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A Survey of Personalized Medicine Recommendation

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ABSTRACT

Mining potential and valuable medical knowledge from massive medical data to support clinical decision-making has become an important research field. Personalized medicine recommendation is an important research direction in this field, aiming to recommend the most suitable medicines for each patient according to the health status of the patient. Personalized medicine recommendation can assist clinicians to make clinical decisions and avoid the occurrence of medical abnormalities, so it has been widely concerned by many researchers. Based on this, this paper makes a comprehensive review of personalized medicine recommendation. Specifically, we first make clear the definition of personalized medicine recommendation problem; then, starting from the key theories and technologies, the personalized medicine recommendation algorithms proposed in recent years are systematically classified (medicine recommendation based on multi-disease, medicine recommendation with combination pattern, medicine recommendation with additional knowledge, and medicine recommendation based on feedback) and in-depth analyzed; and this paper also introduces how to evaluate personalized medicine recommendation algorithms and some common evaluation indicators; finally, the challenges of personalized medicine recommendation problem are put forward, and the future research direction and development trends are prospected.

KEYWORDS

recommended system; clinical decision support; medicine recommendation

Clinical Decision Support System (CDSS)[1] is an important means to improve medical quality, which aims to evaluate and improve medical quality, reduce medical errors, and control medical expenses. Medicine recommendation is an important research problem of CDSS, which can help clinicians to make the most appropriate medication decisions through in-depth analysis of medical records[2]. Choosing medicine in a standard and scientific way plays an active role in promoting one's restoration to health. Therefore, medicine recommendation problem has received extensive attention from many researchers, and some medicine recommendation models have been proposed. Traditional medicine recommendation systems are designed based on rules defined by experienced physicians according to clinical guidelines. These rule-based hard coding methods can make general medical recommendations for specific diseases, but they do little to make personalized recommendations for complex patients. Moreover, these traditional rule-based methods are difficult to implement. Firstly, due to the limitation of personal cognition, relying on doctors to make rules is inevitably insufficient. Secondly, it takes a lot of time and experience to create and maintain rules.

With the emergence and popularization of Electronic Health Records (EHRs), the acquisition and collection of medical data have become more convenient, resulting in the accumulation of a large number of clinical data, such as vital signs, disease diagnosis prescription medicines, medical expenses, etc. At the same time, deep learning technology provides a new technical means for the mining and utilization of medical data. This enables personalized medicine recommendation, so as to make up for the defects of traditional approaches. The goal of personalized medicine recommendation is to use EHR to predict the most appropriate medicines for each patient, which can be used as a reference for doctors to prescribe. The research encompasses acquiring patterns of patient health status changes implicit in EHRs, mitigating side effects caused by Drug-Drug Interactions (DDI)[3], and evaluating medicine treatment efficacy using counterfactual reasoning. Personalized medicine recommendation model can provide better personalized treatment recommendations to doctors and patients to improve the prognosis of patients and make more effective use of medical resources.

Based on the above background, we believe that personalized medicine recommendation is an important research issue. And a large number of related studies on personalized medicine recommendation have emerged at present. However, to the best of our knowledge, there are no investigative papers on this important and rapidly developing field. Moreover, since personalized medicine recommendation is interdisciplinary, that is, requiring expertise in machine learning, medicine, and other aspects, it is difficult for new researchers in this field to grasp the latest developments. To address this problem, we provide a comprehensive survey of the research work of personalized medicine recommendation in this paper, hoping to comprehensively sort out and summarize the personalized medicine recommendation methods under a new perspective. Specifically, we classify existing personalized medicine recommendation methods from different perspectives, analyze the limitations of existing methods, summarize common performance evaluation methods, and propose the possible future research directions and development trends of the personalized medicine recommendation problem.

