probably leads to septicemia.

Besides the set of frequent pattern drugs, the resulting regimen tree also reveals a set of drugs which are not frequently prescribed together. For instance, in the above example, the drug piperacillin is not likely to be prescribed along with metronidazole. Another example is the case of furosemide. Among the patients who were prescribed with vancomycin, furosemide is rarely used without metronidazole. The above examples show the usefulness of regimen trees constructed by our treatment learning method. Physicians can refer to the trees as checklists of sets of frequent and infrequent prescription drugs in each sub-cohort. It can be seen that such patterns may not be recognized easily by merely learning the frequent treatment patterns.

Table 5 summarizes a comparison on different features between our proposed treatment learning method and the related works [10,17,36]. It is worth noting that we can only provide a qualitative comparison since the problem setting of our proposed method and the related works are not easy to be transferred to each other. In other words, their methods could not be applied to our problem straightforwardly.

4.6. Evaluation on treatment recommendation task

To illustrate how the proposed treatment recommendation methods work, we take an example of recommending prescription drugs for a new patient using the non-weighting approach with $K = 5$. We note that the following example is a real one extracted from our experiment for the septicemia cohort.

Table 6 shows the prescription drugs of five neighbors of a test patient, their prescription drugs in a period and the corresponding treatment paths. Each path is selected as a sequence of drugs among the actual drugs delivered to the corresponding neighbor such that they are also prescribed together in his sub-cohort with high frequency. The bold drugs are top five selected drugs based on their path frequencies and the distance priorities. In this example, all five recommendation drugs are matched with the prescription drugs of the new patient. The above example shows the interpretability of our recommendation mechanism. Recommendation drugs are derived from the common drugs of neighbors in combination with the sub-cohort they belong to. To the best of our knowledge, this feature could not be found when using black-box or hard domain interpretable approaches.

Tables 7–9 show the efficacy of the weighting and non-weighting approaches in comparison with the NNTR($K = 1$) and the baselines in best cases on three datasets. The bold values indicate the best values among the competitors while the underline ones indicate the better value among the NWTR and WTR. It is obvious that both NWTR and WTR yield significantly better precision and $F1$ values than the NNTR($K = 1$). This result reaffirms the necessity of taking treatment of many neighbors into the recommendation procedure. In most cases, the WTR perform better than the NWTR. Both approaches, especially the WTR, yield competitive results compared to the ICF+SGD and ICF+ADA and significantly outperforms the ICF+IALS.

Table 10 reports the K values which yield the best performance on each dataset for $M = \{3, 5, 10\}$. It is obvious that the weighting approach requires a fewer number of neighbors to yield the best performance in comparison to the baselines. The

Table 6
Illustration of treatment recommendation procedure.

	Prescription drugs	Treatment path
Neighbor 1	metronidazole, vancomycin, fentanyl, cefepime, ibuprofen, nesiritide,insulin lispro prochlorperazine	**metronidazole**, **vancomycin**, **cefepime**
Neighbor 2	aspirin, insulin lispro, meropenem, vancomycin, hydromorphone, levofloxacin, trimethoprim	aspirin, **insulin lispro**, **vancomycin**, levofloxacin
Neighbor 3	metronidazole, desmopressin, insulin lispro, piperacillin, levofloxacin	**piperacillin**
Neighbor 4	metronidazole, ceftriaxone, acetaminophen, insulin lispro, vancomycin, piperacillin	**metronidazole**, acetaminophen, **insulin lispro**, **vancomycin**, **piperacillin**
Neighbor 5	meropenem, metoclopramide	meropenem

Table 7
A comparison between the proposed recommendation approaches and the baselines on the respiratory cohort.

	Precision			F1 score		
	@3	@5	@10	@3	@5	@10
NWTR	41.33	33.06	21.62	41.94	41.71	33.15
WTR	**42.15**	**33.59**	21.68	**43.06**	**42.38**	33.23
NNTR(K=1)	23.49	14.89	7.49	22.78	18.02	11.29
ICF + SGD	42.13	33.4	**21.75**	42.95	42.03	**33.31**
ICF + IALS	20.1	23.19	17.96	19.7	29.06	27.62
ICF + ADA	**42.15**	33.44	21.72	42.8	42.08	33.25

Table 8
A comparison between the proposed recommendation approaches and the baselines on the septicemia cohort.

	Precision			F1 score		
	@3	@5	@10	@3	@5	@10
NWTR	41.4	35.91	27.81	31.27	36.09	37.01
WTR	41.48	**36.22**	28.26	31.5	**36.35**	37.56
NNTR(K=1)	25.20	16.76	8.46	18.52	16.37	11.09
ICF + SGD	41.49	35.98	28.36	31.34	36.34	37.66
ICF + IALS	17.74	21.57	18.82	13.39	21.91	25.08
ICF + ADA	**41.97**	36.16	**28.51**	**31.97**	36.3	**37.87**

Table 9
A comparison between the proposed recommendation approaches and the baselines on the myocardial infarction cohort.

	Precision			F1 score		
	@3	@5	@10	@3	@5	@10
NWTR	57.51	51.08	41.19	38.89	45.2	47.96
WTR	57.92	51.12	41.36	**39.32**	45.09	**48.14**
NNTR(K=1)	44.85	35.14	21.66	27.79	28.40	24.03
ICF + SGD	**58.36**	51.07	41.16	**39.32**	44.82	47.67
ICF + IALS	34.59	34.1	31.41	21.81	30.54	37.73
ICF + ADA	58.24	**51.38**	**41.38**	39.11	**45.24**	48.04

Table 10
K values that yield the best $F1$ scores on the three datasets.