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This paper is organized as follows. In Section 1, the problem of personalized medicine recommendation is described; Section 2 introduces the classification and limitations of current personalized medicine recommendation methods; Section 3 introduces the commonly used performance evaluation methods for personalized medicine recommendation problems; Section 4 looks forward to the challenges and future directions; and Section 5 concludes the paper.

1 Preliminary

In this section, we give the problem definition of personalized medicine recommendation. Most personalized medicine recommendation models make decisions based on partial data of the EHR, so let us start with an introduction to the EHR.

All the patient's medical records are recorded in the EHR, that is, the EHR stores the patient's diagnoses, medicines, and other information in the form of medical codes. We use a temporal admission sequence $\mathcal{A}_{i,t}=\{a_{i,1},a_{i,2},\ldots,a_{i,t}\}$ to represent the patient p_i's medical data in the EHR, where the total number of admissions for patient p_i is expressed by t. Each admission $a_{i,j}=(\mathcal{D}_{i,j},\mathcal{M}_{i,j})$ is a tuple consisting of all the disease codes $\mathcal{D}_{i,j}$ and medicine codes $\mathcal{M}_{i,j}$ at the j-th admission, where $\mathcal{D}_{i,j}\subseteq\mathcal{D}$ represents the set of codes for diseases (such as heart failure and diabetes) and $\mathcal{M}_{i,j}\subseteq\mathcal{M}$ is the set of codes for medicines (e.g., insulin and cardiac glycosides) prescribed by the doctor based on the health of the patient. $\mathcal{D}$ is the set of all diseases, and $\mathcal{M}$ is the set of all medicines. The above formalized expression of EHR refers to the situation where only the information of the patient's diseases and medicines is used in the recommendation. When the demographic information and laboratory indicators of the patient are also considered, the expression of each admission should be expanded from the binary group to the triplet group, the quadruple group, etc.

As the problem setting of personalized medicine recommendation is different in details under different scenarios, Fig. 1 is the generalized schematic representation of the medicine recommendation problem. Here, we give a simple definition of personalized medicine recommendation: Given the data of the previous $t-1$ admissions of the patient p_i, that is, the historical admission sequence $\mathcal{A}_{i,t-1}=\{a_{i,1},a_{i,2},\ldots,a_{i,t-1}\}$, and information about the patient's disease at the t time of admission, namely $\mathcal{D}_{i,t}$. Personalized medicine recommendation aims to generate a set of medicines $\mathcal{M}_{i,t}$ that are safe and effective for patient p_i based on these information.

In general, personalized medicine recommendation refers to the recommendation of the most suitable medicines for each patient based on the health of the patient. But the choice of how to characterize the condition of the patient is different under different circumstances. For example, in some cases, there is no information about the patient's previous visits, and the recommendation is based only on the patient's current illness; in some cases, demographic information and laboratory indicators can be considered in addition to the patient's previous visits and the patient's disease.

2 Taxonomy

In this section, we will categorize and summarize the current personalized medicine recommendation models from four perspectives: whether it targets specific diseases, whether it considers relationships between drugs, whether it incorporates medical knowledge, and whether it takes into account patient's feedback.

2.1 Medicine recommendation based on multi-disease

Although treating a specific disease, every patient is different, doctors have to consider many factors at once, and there are many medicines to choose from. As a result, some recommendation models make personalized medicine recommendations for specific diseases to help doctors analyze patients' conditions and make better decisions based on complex information. As a chronic and progressive disease, there are many different medicines available for diabetes, and many current personalized medicine recommendation models are targeted at diabetes. Chen et al.[4] developed a decision support system that uses an approach based on multi-criteria decision-making and domain ontology. Subsequently, Chen et al.[5] and Mahmoud and Elbeh[6] proposed diabetes medicine recommendations system based on fuzzy reasoning and ontology technology. Liu et al.[7] used an approach based on patient similarity. Wedagu et al.[8] introduced medical knowledge to obtain recommended medicines. In addition to diabetes, personalized medicine recommendation methods targeting other common diseases have also been proposed, such as cancer[9,10], epilepsy[11], hypertension[12,13], bone marrow transplantation[14], and tuberculosis[15]. Generally speaking, these models can have better recommendation effect for specific diseases. However, on one hand, it is too complicated to develop a recommendation model for each disease; on the other hand, patients often do not suffer from only one disease. In this case, the

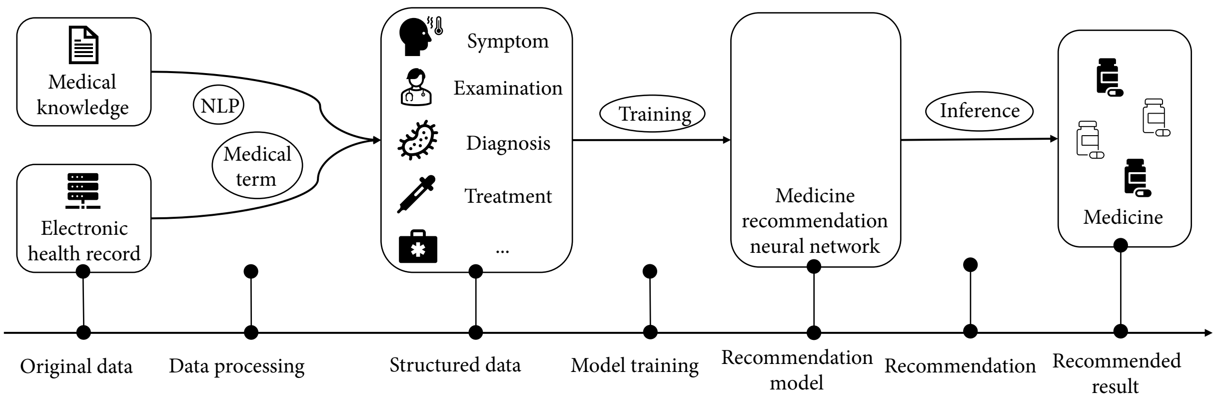

Fig. 1 Generalized schematic representation of the medicine recommendation problem. The medicine recommendations relies on EHR and related medical knowledge, extracting structured information about patients' symptoms, examinations, diagnoses, and treatments using techniques such as Natural Language Processing (NLP). Then, the information is utilized to train a medicine recommendation neural network model. Consequently, for new visiting, the trained medicine recommendation neural network can be employed for inference to obtain appropriate medicines.

medicine recommendation model for specific diseases does not work.

For patients suffering from multiple diseases at the same time, even for experienced doctors, it is difficult to make appropriate recommendations. Considering this problem, some studies have proposed general personalized medicine recommendation models that can solve the problem of multi-disease co-occurrence. The LEArn to Prescribe (LEAP)[16] breaks medicine recommendation into a multi-step process, recommending one medicine at a time and automatically determining the appropriate end of the recommendation. Personalized Prescription for Comorbidity (PPC)[17] aggregates EHR data from many different sources to learn the three levels of patient, disease, and medicine representation, respectively. By merging the different levels of representation, the PPC can achieve personalized prescribing of comorbidities. Wang et al.[18] argued that correlations between medicines should be considered in a disordered manner and proposed Combined Order-free Medicine Prediction Network (CompNet).

Shang et al.[19] introduced the graph structure into the personalized medicine recommendation problem for the first time by integrating the knowledge graph of medicine-medicine interactions as a memory module of the graph convolutional network and modeling longitudinal patient records as queries. Wang[20] used the power of Generative Adversarial Networks (GANs) to learn expressive representations from a specific patient's medical records and provide accurate medicine recommendations to the patient. Montalvo and Villanueva[21] proposed a medicine recommendation system for geriatric patients that takes into account a patient's medical history and medicine interactions. Yang et al.[22] also proposed a mecidine recommendation model that focuses on medicine interactions, called SafeDrug. Unlike previous models, SafeDrug explicitly models DDI and makes DDI controllable. Yang et al.[23] argued that the medicines tend to repeat themselves over a patient's many visits and that the differences between the medicines are more meaningful. They proposed a new model, MICRON, to address this problem by using a recurrent residual network to capture medicine changes. All the above works formulate medicine recommendation as a multi-label classification task to predict medicines. Wu et al.[24] tried to generate medicines through a new replication or prediction mechanism and designed a Conditional Generation Net (COGNet) for this purpose.