	NWTR			WTR		
	@3	@5	@10	@3	@5	@10
Respiratory	200	200	200	30	200	40
Septicemia	200	200	200	50	50	50
Myocardial infarction	200	200	200	200	50	100

obtained results show the advantage of the weighting approach in interpreting the recommendation mechanism.

To evaluate the efficacy of the proposed models with small Ks, we consider the difference between the values of evaluation measures obtained by using a small K and by using K_{best}. Let $F1_{K_{best}}$ be the $F1$ score, obtained with K_{best}, $F1_K$ be the $F1$ score obtained with K. We compute Δ_K^F as the difference between these measures. $\Delta_K^F = F_{K_{best}} - F_K$.

Table 11
Reported Δ_K^F on the respiratory cohort.

	NWTR			WTR		
	@3	@5	@10	@3	@5	@10
K = 7	7.11	7.18	6.73	1.84	3.85	6.6
K = 15	3.56	4.16	3.34	0.79	1.1	2.15
K = 50	1.81	1.82	1.14	0.36	0.24	0.15

Table 12
Reported Δ_K^F on the septicemia cohort.

	NWTR			WTR		
	@3	@5	@10	@3	@5	@10
K = 7	4.08	4.55	7.49	1.41	1.29	6.07
K = 15	2.18	1.97	4.36	0.87	0.28	1.64
K = 50	1.24	0.41	1.61	0.47	0.0	0.31

Table 13
Reported Δ_K^F on the myocardial infarction cohort.

	NWTR			WTR		
	@3	@5	@10	@3	@5	@10
K = 7	2.29	3.22	7.08	0.7	0.8	3.27
K = 15	1.35	1.6	1.77	0.78	0.2	0.51
K = 50	0.75	0.71	0.61	0.53	0.15	0.16

Tables 11–13 report the Δ_K^F for $K = 7, K = 15, K = 50$ on three datasets. The obtained results show that for small Ks, the weighting approach obtains F scores which are better and much closer to the best values than those of the non-weighting approach.

5. Discussion

Our treatment learning method obtains more interesting results in terms of domain incorporation and knowledge representation compared to related works in the literature. First, rather than defining treatment periods as fixed intervals, we track the change of prescription drugs' indications as a hint to discover treatment periods. The idea fits our natural thinking of detecting patients' treatment periods given their prescription records. Second, by representing the learned treatment patterns in a tree form, we not only fully reflect the usage-frequency of prescription drugs but also allow doctors to quickly recognize groups of frequent and infrequent prescription drugs in each patient sub-cohort. Therefore, in terms of knowledge representation, the proposed treatment learning method seems to be superior to most of the current studies that merely focused on discovering frequent treatment patterns.

In the ideal case, our treatment recommendation method can base on the nearest neighbor's treatment to suggest prescription drugs for a new patient. However, the complex interaction between treatment and non-treatment features seems to violate the intuitive assumption that patients with similar symptom, demographic and indicator features are likely to be treated similarly. Indeed, in most cases, treatments of the nearest neighbor patients are not identical. We have addressed this challenge partially by considering K neighbor patients' treatment paths. Our approach captures the fact that physicians usually learn how to derive treatments for new patients by considering typical drugs used for past similar cases. The experimental evaluation shows that combining treatment patterns from many neighbors can considerably improve the efficacy of the recommendation task in comparison to using only the nearest neighbor's treatment.

We have proposed the weighting and non-weighting treatment recommendation approaches which yield competitive results to the baselines when using a relatively large enough number of neighbors. We suggest that among two proposed recommendation approaches, with a relatively small number of K, it is better to employ the weighting recommendation approach for the cohort with high variant treatments. The obtained results show that the incorporated hitting weights of nodes in regimen trees are useful to handle possible "incorrect" identification of neighbors in treatment perspective. It is noted that although both weighting and non-weighting approaches obtain similar results for a large K, in reality, physicians often prefer using a relatively small Ks such that pointing out the K neighbor patients and the recommendation mechanism that leads to the recommendation results remain meaningful.

There are several reasons to explain for the primitive results of our proposed recommendation approaches and even the baselines. First, we address the treatment recommendation problem by neighbor-based approaches. In many cases, there is a highly inconsistent interaction between treatment and non-treatment features. For instance, two far neighbor patients who only share a few clinical features, named activate features, are treated in a very similar way. The challenge is that identifying such features is not an easy task since they vary for each pair of patients. The inconsistent similarity between two kinds of features poses challenges in identifying reliable neighbors. As a result, the prescription drugs of neighbor patients sometimes do not appear in those of new patients, and hence lead to a decrease in the performance. Within the scope of this work, we mainly stress on the necessity of developing a neighbor-based treatment recommendation approaches to enhance the explainability of recommendation models in healthcare perspective. We leave addressing the inconsistent similarity of treatment and non-treatment features for future work.

6. Conclusion

In this paper, we have presented pipeline methods for learning and recommending treatment using electronic medical records. Our proposed treatment learning method is featured with the capability of maximizing data utilization, incorporating medical domain knowledge to handle varying-length prescription records and representing treatment patterns in a more useful way. The proposed recommendation methods provide an explainable recommendation mechanism that can achieve competitive results compared to the hard interpretable methods. In future work, we will address the inconsistent similarity between treatment features and non-treatment features to improve the efficacy of the treatment recommendation task.

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