2.2 Medicine recommendation with combination pattern

Early models of personalized medicine recommendation recommended medicines that are appropriate for patients based solely on their association with each medicine. Zhang et al.[25] developed Cloud-Assisted Drug REcommendation (CADRE), a new cloud-assisted medicine recommendation model, which can recommend the most relevant top-n medicines to the patient based on symptoms. Gong et al.[26] modeled medicine recommendation as a link prediction problem and realized dimensionality reduction through representation learning of three types of data, namely disease, medicine and patient, to obtain their representation in the same low-dimensional space. However, potential interactions between medicines, such as synergies or antagonisms, are largely ignored and may result in recommended medicines being suboptimal or even harmful.

Recently, personalized medicine recommendation models have begun to implement medicine recommendations based on a combination model, that is, considering the final recommended medicine as a complete combination, rather than considering each medicine separately. LEAP[16] used a content-based attention mechanism and treated each medicine as a label, using a recurrent decoder that gets the label one at a time to model label dependencies. CompNet[18] also modeled medicine associations and used reinforcement learning to implement medicne recommendations. By setting the reward function, both the correlation between medicines and the adverse interactions between medicnes are considered.

In addition, some personalized medicine recommendation models attempt to realize dynamic medicine combination recommendation, dividing a patient's admission into multiple time windows and recommending medicines for each time window. To model relationships between multiple medicines, diseases, and patients, Wang et al.[27] applied the policy actor-critic framework. Using a Supervised Reinforcement Learning model based on Recurrent Neural Networks (SRL-RNN), a set of medicines is recommended to patients each day. Liu et al.[14] proposed the first Deep Reinforcement Learning (DRL) framework for estimating optimal dynamic treatment options based on observational medical data.

2.3 Medicine recommendation with additional knowledge

Early medicine recommendation models are based on rules, which are developed by doctors or specialists based on medical knowledge and experience. However, rule-making and maintenance require a lot of manpower, and rule-based models are difficult to personalize. With the wide application of EHR providing sufficient data for clinical decision support related research, more and more studies begin to implement personalized medicine recommendation through data-driven approach.

There are two types of EHR-based data-driven models[19]: Instance-based models only make recommendations according to the diseases and procedures of the patient's current admission, while ignoring the patient's longitudinal history[16]. As a result, the instance-based model is unable to take into account the historical progression of the disease. To address this problem, longitudinal models are designed to take advantage of longitudinal patient histories and obtain temporal correlations[19]. The longitudinal model considers the patient's medical history, integrates the patient's previous admission data into the patient representation, and introduces medicine function description as medical knowledge data.

Some personalized medicine recommendation models try to introduce medical knowledge as auxiliary information on the basis of data drive. CADRE[25] is a personalized medicine recommendation model designed based on user collaborative filtering and introduces medical knowledge data, namely the functional description of drugs. Gong et al.[26] modeled medicine recommendation as a link prediction problem and fused EHR and medical knowledge to build a medical heterogeneous graph. To be specific, Gong et al.[26] used the MIMIC-III, ICD-9 ontology, and DrugBank. By performing representation learning on different types of nodes in heterogeneous graphs, embeddings of different types of medical entities in the same low-dimensional space can be obtained. Zhang et al.[16] also introduced medical knowledge by fine-tuning trained models to avoid adverse medicine interactions. Shang et al.[28] considerd the internal hierarchical structure of the medical code, represented it in terms of Graph Neural Network (GNN), and then integrated the GNN representation into a transformer-based medical encoder.

2.4 Medicine recommendation based on feedback

Although most personalized medicine recommendation models are based on EHR data, there are still a few algorithms that recommend medicines through patients' feedback or patients' interaction with other entities. Different from other personalized medicine recommendation models that are positioned to assist doctors' decision-making, medicine recommendation models in this category are user specific and positioned to assist patients' decision-making, that is, directly recommending the medicines to be purchased to patients. Therefore, this kind of models can only recommend over-the-counter medicines. These models mainly help patients suffering from common diseases (such as cold and gastrointestinal inflammation) or chronic diseases (such as essential hypertension and diabetes) to choose among medicines with similar efficacy. They can also help people without diseases to choose health products. Compared with other personalized medicine recommendation algorithms, medicine recommendation based on interaction or feedback is closer to commodity recommendation.

Patient evaluations of medicines, which have great influence for other patients' decision, will be able to make other patients make more informed decisions. However, most of the previous studies on evaluation focused on the rating prediction and recommendation in the field of e-commerce, and there are few studies in the medical field. In addition, geographical and temporal factors also have a certain influence on medicine recommendation. Li et al.[29] first found and defined the practical problem of non-prescription medicine rating prediction and recommendation in daily life. They designed and developed the model iDrug to solve this practical problem. Specifically, iDrug firstly defines a six-tuple, Mobile Social Rating Network (MSRN), to represent the four entities of patient, medicine, time, and place, and the interaction among them. All patients here suffer from the same disease or have the same symptoms. Then, based on the interaction relationship in MSRN, key geographic and temporal information is extracted to realize the rating prediction and recommendation of over-the-counter medicines.

Garg[30] also used patient reviews to achieve over-the-counter medicine recommendations, and their proposed model targets specific diseases, taking coronavirus as an example in the paper. When the number of patients with a certain disease increases rapidly in a short period of time, resulting in a run on the healthcare system, patients cannot get medication guidance from doctors and can only take medication independently, which may lead to worse health conditions. Personalized medicine recommendation system can solve this problem.

Specifically, Bag of Words (BoW), Word to Vector (Word2Vec), and Term Frequency–Inverse Document Frequency (TF-IDF) are used to vectorize the original data, and then multinomial Naive Bayes, logistic regression, and linear support vector classifier are used to complete the classification task, so as to realize personalized medicine recommendation. Patient comments are a form of patient emotion and can be used as information to recommend the best medicine for a particular disease.

3 Evaluation

According to the problem definition of personalized medicine recommendation, we can see that there are two main requirements for the final recommended medicines: safety and effectiveness. Therefore, the evaluation of medicine combination recommendation model is also from the safety and effectiveness. In the following, we will give the evaluation methods and commonly used evaluation indicators for the effectiveness and safety of personalized medicine recommendations, respectively.

3.1 Effectiveness

In the personalized medicine recommendation problem, doctors' prescriptions are generally taken as the ground truth. Therefore, to evaluate the effectiveness of the personalized medicine recommendation model, it is only necessary to compare the medicines given by the model with the doctor's prescription. This is the same as the traditional item recommendation problem. Therefore, the commonly used evaluation indicators Recall, Precision, and $F1$ in the recommendation system are adopted for effectiveness evaluation. Below, we first give the calculation formula of these evaluation indicators:

$$\text{Recall} = \frac{1}{n}\sum_{i}^{n}\frac{|M_i \cap \hat{M}_i|}{|\hat{M}_i|},$$

$$\text{Precision} = \frac{1}{n}\sum_{i}^{n}\frac{|M_i \cap \hat{M}_i|}{|M_i|},$$

$$F1 = \frac{2\times \text{Precision}\times \text{Recall}}{\text{Precision}+\text{Recall}},$$

where M_i is the prescription given by the doctor to patient p_i, and $\hat{M}_i$ is a collection of personalized recommendation model given medicines. Recall assesses the integrity of a predicted medicine. Precision assesses the accuracy of predictive medicines. $F1$ is a comprehensive evaluation index defined as the harmonic average of Precision and Recall.

In addition, the Jaccard coefficient is often used to evaluate the effectiveness of personalized medicine recommendation. The formula for calculating the Jaccard coefficient is as follows:

$$\text{Jaccard} = \frac{1}{n}\sum_{i}^{n}\frac{|M_i \cap \hat{M}_i|}{|M_i \cup \hat{M}_i|}.$$

It is defined as the ratio of intersection size to union size to compare the similarity and difference between the predicted medicines and the real medicines.

3.2 Safety

Safety is another important factor in evaluating personalized medicine recommendations. Safety here means that when a patient has multiple diseases and requires the use of multiple medicines, there will be no adverse interactions between diseases and medicines and between medicines. At present, only DDI rate is widely used to evaluate the safety of personalized medicine recommendation. The formula for calculating DDI rate is as follows:

$$\text{DDI rate} = \frac{1}{n}\sum_{i}^{n}\frac{|(m_j, m_k)\in M_i \& (m_j, m_k)\in \mathcal{E}_{\text{ddi}}|}{\sum_{j,k}1}.$$

The medicine pair $(m_j,\ m_k)$ in will be counted only if it also belongs to the DDI set $\mathcal{E}_{\text{ddi}}$, and then the count is divided by the total number of possible medicine pairs. At present, the evaluation of safety needs to be improved, because the evaluation of safety needs to know what the adverse interactions are, which involves a lot of medical knowledge.

4 Challenge and Future Direction

Although there have been many researches on personalized medicine recommendation, there are still some problems and challenges.

(1) How to guarantee the safety of personalized medicine recommendation? There are two key issues in this challenge: one is the lack of medical knowledge, that is, the lack of available data on known adverse interactions, especially between diseases and medicines; the second is how to integrate relevant medical knowledge into the model so as to avoid adverse interactions and ensure the integrity of recommended medicines.

(2) How to realize the interpretability of personalized medicine recommendations? Explainable recommendation systems can provide the user with not only a list of recommendations but also reasons for recommending those items. Most importantly, these explanations can help improve the transparency, persuasiveness, effectiveness, and credibility of the recommendation system, which is particularly important when it comes to medicine recommendations.

(3) How to achieve more refined personalized medicine recommendation? We also consider this problem in two ways. On one hand, patients' conditions are constantly changing, so it is necessary to realize dynamic recommendation. On the other hand, some medicines have different usages in different scenarios, and how to determine the dosage of medicines is also a research problem to achieve refined medicine recommendation.

(4) How to combine medicine recommendation and full life cycle health records? By integrating these two domains, a more extensive and multidimensional patient information profile can be achieved, enhancing the continuity and completeness of data. As the volume of available patient data continues to grow, the potential for generating safe, personalized, and effective drug recommendations will expand substantially.

5 Conclusion

This paper reviews the research progress in the field of personalized medicine recommendation in recent years. Firstly, the problem of medicine combination recommendation is defined by a simple formal expression, and the differences of medicine recommendation in different scenarios are illustrated. Then, according to medicine recommendation based on multi-disease, medicine recommendation with combination pattern, medicine recommendation with additional knowledge, and medicine recommendation based on feedback, detailed model classification and analysis are carried out. Next, two important aspects of the evaluation of personalized medicine recommendation algorithm are explained: effectiveness and safety, and several specific evaluation indexes are given. Finally, we put forward three challenges and future development directions of personalized medicine recommendation, which are to ensure the safety of medicine recommendation, to achieve interpretable medicine recommendation, and to achieve more refined personalized medicine recommendation. It is of certain reference significance for the research and development of personalized medicine recommendation in the future.

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